ELSEVIER

Journal of Clinical Epidemiology 66 (2013) 768−774

Journal of Clinical Epidemiology

Clinical experience may affect clinician compliance with assigned treatment in randomized trials

Stephen D. Walter[a,*], Afisi S. Ismaila[a], Deborah J. Cook[a,b], Mohit Bhandari[c], Kari A.O. Tikkinen[a,d], Gordon H. Guyatt[a,b]

[a]*Department of Clinical Epidemiology and Biostatistics, McMaster University, CRL233, Hamilton, Ontario L8N 3Z5, Canada*
[b]*Department of Medicine, McMaster University, Hamilton, Ontario L8N 3Z5, Canada*
[c]*Department of Surgery, McMaster University, Well-Health Building, 293 Wellington Street North, Suite 110, Hamilton, Ontario L8L 8E7, Canada*
[d]*Department of Urology, Helsinki University Central Hospital and University of Helsinki, 00029 Helsinki, Finland*

Accepted 24 October 2012; Published online 6 April 2013

Abstract

Objective: To examine the relationship between clinical experience and clinician compliance with the study protocol in randomized clinical trials.

Study Design and Setting: A recent randomized trial of surgical techniques for tibial fracture fixation. We consider rates of treatment crossovers and other noncompliance as a function of the relevant experience of the surgeon. We also examined the effects of noncompliance on patient outcomes.

Results: Crossovers from assigned treatment to the alternative occurred much more frequently in one arm than the other. The impact of surgical experience on crossovers was less clear, although there was some evidence that noncompliance with more difficult surgery was more frequent for less experienced surgeons. This raises the possibility that experience may be an important factor in other scenarios, affecting both compliance and patient outcomes.

Conclusion: In randomized clinical trials, noncompliance by clinicians with the randomly assigned treatment can be highly detrimental to the power of the study. Further research is needed in this area to identify, quantify, and understand the factors associated with noncompliance, including clinical experience.

Keywords: Clinical trials; Randomization; Compliance; Treatment crossovers; Clinical experience; Expertise; Bias

1. Introduction

Because it takes training and experience to develop expertise, clinicians tend to develop preferences for specific interventions [1]. Newer procedures will tend to be less familiar to clinicians than longer established techniques, which may therefore bias randomized trials in favor of the older methods. This is a particular concern in surgery because the number of procedures required to achieve basic and advanced surgical competence may differ between older and newer techniques.

Randomized controlled trials of surgical interventions may be prone to procedural crossovers. The likelihood of a procedural crossover being initiated by surgeons may depend on their familiarity with the technique and their position on the learning curve for the procedure. Studies of learning curves typically use the number of completed surgeries as the measure of clinical experience. These studies have examined the effects of the learning curve on operation time, costs, or patient-important outcomes [2−12]. However, to our knowledge, the impact of clinical experience on compliance with study protocols in randomized clinical trials has not been examined.

Procedural crossovers violate the randomization protocol for the trial and hence limit the interpretation of study results. If the intention-to-treat principle is adopted, patients are retained in the group to which they were randomized, regardless of the treatment actually received. Crossovers will typically reduce the statistical power of the comparison between randomized groups to evaluate treatment effects and hence should be avoided to the extent possible. Even relatively modest crossover rates can have a serious detrimental effect on study power. It is therefore

Dr Tikkinen was supported by the Finnish Cultural Foundation and the Finnish Medical Foundation.

The authors have no conflict of interest or financial disclosures to make.

* Corresponding author. Tel.: +905-525-9140; fax: +905-577-0017.
E-mail address: walter@mcmaster.ca (S.D. Walter).

0895-4356/$ - see front matter
http://dx.doi.org/10.1016/j.jclinepi.2012.10.015

What is new?

- Little is known about the relationship between clinical experience and clinician compliance with the study protocol in randomized clinical trials. In particular, noncompliance by clinicians with the randomly assigned treatment can be highly detrimental to a study's power.
- Using data from a recent trial of surgical techniques for tibial fracture fixation, we found that crossovers occurred much more frequently in one arm than the other. The impact of surgical experience was less clear, although there was some evidence that noncompliance with more difficult surgery was greater for less experienced surgeons.
- Clinical experience may be an important factor in other trials, affecting both compliance with the study protocol and subsequent patient outcomes.
- Because noncompliance can be detrimental to the power of randomized clinical trials, further research is needed to identify, quantify, and understand the factors associated with noncompliance, including clinical experience.

necessary to consider possible determinants of clinicians' noncompliance with the study protocol.

These issues arose in a recently completed randomized trial of alternative approaches to nailing tibial fractures. There are approximately 500,000 fractures of the tibia and fibula per year in the United States, and they are associated with most of the emergency operating room procedures in most trauma centers [13]. The lack of soft tissue envelope around the tibia limits blood supply to the fractured bone during the healing process. In this situation, the endosteal blood supply (or that from within the bone marrow cavity) becomes a major source of blood supply to the healing bone and surrounding tissues. Opponents of intramedullary reaming before nail insertion argue that reaming destroys the vital remaining supply of blood to the fracture and could impair healing of the bone ends [14,15].

The rationale, design, and characteristics of participants in a large randomized trial to evaluate two types of intramedullary nails in patients with tibial fractures (SPRINT) have been presented in detail elsewhere [16,17]. Briefly, the SPRINT trial randomized patients with tibial fractures to alternative surgical techniques to evaluate rates of secondary procedures and patient function at 1 year. Patients were randomized to fracture fixation using either reamed or unreamed intramedullary nail insertion. The former technique uses a reamer to enlarge the canal of the tibia before insertion of a metallic nail of a larger diameter, whereas the latter nonreamed (or unreamed) technique inserts the nail without prior passage of a reamer. Thus, the key differentiating factor is use of a ''reamer'' before insertion of the nail in the reamed nail group. For simplicity, we will henceforth refer to these two intervention options as ''reamed nails'' or ''unreamed nails.''

Randomization of patients to an intervention took place as soon as possible before the surgery to avoid unnecessary withdrawals or other protocol violations. Despite these precautions, for some patients, surgeons did not perform the assigned intervention and instead used the alternative intervention to which the patient was not randomized. These procedural crossovers may have occurred for several reasons. For example, after a more detailed intraoperative assessment of the fracture, the surgeon might have decided that the most appropriate course of action was to crossover the patient from the randomly assigned treatment to the other treatment. If the surgeon found the case challenging and the patient was assigned to the intervention in which the surgeon had less experience, then the surgeon may have reverted to the treatment approach with which they had greater experience.

For the SPRINT trial, all patients for whom the randomly assigned treatment was not implemented were retrospectively reviewed by a six-member blinded adjudication committee. The committee verified that these patients were eligible (specifically, they would have been able to receive either of the two potential treatments). This was to avoid possible bias if, for instance, patients assigned to reamed nails were being deemed ineligible during surgery because of the slightly larger tibial dimensions required for the insertion of this type of device. Overall, six patients (3 from the reamed group and 3 from the unreamed group) were found to be ineligible for both reamed and unreamed nails and were administered other interventions.

The aim of this report is to examine whether the probability of compliance with randomized treatment assignments depends on clinical experience, using the SPRINT trial as an example. We also examine the effect of these differential crossovers on patient outcomes.

2. Methods

At the start of the SPRINT trial, a self-administered postal survey was conducted among 139 surgeons then participating in the trial to estimate the potential for differential expertise bias [18,19]. A total of 80 surgeons (57.6%) completed the survey. Concern about this type of bias was raised because the unreamed nail technique was being used considerably less frequently than reamed nails. Greater familiarity and surgical expertise with the reamed nail might therefore have disadvantaged the unreamed nail method when evaluated in the trial. The unreamed intervention was generally regarded as more technically challenging than the reamed procedure because, unlike the