ELSEVIER

Journal of Clinical Epidemiology 58 (2005) 350–356

Journal of Clinical Epidemiology

The validity and ethics of giving placebo in a randomized nonpharmacologic trial was evaluated

M.G. Spigt*, P.G. Knipschild, C.P. van Schayck, J.A. Knottnerus

Department of General Practice, University of Maastricht, Research institute Caphri, P.O. Box 616, 6200 MD Maastricht, The Netherlands

Accepted 23 August 2004

Abstract

Objective: When studying the effects of a non-pharmacologic intervention, the choice of a control group is often difficult. In a study on the effectiveness of increased water intake on voiding dysfunction in elderly men we used an unusual design. This article addresses the internal validty and ethics of this design.

Study Design and Setting: The randomized trial we evaluated had a 6-month follow-up period and was carried out among 141 elderly men with moderate lower urinary tract symptoms. The experimental group was given the instruction to drink more water, the control group received placebo medication. The participants were not informed that there was a 50% chance of receiving placebo. We measured whether the prior expectations and preferences were comparable for the two study groups, whether blinding was preserved throughout the study period, and whether the participants considered this design ethical.

Results: Prior to randomization, patients had higher expectations for the experimental intervention, but there was not statistically significant difference in their preference. During the study period, two out of 71 patients in the control group unmasked the placebo. In general, both groups fully agreed with the informed consent procedure.

Conclusion: This design can be considered when the effects of a non-pharmacologic interventions are studied.

Keywords: Randomized controlled-trials; Placebo; Research method; Ethics; Blinding; Life style advice

1. Introduction

In 2001, we started a study on the effectiveness of increased water intake on lower urinary tract symptoms in elderly men. We wanted to study if it was possible to train the human elderly bladder by increasing the urine output. We hypothesized that by training the bladder, frequently reported urinary symptoms, such as weak stream and incomplete emptying, might be prevented [1]. We used an unusual design. In a randomized trial, we gave the experimental group the instruction to drink more water, whereas the control group was given a placebo (one spoon of inactive syrup per day during dinner). The participants were not informed that there was a 50% chance of getting a placebo. In this article we do not report on the effectiveness of drinking water on bladder function, but we describe the methodologic considerations that led to this design, and we subsequently describe the evaluation of this design as regards internal validity and ethics.

2. Methods and Observations

2.1. Background

A placebo control group is often the best option and is still the standard, although it is increasingly considered unethical to use placebos when alternative effective interventions are available [2,3]. In pharmacologic trials, the fabrication of a placebo drug is relatively easy. However, in many other cases, such as psychotherapy and physical therapy, the experimental therapy is less easily transformed into a placebo or sham treatment [4–9]. The substitute design that is often used is a design in which the control group receives no intervention or usual care. Occasionally, some ingenious control intervention is used, such as sham traction [10] or sham spinal manipulation [11] for low back pain, placebo acupuncture [12], or placebo Transcutaneous Electical Nerve Stimulation [9].

Finding a proper control group is particularly difficult when one wants to study the effects of a lifestyle advice [4]. Giving advice is an important aspect of medical care and may have placebo effects that the researcher may want to control for. However, an advice is impossible to copy into a placebo, and unless the lifestyle advice is changed into

* Corresponding author. Tel.: +31 43 3882309; fax +31 43 3619344.
E-mail address: m.spigt@hag.unimaas.nl (M.G. Spigt).

0895-4356/05/$ – see front matter
doi: 10.1016/j.jclinepi.2004.08.009

Table 1
The pros and cons of different possible designs when studying the effects of a lifestyle advice

Control group receiving	Comparability of nonspecific treatment effects (expectancy)	Blinding patients for hypothesis[a]	Adherence to the experimental intervention	Avoidance of co-interventions	Avoidance of contamination	Avoidance of drop-out	Ethics	Score
No treatment[b]								
Informed consent before randomization	− − −	− − −	+ + +	− − −	− − −	− − −	+ + +	−9
Informed consent after randomization	− −	− −	+ + +	− −	+	−	−	−4
Alternative intervention								
Unequally attractive[c] (expected to be more or less effective/ bothersome)								
Informed consent before randomization	− − −	+	− −	− − −	− − −	− −	+ + +	−8
Informed consent after randomization	−	+ + +	+ +	+ +	+ + +	+ +	−	10
Equally attractive (expected to be as effective/equally bothersome)								
Informed consent before randomization	+ +	+ + +	+ +	+ + +	+ +	+ + +	+ + +	18
Informed consent after randomization	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ +	20
Sham advice	+ +	+ + +	+ + +	+ + +	+ +	+ + +	+ +	18

Scoring legend: − − −, surely a problem; − −, probably a problem; −, maybe a problem; +, likely no problem; + +, probably no problem; + + +, surely no problem. Example of scoring the "nontreatment/informed consent after randomization" option: Unlike the control group, the intervention group receives an intervention with the associated nonspecific treatment effects. These effects are not present in the control group, and therefore this design scores poorly on "comparability of nonspecific treatment effects."

[a] Scoring of the blinding of the care provider, patients (for the treatment), data collector, and data analyst is omitted from this discussion because these factors depend on the conduction rather than the design of the study.

[b] Only the no-treatment option is considered. In some cases, however, a "usual care" control group may be possible. The results for this design may be slightly more positive than the "no treatment" option.

[c] In the patients' perception, the interventions may be regarded as unequally attractive, although there is (ethically required) equipoise on the evidence for this.

a complex intervention such as a complex exercise program, living by such an advice is possible for everyone. A potential control group, hearing of a promising new advice, could easily implement the experimental advice into daily life, resulting in contamination bias.

2.2. Evaluation of different designs

The idea to use a placebo in the control group occurred to us after we explored several conventional designs. Table 1 shows the different designs that we initially considered for our water study. For each design, we considered the pros and cons regarding internal validity. Although Table 1 may be applicable to other studies and gives insight into the strengths and weaknesses of different designs, the scoring is arbitrary, and practical aspects often determine the final decision. From our analysis we concluded that a no-treatment control group with a conventional randomization procedure seemed to be the least desirable design in that, for example, only the experimental group would feel treated, and the disappointed control group might want to seek treatment outside the study. As is shown in Table 1, finding a comparably attractive alternative intervention and using prerandomization would be a much more promising approach [13,14]. In our case, however, there was no standard urologic preventive lifestyle advice that we could use as an alternative intervention. The next option we considered was to use a sham advice. For our study, we considered advice such as to wear thermal undersocks or to avoid eating some specific products (e.g., organ meat or shellfish). However, we could not be sure that these advices would be inactive. Furthermore, the advice to wear thermal undersocks might seem a bit ridiculous in summertime. Using a "real" placebo, such as a tablet without active elements, was not considered from the beginning and is therefore not presented in Table 1. We figured that participants who are informed that there is a placebo involved would probably reason that, because a tablet can easily be turned into a placebo, the advice should be the real intervention. So it appeared that we were stuck on the no-treatment possibility.

However, because the critical aspect of not being able to use a placebo was in the information given to the patient,