CHOICE OF CONTROL GROUP IN THERAPEUTIC DEVICE TRIALS

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Abstract Recent advances in technology have given medical devices the potential to restore function and quality of life in patients where medication is not completely effective in controlling symptoms or causes severe side effects. This talk focused on modifications of customary designs that allow for ethical, practical and scientifically valid placebo-controlled device trials. The FDA requires at least one pivotal controlled trial to demonstrate safety and efficacy for a device in support of a premarket approval (PMA) application. However, choice of a control in medical device trials can be problematic. The ethics of withholding treatment from patients or performing sham surgeries has been a topic of debate. The controls considered in the E10 guidance document by the International Conference on Harmonization (ICH) include: placebo, no-treatment, dose-response, active, and external. Pilot studies can help choose an appropriate control group. Some design options in device trials are crossover study; three-arm study with new treatment, standard treatment, and placebo control; or having subject serve as own control. Examples from the therapeutic device industry were discussed.

Background

The choice of control in medical device trials can be a difficult decision. The FDA has published a Guidance for Industry "E10 Choice of Control Group and Related Issues in Clinical Trials". This document .provides information on many types of controls which can be used and tips on when each may be appropriate. The purpose of including a control group is to discriminate patient outcomes caused by test treatment from outcomes caused by other factors. Randomization and blinding (masking) help minimize the chance of bias.

Some types of control group

Types of control include: placebo concurrent control, no-treatment concurrent control, dose-response concurrent control, active (positive) concurrent control, external control (including historical control), and multiple control groups.

Some controls used in implantable medical device studies include: medically managed, previous product (similar but not the same), (concurrent or historical), placebo control surgery (no device), sham surgery (non-operational device), or standard treatment (e.g. a non-device surgical treatment).

It is important to be careful in maintaining a preplanned level of blinding (masking). In the medical device situation, the statistician and surgical implanter are not blinded. Patient care and coordinating center personnel may be blinded. Maintaining patient masking can take a great deal of thoughtful planning in advance of the clinical trial.

Some types of study design

Some design options used in implantable medical device studies include: treatment group only, measuring change over time, subject serves as own control, crossover study, and three-arm study with new device treatment, standard treatment, and medically managed

There are advantages and disadvantages to keep in mind when considering use of the crossover design. Each patient gets both treatment and control, minimizing patient variability and the sample size needed. However, period and carryover effects can be present. Period effects may be important in rapidly progressive disease. Crossover may be a good design if patient does not perceive operation of device (e.g. pacemaker). It may not be a good design if patient is able to notice operation of device (e.g. neurostimulator). It may be difficult to keep the blind once patient has experienced operational device treatment.

Placebo surgery ethical issues

A placebo surgery control group may be needed to test for "placebo effect". This effect results

when patients expect to benefit (or suffer) from a surgical procedure/medical device. Patients may also expect to benefit from the clinical procedure ("Hawthorne effect"). If no surgery, patient knows treatment did not occur. "Regression to the mean" effect.

The Nuremberg Code and Declaration of Helsinki treaties have mandated that the patient's welfare is more important than society in general. It is the declared mission of the medical profession to "do no harm". Risk from surgical procedure may include adverse events such as infection and bleeding. If a device does not work properly or a battery runs out, the device may need to be surgically explanted.

There are also ethical issues for informed consent in a randomized placebo-controlled trial. One point of view holds that if patients are well informed, they can decide for themselves (principle of autonomy). Proponents also note that all clinical trials are approved by review boards at US NIH and FDA. They feel that risks for patients are reasonable relative to possible benefits from study (Dr. Thomas Freeman, University of South Florida, discussing fetal brain cell implants for Parkinson's disease patients).

Another point of view states that placebo surgery "…violates ethical and regulatory principle that the risk of harm to subjects must be minimized in the conduct of research" (Dr. Ruth Maklin, Albert Einstein College of Medicine, N.Y.). Opponents consider patients vulnerable and not as well informed as medical personnel. Patients may want a treatment (surgery or device)which may not be available except through a clinical trial. They may want the clinical care available from serving as a subject in a medical study. Patients often wish to please their doctor and may agree to participate for that reason.

<u>Examples of proposed or current surgery/device clinical trials incorporating placebo surgery.</u>

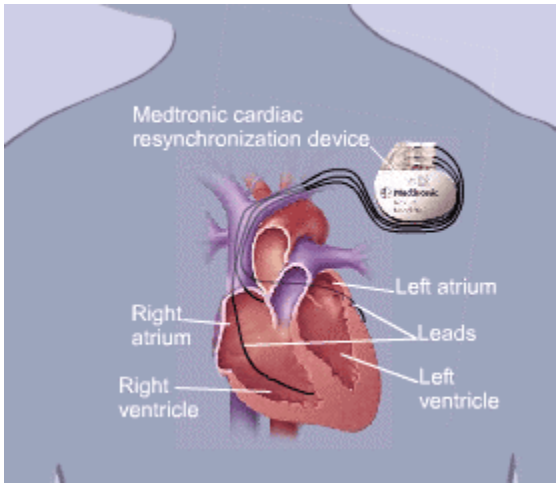
A recent clinical trial including a placebo surgery arm studied arthroscopy (debridement and lavage) for osteoarthritis of the knee (NEJM, July 11, 2002). More than 650,000 such procedures are performed each year, at an approximate cost of $5000 each. Previous treatment-only studies showed "impressive effect" for lavage compared with closed-needle sham control (saline placebo injection). Moseley et al conducted a three-arm randomized clinical: trial. The three arms were: lavage, debridement, and a sham-arthroscopy control group. There were 60 patients per group, with patients and evaluators blinded to treatment assignment. One surgeon at the Houston VA Medical Center did all procedures for consistency. The primary end point was knee pain at 2 years. The treatment groups pain perception was no better than placebo surgery group. "Indeed, at some points during follow-up, objective function was significantly worse in the debridement group than in the placebo group".

A placebo controlled trial of surgery for epilepsy was published recently (NEJM, July 2002). Surgery was very successful, so it had been thought unethical to use no treatment control group. There was a "wait list" for the surgery of over one year. In this study, the wait list group was used as the no treatment control group, with a one year end point.

A proposal for an NIH study of deep brain stimulation (DBS) for Parkinson's disease is designed as a prospective, randomized CT of DBS in globus pallildus (GPi) and subthalamic nucleus (STN) for treatment of advanced Parkinson's disease (PD). Medical therapy is successful; however over time patients relapse and also develop incapacitating motor fluctuations and dyskinesias. Surgery is ablative GPi pallidotomy. DBS has the important advantage of being reversible. Stimulation parameters can be adjusted to different area of brain. Bilateral DBS does not have high incidence of complications as does bilateral pallidotomy.

The new proposed NIH DBS for PD study compares GPi vs STN. NIH has a current study comparing pallidotomy versus medical management for PD. It is proposed to use the current cohort of patients in the pallidotomy clinical trial for comparison to DBS. Three key objectives include: to compare GPi,-DBS, STN-DBS, and GPi pallidotomy, to investigate which patients are best candidates for DBS, and to investigate whether bilateral stimulation (GPi or STN) is superior to combined GPi pallidotomy and DBS. Motor, cognitive and psychiatric

functioning and quality of life will be studied.



Medtronic InSync®: pacemaker for congestive heart failure

In the Medtronic MIRACLE clinical trial, 453 patients with moderate-to-severe symptoms of heart failure and an intraventricular conduction delay were randomly assigned to: the cardiac-resynchronization (CRT) group (pacemaker implanted and turned on), or the control group (pacemaker implanted but no CRT therapy). Data was analyzed from baseline to 6 months interval.

Three primary end points (any one is a success) included: New York Heart Assoc (NYHA) functional class, quality of life (QOL), and distance walked in 6 minutes. The Hochberg Multiple Comparison Procedure was used to adjust for using three endpoints.

Medtronic InSync®: clinical trial results were:

NYHA: 38% of control and 68% of CRT patients showed improvement of 1 or more NYHA class (baseline to 6 months);

QOL: The median change for the control group was –9 and the median change for the CRT group was –18.5 (low is better); and

6-minute hall walk: The median improvement for the control group was 10 meters and 40 meters for CRT patients.

Results were all statistically significant using the Wilcoxon rank sum test.

It was concluded there was a “placebo effect” in that improvements were seen in the control group, but the levels of improvement were not as much as in the CRT group. (Note that to be eligible, patients did not have indications for a pacemaker, so the device implanted in the control group was not a treatment for them.)

Conclusion

Several ways to make placebo (sham) surgery ethical are suggested. If the treatment is shown to be safe and effective during the study, delayed treatment should be provided for control group patients who desire the treatment and are appropriate medical candidates in the judgement of study physicians. The study can provide device/clinical care patients could not get otherwise. The device/surgery can be provided as an adjunct treatment so patients still get their usual medications (“medically managed” arm), so patients are still being treated for their medical condition. In some situations, “wait list” patients could be used for control group. Bayesian methods could be used to set a prior on the control group. This may allow a historical control or data from a previous medical device study to be used instead of including a concurrent placebo control arm.

Be sure informed consent is clearly understood and patient does not feel pressured into the trial.

Bibliography

Available on request from the author

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