Original article

Study designs in wound care

ABSTRACT

A common issue in all types of research, including studies involving wound care, is deciding on the most appropriate and effective study design in order to facilitate collation of optimal levels of evidence and therefore promote best research practice. The two main types of study design – experimental and non-experimental – are outlined here, and examples of their different methodologies are discussed in more detail, with particular reference to wound care research.

Keywords Experimental study design, non-experimental study design, variables, sampling, analysis

For referencing Stephenson J. Study designs in wound care. WCET® Journal 2022;42(1):12-15

DOI https://doi.org/10.33235/wcet.42.1.12-15

Submitted February 2022, Accepted March 2022

INTRODUCTION

Clinical research in wound care has a shorter history than other medical disciplines, and faces specific challenges. Patients will often present with multiple and complex wounds which may require highly visible interventions, treated by different staff members over extended periods of time. An issue facing many researchers in wound care is the appropriate design of a quantitative study to answer a particular research question of interest. Design-related decisions need to be taken at an early stage of the process; however, all too often, research design becomes an afterthought, taken after data has been collected, and possibly determined solely by the statistician given the job of analysing the data, without any clinical input at all. In this editorial, the main types of research design available to wound care researchers will be covered, alongside some of the key issues that need to be considered in the design of an effective wound care study.

EXPERIMENTAL STUDY DESIGNS

Parallel trials

The first decision that may need to be made is whether to adopt an experimental or non-experimental design. An experimental design is one in which the researchers manipulate participants by assigning them to groups, either to one or more intervention groups or to a control treatment, usually standard care. The classic experimental study is the parallel randomised controlled trial (RCT) in which allocation to treatment groups is made on the basis of some randomisation method, and each participant receives one (and only one) of the treatments being compared. Outcomes are compared across groups using a statistical method based on considerations such as number of groups to be compared, distribution and type of data size of sample and so on.

This form of study design is known to provide high levels of evidence, but is relatively rare in wound care, possibly because of the complexity of typical treatments. Taheri et al.[1] conducted a parallel RCT to assess the effect of olive cream on pain severity and healing of C-section wounds, finding pain severity and wound healing were both reduced by the use of olive cream compared to both a placebo group and a control group receiving standard care ($p<0.05$ in both cases).

The main outcomes in the Taheri study were assessed at one specific timepoint. A variant on this design is the follow-up parallel RCT, in which measurements are made on groups at baseline and at some post-implementation point, with change scores computed for all participants and compared across groups. This design is often adopted when a significant time component is envisaged and there is some reason to expect that time-related changes may occur in participants receiving standard care in the control group, as well as in participants receiving the intervention. This approach was adopted by Gould et al.[2] who assessed the impact of a processed microvascular tissue (PMVT) allograft on wound closure and healing in an RCT of patients with chronic neuropathic diabetic foot ulcerations. Outcomes included changes in wound area from baseline to 12 weeks – the researchers found significantly greater reductions in the PVMT group than in a control group ($p<0.001$).

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Crossover trials

Although the majority of RCTs, whether comparing post-treatment outcomes or changes from baseline, are parallel, in some circumstances a crossover design may be utilised. In these trials, all participants receive both treatments (in a random order) and analysis is made on the basis of within-participant comparisons. Khadra et al.[3] used a crossover design to examine the effect of a water-friendly projector-based hybrid virtual reality (VR) dome environment combined with standard pharmacological treatment on pain in young children undergoing burn wound care in hydrotherapy. In this trial, all children received both treatments (hybrid VR and standard care) in a random order. The researchers found that hybrid VR significantly reduced procedural pain levels ($p=0.026$) and significantly increased patients' comfort levels ($p=0.002$). Crossover trials, however, are generally only suitable for treatments which temporarily alleviate symptoms, and in which the response time is not prolonged. They also require a washout period between the administration of each treatment to allow any residual effects of the first treatment to dissipate before the second treatment is applied. These and other constraints mean that crossover trials make up only a small proportion of all RCTs in wound care and other clinical fields.

Cluster trials

Some researchers in wound care collect data from multiple clinics or hospitals. In many cases, it is not practical to assign different treatments to different patients within the same institution, for example, due to staffing constraints or if a risk of contamination of treatments (i.e. when interaction between trial participants causes some participants to receive features of a treatment to which they were not assigned) is perceived. In such cases a cluster randomised design is appropriate, in which all participants in a single institution are randomised to receive the same treatment. Carville et al.[4] conducted a cluster RCT to evaluate the effectiveness of a twice-daily moisturising regimen as compared to 'usual' skin care for reducing skin tear incidence in which 980 participants were drawn from 14 facilities but where randomisation occurred at the facility level, rather than the individual level. This study found a reduction in incidence of about 50% under the moisturising regime.

One common problem with cluster randomisation is recruitment bias, the tendency of patients recruited at one cluster to be different from patients recruited at another cluster. Carville et al.[4] mitigated this effect in their study by creating seven pairs of institutions from the 14 included in the study, matched on size and type of care provided. One institution in each pair was allocated to the control treatment, and one to the new regimen.

NON-EXPERIMENTAL STUDY DESIGNS

Quasi-experimental studies

Although RCTs are recognised as providing very high levels of evidence, their appearance in the field of wound care is relatively rare. Other common research designs in wound care are the quasi-experimental study and the observational study. Ousey et al.[5] conducted a quasi-experimental study to compare quality of life (QoL) experienced by patients undergoing negative-pressure wound therapy (NPWT) as part of their wound care treatment compared to patients receiving standard wound care, finding no significant effect of therapy on QoL ($p=0.317$). In this study, patients were assigned to groups depending on whether or not they were already receiving NPWT, rather than by random allocation as would be the case in an RCT. Quasi-experiments are generally cheaper and less time-consuming to conduct than RCTs, and casting a study as a quasi-experiment may allow a better test of effectiveness (rather than efficacy) than would be obtained from a corresponding RCT. Hence, quasi-experiments can show good external validity. However, the non-randomised design of the quasi-experiment can lead to an overstatement of any effect sizes that may be determined, and the design lacks the level of internal validity that may be obtained from an RCT.

Cohort studies

Probably more common than RCTs in wound care are observational studies in which researchers simply observe participants in self-selecting groups without attempting to assign them to treatments. Observational studies are generally considered to provide lower levels of evidence than experimental or quasi-experimental studies due to possible confounding bias; however, a well-constructed observational study may provide high levels of research evidence. The cohort study is probably the most familiar type of observational study. This can take the form of a grouped analysis where the effects of, for example, gender, or the presence of a particular co-morbidity on some outcome can be assessed; it is not possible to randomise patients to take male or female gender, or to have or not have a certain co-morbidity. Guest et al.[6] assessed 6-month clinical outcomes, including wound healing, in a cohort study comparing patients with venous leg ulcers treated with either a two-layer cohesive compression bandage (TLCCB) or two-layer or four-layer compression systems, finding higher rates of healing in the TLCCB group ($p=0.006$). However, many cohort studies in wound care are not primarily concerned with comparisons across groups and may simply report, for example, prevalence values in a single group. In a cohort study of atypical pressure ulcers (APUs), Jaul[7] calculated APU prevalence in patients with pre-existing pressure injuries, finding 21% prevalence over approximately a 3-year period.

Case-control studies

Another common observational study design is the case-control study. This is a retrospective design in which exposure factors are compared in cases (those with the condition of interest) and controls. The case-control study design is a good choice when the condition of interest is rare, or where the researcher has limited time to collect data, as generally extant patient data records are used as the data source. This can help to control for the unwanted effects that may be introduced by imbalances in the characteristics of cases and controls. Lewin et al.[8] used a case-control design to identify risk factors associated with the development of skin tears in 453 patients

analysing two controls for each case and identifying several risk factors. Such a design involves careful consideration for case eligibility to avoid skewing the case-control relationship if, as is often the situation, there are more records of potential cases available than can be usefully included. As for certain other types of study design, many case-control studies use a matching process in which each case is matched to one or more controls on the basis of key demographics, typically age and sex, and possibly other health-related factors.

Single sample studies

One of the simplest, and possibly the most common study design in wound care, is the single sample study in which changes in patient outcomes between two timepoints are analysed – normally baseline and some follow-up measure taken post-intervention. This can be considered to be a specific type of cohort study, but is more commonly referred to as a 'pre-post' or 'paired' study design although, despite its name, it involves only a single group of patients – the word 'paired' arises from the fact that each participant typically provides a pair of values for analysis. In a pre-post study, participants act as their own controls. This makes this design an attractive option to researchers who may experience difficulties in recruiting enough patients for an RCT or grouped cohort study, where a minimum of two distinct groups of participants are needed for analysis. Another advantage of the pre-post design is that having participants act as their own controls usually reduces between-group differences, as the baseline and post-intervention groups are physically the same people, generally leading to higher statistical power. Using the pre-post variant of the paired design, Gethin et al.[9] analysed changes in surface pH and size of 20 non-healing ulcers following application of Manuka honey dressing after 2 weeks, finding that use of the honey dressings was associated with a statistically significant decrease in wound pH ($p<0.001$) and reduction in wound size from baseline ($p=0.012$).

The pre-post design can also, in principle, be extended to include multiple assessment points such as follow-up measures taken some time after active treatment is ended to assess long-term effects. In such studies, sometimes referred to as longitudinal studies, it may be necessary to specify the time at which the primary comparison of interest is to be made – for example, the change from baseline to the end of active treatment – with other comparisons considered to be secondary measures. Any longitudinal study is subject to attrition, and excessive loss can potentially compromise both internal and external validity. Careful thought needs to be given to the treatment of missing data arising from longitudinal studies, with the problem likely to become increasingly profound with each subsequent timepoint.

Simple pre-post designs are popular with wound care researchers, but the design is not without its problems. In certain contexts, some pre-post changes in addition to the introduction of the intervention may be expected, particularly in studies with long follow-up periods. Participants may change their habits while under treatment – they may take up exercise, start or stop smoking, develop a co-morbidity, or experience a bereavement or some other event that may have some bearing on their response to the intervention. This lack of internal validity can be problematic; it is not generally possible to know how much (if any) of the recorded pre-post changes' outcome can be ascribed to the treatment given, rather to these, often unknown, factors. Another issue is the effect of regression to the mean. This is a statistical phenomenon that can make natural variation in repeated data look like real change. As people who sign up for clinical studies are rarely typical of the population they purport to represent – they are usually sicker – any improvement observed between pre-treatment and post-treatment observations could have happened anyway without treatment.

The reason that these issues can be a problem in the pre-post design arises from the lack of a control group in this design. In an RCT, while the effects may still exist, there is not normally a reason to expect them to be manifest in one study group any more than in the other group, if the randomisation process has done its job properly; hence, the factors should cancel out.

GENERAL DESIGN ISSUES

Random allocation

Any kind of randomised study requires an appropriate random allocation method. Simple randomisation (for example, by a coin toss or computer-generated random numbering) maximises allocation concealment (the undesired effect whereby the allocation of some participants is known in advance) but may lead by chance to large imbalances in group sizes, lowering study power. A common alternative is block randomisation as was used in the study by Taheri et al.[1]. This method is normally accomplished via the opaque sealed envelope mechanism, and involves allocating participants to groups in small 'blocks' with equal numbers allocated to each group in every block. This facilitates recruitment to groups at approximately equal rates, and is good option if there is a concern that recruitment may have to be halted early. Block randomisation can be combined with cluster randomisation – as was the case in the study of Carville et al.[4] – or with some other method such as stratified randomisation in which randomisation schemes are conducted concurrently in subgroups defined by some key characteristic if it is thought necessary to ensure that groups are well balanced by that characteristic.

Blinding

If participants and/or assessors in a clinical trial are aware of treatment allocation, assessment bias may be introduced. This is particularly associated with subjective patient-reported responses such as pain or quality of life. Hence, where possible, researchers should consider masking treatment received from participants. However, wound care researchers have a particular problem with blinding. Most wound care studies are open label – the nature of the field is such that it is not usually possible to blind participants to the treatment they receive, for example, by performing a sham procedure. But even if

masking of treatment from patients or assessors cannot be accomplished, researchers may consider conducting single-blinded studies in which group allocations are masked from the data analyst.

Units of analysis

In most medical studies, whether experimental or observational, researchers usually collect data, and are interested in the outcome at the level of the individual patient. However, some context in wound care allows for different units of observation. Barakat-Johnson et al.[10] assessed the efficacy of a heel offloading boot in reducing heel pressure injuries in intensive care patients, in which the unit of analysis was the heel rather than the patient. While this approach, which could equally well be applied other anatomical sites such as the shin, arm etc., leads to a doubling of the sample size without further patient recruitment, care is needed in the analysis to account for the likely commonalities that will arise from the analysis of multiple anatomical sites within the same patient.

Variables

The primary endpoint, or outcome, of a study should be the one with the potential to most accurately demonstrate any benefit of a new treatment. Additional outcomes, designated as secondary outcomes, may also be defined. Typical endpoints in wound care studies are complete wound closure, percentage reduction in wound size, time to wound healing, wound leakage, reduction in sloughy tissue, pain, quality of life and cost-effectiveness of treatment. The key prognostic variable in most studies is usually treatment status; additional controlling variables such as age, sex, co-morbidities, medications, and length, type and duration of pre-existing wounds may also be recorded. Recording of such variables is critical for non-experimental studies in particular; in a well-conducted RCT, the randomisation process is usually effective in eliminating group imbalances at baseline, leaving the treatment status as the only systematic difference across groups. For a quantitative design, all variables should be measured on numerical scale, or comprise ordered or unordered categories; appropriate statistical methods can be utilised to analyse all combinations of variable types.

Sampling

The majority of wound care studies, in common with other clinical studies, use convenience (non-random) samples as random sampling methods are rarely practical. However, care should be taken to ensure that the sample characteristics represent the parent population in terms of key prognostic indicators, possibly with the use of quotas. The choice of a sample size, based on whatever units of analysis are appropriate, is critical for all study designs, particularly those that involve direct patient participation, and will generally involve a formal sample size calculation to be conducted. Such calculations require estimates of effect which are not always easy to determine, particularly in the trial of novel treatments, and a pilot study may be needed to provide the required estimates. It is not ethical to recruit patients to a study that is unlikely to be able to answer its own research question because the study sample is too small. As for all clinical studies, wound care studies require appropriate ethical approvals to be met.

SUMMARY

Effective research in wound care requires careful selection of an appropriate design. Rigorous design options such as the RCT require additional consideration of issues such as random allocation and blinding; simpler designs, such as the single sample pre-post design, can also be effectively utilised to provide good levels of evidence. All designs require consideration of the unit of analysis, variables to be measured, sampling issues and ethics.

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