The essence of a good clinical trial in diabetic foot disease

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Article points

1. The evidence base for treatments for diabetic foot ulcers is generally poor
2. There is therefore an urgent need for better evidence to be produced and for studies to be of good quality
3. A recently published 21-point checklist enables clinicians to identify the quality of published trials

Key words

- Reporting standards
- Trial design
- Ulceration

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The evidence base for treatments for diabetic foot ulcers is generally accepted to be poor. Repeated systematic reviews have concluded that the data to justify the use of any one intervention are weak. There are too few clinical trials and many of those that have been published are of poor quality. There is an urgent need for better evidence to be produced and for studies to be of good quality. Given the paucity of available evidence, clinicians should participate in trials whenever possible. This article outlines essential aspects for running a good clinical trial in diabetic foot disease.

It is generally accepted that the evidence base for the various treatments available for diabetic foot ulcers is poor. Repeated systematic reviews have concluded that no matter what the intervention — whether education, dressing choice, advanced wound care products or systemic treatments — the data to justify the use of any one are weak (Dumville et al, 2012; Hoogeveen et al, 2015; National Institute for Health and Care Excellence, 2015; Game et al, 2016; Armstrong et al, 2017).

There are too few clinical trials and many of those that have been published are of poor quality. The only exceptions to this generalisation are offloading for plantar ulcers and possibly topical negative pressure and hyperbaric oxygen. The jury is still out on the latter two, particularly with regard to the health economic case. The group of treatments for which the evidence is most weak is that of wound care products and dressings. It is for these reasons that most guidelines suggest that in the absence of evidence, newer expensive treatments have no proven benefit over those with a lower unit cost.

The need for quality evidence is essential — not least because of the enormous variation in amputation incidence in different parts of England, which indicates that the current heavy reliance on professional opinion is not good enough (Holman et al, 2012). The field where the evidence is weakest is that of dressing choice, which may contribute to the very high community cost (estimated around £700,000 per annum) of managing diabetic foot disease (Kerr, 2017). Community costs account for >60% of the total costs of management, which in itself accounts for 0.72–0.83% of the total NHS budget (Kerr, 2017). Every aspect of treatment should be based on strict adherence to agreed protocols, assuming there is evidence to justify them. It follows that there is an urgent need for better evidence to be made available and for any studies to be of good quality.

Quality of evidence

Studies of wound care treatments are usually designed to provide evidence that a product improves healing: reduced time to healing, more ulcers healed by a fixed time, or more people being free from any ulcers (ulcer-free days) over the same time. The quality of the evidence is dependent on the design of the study and the way in which it was conducted.

The best-quality evidence is free from possible bias — where the term 'bias' applies to the extent to which any factor other than the treatment being studied could have contributed to the effect demonstrated. There are multiple sources of potential bias and these are greatest

in studies of the weakest design: case reports and case series, both of which are insufficient for the purpose (and yet both provide the bulk of the marketing evidence used to sell wound care products).

At the very least, a study should be based on a controlled series in which the effect of the treatment being tested is compared with usual care. The controls can be treated either in the same centre or elsewhere. The best-controlled studies are randomised; those that are not may be referred to as cohort studies.

The randomised controlled trial

Population

The choice of study population is crucial. Many clinical trials are conducted on people with clean neuropathic ulcers and without infection or significant peripheral artery disease. This group is, however, one for which there is strong evidence for the beneficial effect of well-designed offloading and, therefore, there is little need to evaluate special wound care products until all clinical centres are using the recommended standard of offloading. Research planners are reluctant, however, to embark on studies of people with ulcers that have persisted despite the use of good standard care, including offloading, in expert centres. These are the most common group, for whom effective treatments are urgently sought.

It is imperative that the studied population is well described so that clinicians can easily decide whether this is a population that is relevant to their own clinical practice or one that they have particular problems with. Details such as the age, gender and ethnicity of the participants, as well as details of their diabetes, of the limb (arteriopathy and neuropathy) and of any foot lesion (risk status if pre-ulcerative, description of ulcers if relevant) must be included (Jeffcoate et al, 2016).

Page points

1. A study should be based on a controlled series — the 'controls' being treated either in the same centre or another — in which the effect of the treatment being tested is compared with usual care.
2. The randomised controlled trial is currently accepted as the gold standard for studies designed to show that a treatment may or may not work.

"A dedicated clinical triallist can expect that a trial of a wound care product will take at least 5 years to bring to completion and will cost well in excess of a million pounds."

Randomisation

The randomised controlled trial (RCT) is currently accepted as the gold standard for studies designed to show that a treatment may work. In the hierarchy of evidence, only systematic reviews and meta-analyses stand above the RCT — and both are themselves dependent on data from already published RCTs.

The key feature of the RCT is that participants in the trial (comparing the treatment being tested with usual or accepted care) are randomised to either one group or the other and that this is done by someone independent from the study, and generally using a computer-generated random number sequence. This is to avoid researchers unwittingly using bias when they allocate a particular person to either the new treatment or the control group.

Control group

A major weakness of many published trials is the lack of attention given to the control group (especially if it is a 'usual care' group). If the treatment being tested is being compared with what the patient would otherwise have been treated, it is essential that care of the control group is of the highest possible standard if the aim is to demonstrate that the new treatment represents a real advance.

The components of good usual care should, therefore, be specified in the design of any trial. These cover ulcer assessment at each trial visit, offloading, debridement, dressings, antibiotics when needed, nutrition and self-care, glycaemic control, management of peripheral arterial disease and continued close observation. These have been listed in more detail elsewhere (Jeffcoate et al, 2016). A failure to ensure that the best possible usual care was provided to the control group is why the results of some classic RCTs have been judged unreliable.

Blinding

Ideally, the researchers should also be blinded to the group the patient is in while the study is in progress. This is to remove any bias — or belief about the actions of the new treatment — affecting clinical judgements made during the conduct of the study. Of course, it is not always possible for the researcher or the patient to be unaware of the group they are in, but it is essential that decisions about the outcome are made by someone who is.

Primary outcome

The RCT should set out to demonstrate a statistically significant difference between the new treatment (called the intervention) group and the controls. The outcome should be pre-specified and the anticipated difference between the two groups should have been used in advance as the basis for a sample size calculation. This calculation is necessary because a smaller difference between groups will need many more people to be studied if a difference can be judged statistically as being unlikely to be the result of chance.

Other outcomes

Trials will also pre-specify other differences that might be found between the groups. Because these differences have not been the basis of the sample size calculation, their significance may be weakened. Readers assessing the quality of a published study should look carefully to ensure that any differences in secondary outcomes are not being over-emphasised when the primary outcome — which was the statistical basis for the study — showed no difference.

Sample size and completion

Although it may be relatively easy to plan an RCT, it can be notoriously difficult to complete the planned recruitment — especially when the study is a big one (as most are) and being undertaken in a number of clinical centres.

Many trials do not complete recruitment. An RCT that does not complete recruitment is underpowered and while any statistically significant difference between groups may reflect a clinically significant effect, it is not certain. Absence of difference in an underpowered trial is clinically meaningless.

A particular problem with trials of diabetic foot ulcers is that care is often shared by many different healthcare professionals, in both hospitals and the community. It can be

Box 1. 21-point scoring system for reports of clinical studies of aspects of the prevention and management of disease of the foot in diabetes (Jeffcoate et al, 2016.

Study design – population

1. Are appropriate definitions included for the terms 'ulcer', 'healing' and all other required aspects of the population and the outcomes?
2. Is the choice of study population appropriate for the choice of intervention and for the stated conclusions?
3. Was there a control population which was managed at the same time as those in the intervention group(s)?

Study design — intervention

4. Is the intervention sufficiently well described?
5. Were the components of other aspects of care described for the intervention and comparator groups?

Study design and sample size

6. Were the participants randomised to intervention and comparator groups?
7. Were the participants randomised by an independent person or agency?
8. Was the number studied in the trial based on an appropriate sample size calculation?

Study design — outcome measures

9. Was the chosen primary outcome of direct clinical relevance?

Study design — blinding

10. Was the person who assessed the primary outcome(s) blinded to group allocation?
11. Were either the clinical researcher who cared for the wound at research visits or the participant (patient) also blinded to group allocation?

Study conduct — recruitment

12. Did the study complete recruitment?

Study conduct – retention/attrition/protocol violation

13. Was it possible to document the primary outcome in 75% or more of those recruited?

Study conduct — analysis

14. Were the results analysed primarily by intention to treat (ITT) analysis?
15. Were appropriate statistical methods used throughout?

Observations — realistic performance of comparator group

16. Was the performance in the control group of the order that would be expected in routine clinical practice?

Observations — equivalent results from all participating centres

17. Were the results from all participating centres comparable? Answer 'Yes' if the study was single-centre.

Study reporting — missing or inconsistent data

18. Is the report free from errors of reporting such as discrepancies between data reported in different parts of the paper?

Study reporting — strength and weaknesses of the study

19. Are the important strengths and weaknesses of the study discussed in a balanced way?
20. Are the conclusions supported by the findings?

Study reporting — declaration of potential conflicts on interest

21. Is the report free from any suggestion that the analysis or the conclusions could have been significantly influenced by people with a commercial or other personal interest in the findings?

difficult to maintain continuity of the care specified by the trial if, for example, a patient is admitted under another department with unrelated problems.

The effect of such factors is that even more participants need to be included to account for withdrawals or patients unable to complete the trial because of the comorbidities that are so prevalent in this population. Obviously, if there is a lengthy follow-up period for a trial, the number of patients unable to complete the protocol may increase, and so withdrawals in this patient population may be higher than expected when compared with trials in other disease areas.

Trials of wound care products can present difficulties because dressing changes may sometimes be neglected if another medical problem dominates. Uninvolved healthcare professionals may also exercise their own clinical judgement concerning the best care of the foot ulcer and advise the patient to use a treatment that they personally favour and not to agree to continue with the experiment. While understandable, this approach does not encourage the advancement of clinical science.

Cost of interventions

The term "cost effective" is frequently heard as clinicians continue to work in a more cash limited environment. Quite simply, it means a new treatment needs to be good value, with the benefits and usage worth at least what is paid for them. Therefore, it is important that new treatments for diabetic foot disease are evaluated not just for their effectiveness, but also their cost effectiveness before adoption into clinical practice, even if this is not the primary aim of the trial.

Scoring the quality of reported trials

While these are some of the dominant factors determining the quality of a study, more details

can be found in a detailed report recently published on behalf of the International Working Group on the Diabetic Foot and the European Wound Management Association (Jeffcoate et al, 2016). This describes in detail the factors to be considered in all trials in the field of diabetic foot ulcers, including prevention, treatment and prevention of ulcer recurrence. This paper also presented a 21-point scoring system for study quality, with scores awarded for trial design, trial conduct and reporting (*Box 1*).

Drawbacks of clinical trials

The advancement of clinical knowledge (and hence the principals of good clinical care) depend on the conduct of RCTs, yet there are many barriers to be overcome. RCTs are extremely difficult to design and even more difficult to conduct. They are also extremely expensive and a dedicated clinical triallist can expect that a trial of a wound care product will take at least 5 years to bring to completion and will cost well in excess of a million pounds.

There are particular problems inherent in the conduct of trials in the field of diabetic foot ulcers. These also contribute to the number of trials that have neutral results (that is, show no difference between groups) and hence to the lack of evidence. The most important problem is the complexity of the disease — and of the many factors that are preventing ulcers from healing. These factors may vary considerably from person to person and even within the same person from time to time. This means that new treatments which may be very effective in reversing just one factor may not appear to be effective in all wounds when tested in a trial which (correctly) uses healing as its primary outcome. The benefit of such a treatment will only become apparent in those wounds that have the defect which the treatment will reverse.

Responsibility of clinicians

Given the paucity of available evidence, clinicians should participate in trials whenever possible. They should also be aware of treatment costs. If they are encouraged to adopt a particular product, they should question the evidence of both effectiveness and cost effectiveness justifying its use. They should also question clinical colleagues (including wound care experts) and ask them why they recommend any products for which the evidence base is slim.

The available evidence in the field of diabetic foot ulcers — a field in which there is evidence of very widespread differences in outcome (such as major amputation) — suggests that expert opinion is not enough on its own. Robust evidence is required before any therapy is used and if such evidence is not available, it is the authors' opinion that clinicians should use the cheapest and most suitable product available. ■

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