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Royal College of Surgeons

Position Statement

Use of placebo surgery in surgical research

Summary

In order to deliver the best clinical care to patients, treatments need to be based on evidence gained through clinical research. Randomised controlled trials (RCTs) are considered to be the gold standard of clinical evidence. However, while the vast majority of drug trials include a placebo control group, placebo-controlled surgical trials are rare, with only 75 published up to October 2015 (over a quarter of which were published since November 2013).[1] To put this into context, the NIHR funded 1900 new clinical research studies in 2014/15 alone.[2] Although the number of clinical trials in surgery continues to rise, many trials still are not benefiting from the use of randomisation to improve the evidence base for surgical interventions.

The College recommends that placebo interventions should be considered more often in surgical studies, to produce the best research evidence and provide the greatest benefit to patients. These studies must comply with ethical guidelines (set out below) and placebo surgery should never replace treatment in a control arm that is known to be effective. As long as these conditions are fulfilled, increasing placebo surgery in the design of some trials would help to ensure that more effective surgical procedures are used, thereby improving patient outcomes and value for money for the NHS.

Through this statement we endeavour to increase awareness of the benefits of placebo-controlled surgical trials, and tackle the misconceptions around placebo surgery. This issue merits considered debate by the medical community, so that it becomes more accepted as a legitimate option in clinical research. We encourage surgical researchers to put forward more proposals for placebo-controlled surgical trials, and funders to solicit such applications and fund them more often.

Background

What is placebo surgery and why should it be used?

The placebo effect can significantly improve a patient's condition,[3] so a placebo control group is necessary to separate the placebo effect out from the specific impact of a novel treatment or technique. Surgical placebo controls can vary from minor procedures such as making a small incision in the skin (so that a patient does not know whether they have had the procedure) through to a full surgical procedure with the critical surgical element or delivered component (such as a medical device) under investigation omitted. The latter approach is used to control for both the placebo effect and the biological effect of the surgery.

In half of the 53 placebo-controlled surgical trials published up to 2013, surgery was no more effective than a placebo operation.[4] For example, in treating osteoarthritis of the knee, a rigorously controlled trial found no advantage over placebo for either of the commonly performed procedures arthroscopic lavage (washing out of the knee joint) or debridement (removal of damaged tissue from the joint).[5] This called into question the use of these surgical procedures for this condition.

However, placebo surgery should never replace treatment known to be effective and should only be considered when certain criteria are fulfilled: there is uncertainty about the relative benefits of the experimental intervention and placebo (known as equipoise); assessment of the impact of the surgery is subjective; and the placebo operation is not associated with excessive risk (see overleaf for guidelines).

For further information please contact Grace Gottlieb, RCS Policy Officer, at ggottlieb@rcseng.ac.uk or on 020 7869 6049.

Arguments against the use of placebo surgery

- **The 'do no harm' principle**

It has been suggested that because placebo surgery is more invasive than placebo drugs, and thus potentially involves greater physical harm, it is much more difficult to justify its use in research.[6,7] Use of the misleading term 'sham surgery' to describe placebo surgery has likely perpetuated this view.

However, ethical review ensures that any harm involved is minimised, reasonable and justified by the potential individual and societal benefits. It also ensures that participants are given information to make an informed decision about the benefits and risks.

In a systematic review of placebo-controlled surgical trials by Wartolowska and colleagues,[4] three-quarters of the trials saw improvement in the placebo group, and serious adverse events were less common than in the experimental arm. Furthermore, the use of placebo controls in surgical trials potentially avoids future harm to patients from ineffective treatments adopted into clinical practice.

- **Deception**

It has been suggested that the use of placebo surgical controls involves deception of the participant. However, where a participant in research is fully informed as to the possibility of being randomised to either the group who receive the placebo or the investigational intervention, this 'deception' is no more problematic than in placebo-controlled drug trials.

- **Denying patients effective surgical treatment**

It may be argued that placebo trials will involve patients being denied effective treatment. However, placebo controls used in any research should not normally replace treatment known to be effective. Research should only be conducted where there is equipoise – genuine uncertainty regarding the relative therapeutic merits of the experimental and placebo interventions involved in the research.

Guidelines on the ethical use of placebo surgery

While the College encourages the use of placebo surgery as part of our support for evidence-based medicine, we stress that this is strictly subject to certain conditions being fulfilled. The College's guidelines on clinical research are set out in *Good Surgical Practice*. For example, the guidelines advise that surgeons should fully inform patients in randomised trials about the procedures being compared and their risks and benefits.

Below we set out further ethical guidelines, specifically on when placebo surgery should be considered:

- There should be clinical equipoise – genuine uncertainty about the relative merits of the experimental intervention and placebo control.
- When the assessment of interventions is clearly objective and therefore not subject to a placebo effect (for example the outcome of cardiac transplantation), then a placebo group may not be necessary to control for the placebo effect, and a 'no treatment' group may be a sufficient control. The exception to this would be when a placebo control is needed to differentiate between the biological effect of surgically delivering a substance and the effect of the substance itself.
- If the placebo intervention is associated with significant risk then it may not be ethical to use it unless the potential individual and societal benefits far outweigh this. For example it would never be ethical to have a placebo control group for a trial on open heart surgery, transplant, tumour removal, or amputation.
- The level of invasiveness and biological impact of a surgical placebo (superficial vs. deep incision, use and time period of anaesthesia, and so on) should be carefully considered on a case-by-case basis, to balance the needs of scientific rigour and harm minimisation.
- Every study should be considered on its merits, using standard approaches that are well developed for drug studies involving placebo.

For more detailed information, see the article in the RCS *Bulletin* '*When should placebo surgery as a control in clinical trials be carried out?*',[8] and the American Medical Association ethical guidelines on surgical placebo controls.[9]

This statement was developed following a workshop initiated by the Nuffield Council on Bioethics, co-hosted with the Health Research Authority.

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References

[1] Information not yet published
[2] NIHR Clinical Research Network Key Statistics. Accessed 24.11.15. Available from: https://www.crn.nihr.ac.uk/about-crn/our-performance/key-statistics-2/
[3] Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Placebo Effects: Biological, Clinical and Ethical Advances. Lancet. 2010; 375: 686–695
[4] Wartolowska K, Judge A, Hopewell S, Collins GS, Dean BJF, Rombach I, Brindley D, Savulescu J, Beard DJ, Carr AJ. Use of placebo controls in the evaluation of surgery: systematic review. BMJ 2014; 348:g3253
[5] Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002; 347:81-88
[6] Macklin R. The Ethical Problems with Sham Surgery in Clinical Research. N Engl J Med 1999; 341:992-996
[7] London AJ, Kadane JB. Placebos that harm: sham surgery controls in clinical trials. Stat Methods Med Res 2002; 11:413-27
[8] George AJT, Collett C, Carr AJ, Holm S, Bale C, Burton S, Campbell M, Coles A, Gottlieb G, Muir K, Parroy S, Price J, Rice ASC, Sinden J, Stephenson C, Wartolowska K, Whittall H. When should placebo surgery as a control in clinical trials be carried out? The Bulletin of the Royal College of Surgeons of England. 2016 February.
[9] Tenery R, Rakatansky H, Riddick FA, Goldrich MS, Morse LJ, O'Bannon JM, Ray P, Smalley S, Weiss M, Kao A, Morin K, Maixner A, Seiden S. Surgical "Placebo" Controls. Ann Surg 2002; 235:303-307

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