Special Series on Research Methodology

Which Treatment Is Better? Ascertaining Patient Preferences With Crossover Randomized Controlled Trials

David Hui, MD, MSc, Donna S. Zhukovsky, MD, and Eduardo Bruera, MD
Department of Palliative Care and Rehabilitation Medicine, University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

Abstract

Context. The difference in patient-reported outcomes between study arms can often be difficult to ascertain in randomized controlled trials (RCTs) using a parallel design because of wide interindividual variations in baseline characteristics and how patients interpret the outcome measures. Furthermore, the minimal clinically significant difference is often not available for many outcomes, and even when available, not individualized for each patient. Crossover RCTs are designed for intraindividual comparisons, which can address these issues by asking patients to directly compare the interventions with regard to effectiveness, adverse effects, and ease of use and to provide an overall choice.

Objectives. We discuss the key design elements for crossover trials, their advantages and disadvantages relative to parallel designs, and their utility in palliative care research using a number of case examples.

Methods. This is a narrative review.

Results. Crossover studies randomize patients to a sequence of treatments. In addition to facilitating intraindividual comparisons, they often require a smaller sample size for the same statistical power compared with parallel designs and are thus less costly. However, crossover studies are only feasible when the condition being studied is relatively stable and the intervention has a short-term effect. Crossover studies with inadequate washout periods may be difficult to interpret. The risk of attrition also may increase because of prolonged study duration.

Conclusion. By facilitating intraindividual comparisons and eliciting patient preferences, crossover studies can provide unique information on the superior intervention. Crossover designs should be considered for selected palliative care studies. J Pain Symptom Manage 2015;49:625–631.

Key Words
Clinical trials, crossover studies, palliative care, randomized controlled trial, research design, statistical data interpretation

Introduction

In the era of evidence-based medicine, randomized controlled trials (RCTs) are considered the gold standard to inform clinical practice because they help to minimize selection bias and ascertainment bias. A large majority of RCTs in supportive/palliative care are parallel in design, in which patients are randomized to receive one of the study interventions (e.g., active intervention(s) or control).[1,2] The primary and/or secondary outcome measures of many supportive/palliative care trials involve patient-reported outcomes (PROs), such as pain, fatigue, quality of life, satisfaction, and preferences. With regard to ascertainment of outcomes for RCTs, there are three important questions:

1. Are there any statistically significant benefits and risks associated with the active intervention?
2. If yes, is the magnitude of the benefits and risks clinically meaningful?
3. What is the overall patient preference, taking into account both the risks and benefits? This information is particularly useful if the choice is made in a blinded fashion.

Address correspondence to: David Hui, MD, MSc, Department of Palliative Care & Rehabilitation Medicine, Unit 1414, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA. E-mail: dhui@mdanderson.org

Accepted for publication: November 13, 2014.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2014.11.294

Parallel RCTs, when adequately powered, are generally well equipped to answer Question 1; however, Questions 2 and 3 may not be addressed. To illustrate this, we use an example of a parallel RCT examining an intervention for dyspnea (Fig. 1a). The average intensity of dyspnea over the past 24 hours was assessed using a numeric rating scale (NRS) from 0 to 10, where 0 = no dyspnea and 10 = worst possible dyspnea. Patients randomized to an active intervention experienced an improvement of three points (from 7 at baseline to 4). Patients randomized to the control intervention also reported an improvement of two points (from 7 at baseline to 5). Thus, the active intervention was associated with an improvement in dyspnea by one of 10. Assuming that this difference is statistically significant (Question 1) because the study was adequately powered, we would then need to know if a change of one point on the NRS is clinically meaningful (Question 2).

Whether this difference was clinically meaningful would depend on the minimal clinically significant difference (MCID). MCID is defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management".[3] MCID is determined by either the anchor-based approach or the distribution-based approach.[4,5] The anchor-based approach is generally preferred and involves either asking a cohort of patients after an intervention whether their outcome of interest has changed or using an external criterion such as the frequency of rescue medication used in the case of breakthrough pain.[5–7] Unfortunately, the MCID is not available for many questionnaires, making it difficult for us to know if an observed change is clinically relevant. MCID may not always be applicable even if available because the study population and intervention often differ between the study of interest and the study in which MCID was derived. Finally, because the MCID cannot take into account individual preferences, Rennard[8] argues that it may be more appropriate for research instead of clinical practice.

The third measure of the effect of an intervention is overall preference. Overall preference is a pragmatic outcome because it represents a final choice, taking into account all the risks and benefits experienced by the individual, along with their relative weights. In this parallel RCT, the patients' overall preference (Question 3) could not be determined because patients did not have the opportunity to try both interventions.

Crossover RCTs randomize patients to a sequence of treatments and allow investigators to overcome many of the methodological limitations of parallel RCTs to ascertain treatment differences and preferences. Crossover trials are designed for intraindividual comparisons, and participants are asked to directly compare the interventions with regard to effectiveness, adverse effects, and ease of use and to provide a final overall choice. Crossover trials can thus provide valuable information about which intervention is superior beyond what can be achieved in parallel studies.[9] In this article, we discuss the key design elements for crossover trials, their advantages and disadvantages relative to parallel designs, and their utility in palliative care research, using a number of examples.

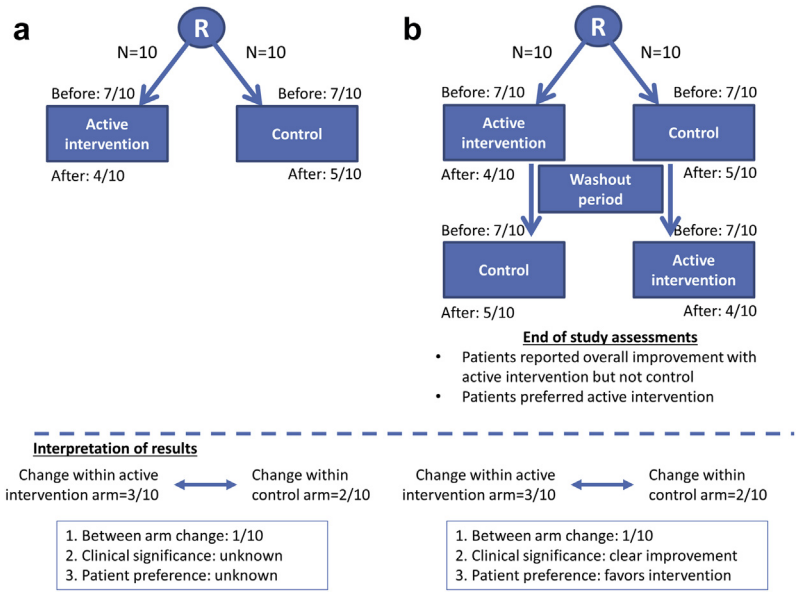

Fig. 1. Randomized controlled trial design. a) Parallel trial and b) crossover trial.