J Anesth (2007) 21:102–105
DOI 10.1007/s00540-006-0440-7

Journal of
Anesthesia

Miscellaneous

Not all placebos are the same: a debate on the ethics of placebo use in clinical trials versus clinical practice

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Key words Placebo · Ethics · Randomized Controlled Trial · Declaration of Helsinki

The case

During the 2005 meeting of the Special Interest Group in Ethics of the American Pain Society, the use of placebo[1] in the management of pain medicine was debated. The practice of intrathecal saline (placebo) injections for determining the need to implant intrathecal drug delivery systems (IDDS) was presented and discussed, followed by the question: Is this practice ethical? The goal of this article is to respond to this question and to focus on the ethical framework for the use of placebo drugs and surgery in research and in clinical care, while pointing out the fundamental difference between placebo use in the research and clinical care settings.

The use of placebo drugs in clinical trials

The use of placebo in the clinical setting may be seen in two distinct situations. First, eliciting a placebo effect to determine the clinical efficacy of a treatment, and second, as a control in an experimental situation [1]. Although the discussion of the ethics in our case is in regard to the first situation, we shall begin with a discussion of the ethics of the latter, because it is there where most of the normative ethical reflection on placebo use is found.

The Declaration of Helsinki (DoH), first adopted in 1964, indisputably serves today as the ethical guideline for physicians and those who practice medical research. It elevates concerns for the health and rights of individual patients currently being treated over those of future new potential patients, as well as those of society and science. Therefore, it is not surprising that the DoH states that *"every patient, including those of a control group, should be assured of the best current diagnostic and therapeutic method"*, thereby proscribing the use of placebo control when a proven therapeutic method exists [2]. This concept is referred to by certain authors as "clinical equilibrium" (equipoise), where every patient is guaranteed a medical treatment [3]. Thus, testing a new drug with placebo or no treatment when a known effective therapy exists would be, in fact, contrary to patients' interests. Unfortunately, in reality, many placebo-control and not active-treatment controlled trials are conducted, despite the availability of adequate treatment [4–8], perhaps due to the fact that placebo control has the stature of a "hallmark of good science", together with blinding and randomization, without sound justification.

The most recent (fifth) revision of the DoH, adopted in 2000 by the World Medical Association (WMA), seemed to reiterate the longstanding prohibition on using placebo instead of effective therapy when a beneficial treatment for a condition has already been recognized [9], until a clarification note to article 29 appeared in 2001 [10]. Unfortunately, this addendum permitted a less restrictive interpretation of the article, introducing ambiguity by leaving room for the use of placebo when "*scientific methodological reasons*" or "*minor conditions*" dictate so. This clarification in fact

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Received: April 25, 2006 / Accepted: July 28, 2006
[1] The term "placebo" is difficult to define satisfactorily, because many interventions (invasive or not) are referred to as placebos, but are not (pills, capsules, bandages, images, pictures). We prefer the idea of a "specific" versus a "non-specific" intervention and thus we shall refer to placebo as ". . . a control treatment with similar appearance to a study treatment, but without its specific activity . . ." (see PC Gotzsche, in *Lancet* 1994; 344:925–926). Discussion on nocebo (adverse effects of placebo) is beyond the scope of this text

does not clarify at all and does not give details regarding the "*methodological reasons*" for which the use of placebo is justified, nor does it give details of what are the "*minor conditions*" in which the use of placebo will cause the subject only "minor" harm.

Both ethical and scientific arguments have been raised in the defense of not using placebo in place of an existing treatment. As for the ethical arguments: first the DoH states clearly that patients must receive best current treatment, even if it is a not-proven treatment. Thus, comparison between standard and novel therapies is ethically preferred to comparison between placebo and no treatment. This, of course, presupposes that a "standard" treatment exists. Because "standard" suggests "normative", this poses some difficulties when only non-standard treatments are available. For this reason, "best proven therapy" has been the preferred definition, conveying the idea that often no single "standard" treatment really exists.

Second, there seems to be no moral justification for patients having to endure even "minor" discomfort associated with placebo treatment, when in fact this discomfort is prohibited in active treatment. Third, the utilitarian argument (a few suffer for the good of many) is ethically questionable (as opposed to the case of vaccinations, for example), because the immediate needs of the patient always take precedence over the interests of science and society [11]. This "moral" hierarchy provides the practitioner with a coherent approach when patient welfare and the utility of scientific knowledge conflict. Finally, true patient autonomy can be accepted only when patients consent not only to the trial but also to the trial design (i.e., a patient willing to participate in a trial may actually prefer to enroll for a best proven available treatment rather than for a placebo control study).

Further, not only ethical but also scientific arguments challenge the need to incorporate placebo in our practice. First, there is increasing evidence that the magnitude of the placebo response varies according to prior conditioning, expectancy, and subject attention [12]. The activation of specific brain areas during placebo can, in fact, mimic similar changes seen with active treatments [13,14]. Thus, if placebo and active responses (e.g., pain relief) share similar neuronal networks, the idea that placebo is an "inert" non-intervention is incorrect. Second, not only are placebo responses as potentially variable as active treatments, the latter in fact may provide a more regular and consistent physiological response. Third, most physicians prefer to know that treatment with X is better than treatment with Y, rather than knowing that X is better than no treatment at all. Last, methodological developments in statistics raise questions about the need for the use of placebo as a research tool [15].

The use of placebo in clinical care

The idea of using placebo in clinical care appears to respect the principles of beneficence and non-smaleficence. Doctors should not expose patients to risks if there is no prospect of possible benefit from a treatment, and doctors should always bear the moral responsibility to act in their patients' best interests. This statement, however, confounds the ethics of clinical *research* and the ethics of clinical *care*. As we have already mentioned, the DoH specifies that patients' interests need not be "sacrificed" when they are participating in a clinical trial. However, clinical trials are **not** designed to promote the patient's best interest; they **are** designed to answer valuable scientific questions. Thus, although the ethical argument behind the use of placebo-control in clinical trials is that only with the use of a valid research method (i.e., placebo-control) is the patient's well-being protected, in clinical care it is the other way around. First the patient, then the science [16].

But others will continue to argue that, for over 20 years, hundreds of patients were encouraged to undergo ligation of the internal mammary artery, a risky open chest surgery with unproven efficacy for the treatment of angina pectoris, until two placebo-controlled studies demonstrated it to be no more efficacious than sham surgery [17,18]. Similarly, Moseley et al. [19] showed that arthroscopic surgery of the knee for osteoarthritis yielded effects similar to those of a placebo operation. Because the use of a placebo control is regarded as the gold standard in clinical trials [20], it seems logical and ethical to incorporate placebo use into our research. But is it ethical, for example, to perform sham surgery?

One of the consequences of the limitations of current medical treatments is the proliferation of devices and the explosion of minimally invasive surgery techniques. For investigators and clinicians living through this recent growth spurt of novel treatments, it is clear that an implanted device or surgery is not a drug [21]. The clinical effect of a drug (as long as the dose is correct) is not dependent on the talent of the presciber, whereas clinical success in surgery is highly dependent on the operator's skill. Randomization between "medical" and "surgical" treatments may be emotionally difficult for both patient and investigator, thus inducing methodological flaws and the need for large sample sizes to prove benefit.

The recent use of sham surgery in randomized controlled trials raises three major ethical questions. First, how do we negotiate the conflict between the need for a placebo-designed trial and the exposure of the patient to the risks of sham surgery (principle of non-maleficence)? Second, how do we assess the real risks and benefits of sham surgery? Third, does the require-

ment of informed consent imply that potential subjects are free to assume any risk, even if they are informed [22]? Although defenders of sham surgery may support its need from a methodological point of view or by claiming a standard similar to that for drug trials (placebo drug trials are ethically permissible when no alternative treatment exists), performing sham surgery in fact poses a real risk of harm to patients. Sham surgery is not an inert substance,[2] and performing a procedure that has no expected benefit violates the principle of minimizing the risk of harm, which violates the principle of non-maleficence (do no harm).

Assessing this risk, however, is not straightforward. Risks are not only limited to the morbidity of the intervention, even if this is rare, but, also, what is considered "not risky" by the professional may be considered "extremely risky" by the lay person (e.g., "drilling holes in the head is as risky as drilling a hole in a tooth") [23]. Finally, disclosure of the research design does not eliminate the known placebo effect of surgery, nor does it justify the exposure of patients to risks that would not be imposed by an alternative research design. Although the current vogue is to respect patient autonomy (hence creating a reluctance for any paternalistic protective approach by physicians), consent forms frequently overstate the benefits and understate the risks of research protocols. But even when consent forms are accurate, the expectations of patients may remain unrealistic, rendering autonomy a relative state of mind.

The final and perhaps most important ethical concern when using placebo in clinical care is the deception associated with its use. The fact that the use of placebo in clinical care necessitates complete ignorance on the part of the patient (as opposed to patient information in clinical research) renders this approach morally intolerable. This use of placebo contravenes the "pact of confidentiality" in the doctor–patient relationship, which is the nucleus of the therapeutic dialogue [24]. Furthermore, the belief that use of a placebo may distinguish between organic ("real") and functional ("unreal") conditions, revealing malingerers or placating insistent patients ("placebo" in Latin: *I shall please*) is simply incorrect, because in any case the placebo provides a response even if it is a "non-response". The deceptive use of placebo not only violates the fundamentals of the physician–patient relationship but harbors in it the potential for an intentional act of fraud [25]. Even informed consent cannot completely exonerate physicians from responsibility, and they should not attempt to pass the ethical responsibility over to the patient. Patients are rarely if ever as well informed about their treatment options as their physicians, and patients are seldom disinterested enough to reach a rational decision regarding their treatment options. Finally, "successful" placebos may be even more dangerous than "failed" ones, because they perpetuate the deceit by leading to lying, or the avoiding of truthful answers to legitimate questions patients might have regarding side effects, drug interactions, and other aspects of informed consent [26].

[2] One may imagine a "hierarchy of placebo effects" as: active treatment > sham surgery > placebo drug (suggested as an active drug) > inert substance (no suggestion made) > no treatment

Conclusions

In summary, the use of placebo in research is not fundamentally unethical under certain conditions (informed consent; "clinical equilibrium"). On the contrary, the use of placebo in clinical care, even when patients are informed (if this is possible) endangers the foundation of care and trust between patients and physicians and is thus morally unacceptable [27]. So, back to our case—the use of intrathecal saline (sham surgery) to determine the need for an implantable device—the only way, in our opinion, to morally justify this practice (with the danger of becoming paternalistic) is to fulfill the following conditions: (i) the placebo effect is examined in a research context, and (ii) all other attempts to find a nondeceptive alternative to placebo have failed. If these conditions are not fulfilled, the use of placebo in pain practice should be discouraged.

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