# Placebo surgery: fake news or real deal

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The word placebo is a familiar term in the world of drug trials and the concept of using a dummy or 'sugar' pill void of any known therapeutic value has helped distinguish 'useful' from 'not so useful' drugs for many decades.

Placebo controlled studies provide a level playing field for evaluation and account for any tricks of the mind and body that can produce or reinforce health benefits, be they behaviour based or more physiological. The placebo effect is real, powerful, often inconsistent, and fascinating.

But when at the dinner table someone says they design and conduct placebo trials in surgery, yes that's right, surgery, involving tissue damage and blood loss, how can it not cause a wrinkled brow to the uninformed? Really? Surely not? Why? And How? Is the usual response.

There is lots to cover here. Why do we need such comparisons for surgery? Is it ethical (find out from our Canadian ethicist colleague Charles Weijer in the next article), how do we go about it? (dealt with by Naomi Merritt and Marcus Jepson in a later article), and what do surgeons think about using placebo control in surgery (see the final article in this subspecialty section, our Trainee Surgeon perspective from Shiraz Sabah).

Starting with the **'Surely not?'**. Well yes, and there is reasonable evidence to support this. There have been over 90 placebo-controlled trials in surgery performed to date in specialties ranging from orthopaedics (our world for the JTO) to hernia repair[1]. They tend to be chosen for surgical procedures that have low invasiveness, those which are more questionable in terms of true therapeutic effect and those which rely on subjective measures such as reduction in pain as a measure of success. This is eminently sensible. Few would volunteer for a placebo-controlled trial of open fracture fixation after falling off a ladder.

There is a broadest aspect of **'Why'** and that is to both support and promote any surgical treatments that are proven to work (especially new ones), and to reduce or stop surgical treatments that do not. There is always some risk to a surgical operation and it seems foolish (and, more fundamentally, unethical) to expose anyone to risk if the treatment is largely ineffective (we say largely because trials are all about averages and no one can ever be certain). Likewise, if a new surgical treatment (device or procedure) is suggested, it is appropriate to test it fully before releasing its use into the world at large – just like in the pharmaceutical industry. The placebo control surgical design allows this. It is beefy, authoritative and often practice changing, but needs to be treated with respect and careful consideration. It is a complex design, rather 'prima donna' in characteristics and can easily fall over. It also carries risk, so needs careful justification and planning.

In terms of a more specific **'Why'** it comes back to the level playing field. All trials need a comparison treatment (or a comparison against no treatment) on which to base the assessment of benefit or not. Because the entire process of surgery, from listing to anaesthetic to recovery, can have components that influence the final outcome (over and above the actual surgical treatment), it is important that any comparison treatments assessing fundamental efficacy mimic each other as closely as possible. The only difference should be the feature (or features) thought to produce the benefit – that is then omitted from the treatment for one 'arm' of the study. This is done 'blind', without anybody (except the surgeon) knowing which treatment group is which – including the patient. This is just the same as a drug trial

where the active ingredient is removed from a drug to form a placebo. Unfortunately, it can be a little more complicated in surgery as it is not always clear what part of the surgery is responsible for giving the benefit. Regardless, the placebo-design is a unique method to find out whether any benefits are just the result of going through the (elaborate) surgical 'process' or are genuine effects of the operation. It means that clinicians and commissioners of healthcare can make well informed decisions on what they provide for patients. Patients can be reassured that the surgery they are receiving has been proven to be beneficial. Everybody is happy – or are they? Specific aspects will be covered in the next two articles, but let's look at some of the potential trip hazards of placebo controlled surgical trials in 'How'.

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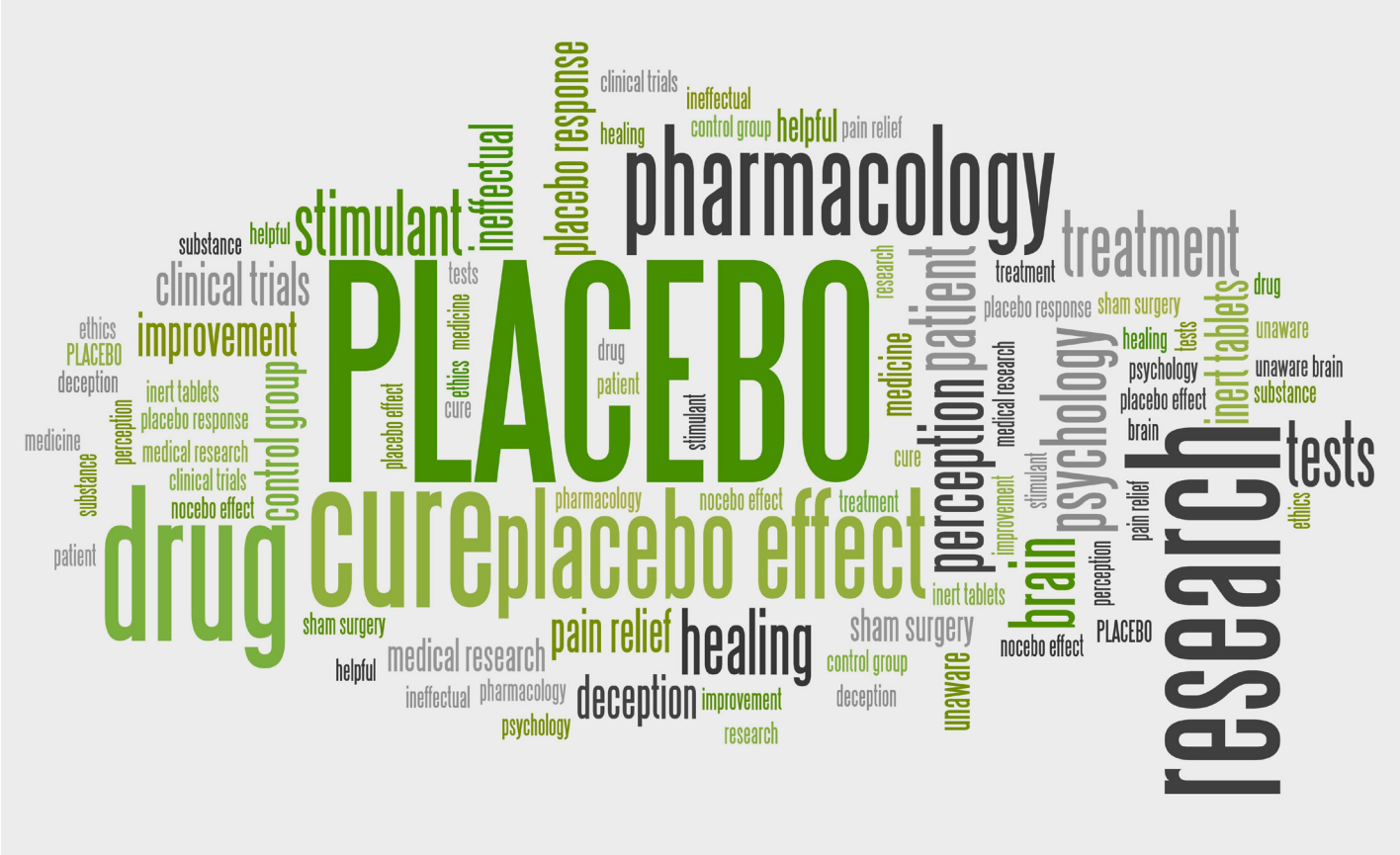
The **'How'** can be a long story. From the early designs, trials with a placebo arm have become more sophisticated and better understood over time. There are firm roots in orthopaedics with famous trials of knee arthroscopy in which patients underwent full simulated surgery (a sham or placebo procedure) to find out its true effects[2]. However, for this article, we can limit discussion to the more controversial aspects of placebo control, as all trials have at least some design issues.

Dealing with the component parts of the placebo control is the first thing to consider. Taking out the surgical component that hypothetically provides the benefit can be a problem in placebo trials. Firstly identifying it, and then ensuring that it can be isolated. For example in the placebo controlled trial of laminectomy, currently being conducted in Australia (SUCCESS), the placebo arm involves all aspects of surgery except the decompression or removal of the bone. Not all surgical procedures lend themselves to this process of critical surgical element isolation and any observed benefit may be cumulative or confounded by unidentified 'active elements' within the surgical procedure. We have tried to make this process easier to understand by developing the 'DITTO framework' which may well be worth a further read[3].

One of the most difficult operational aspects to navigate is overcoming the natural persona of surgical colleagues (i.e. that of a decision maker) to allow trial recruitment to occur under a heading of uncertainty. All studies of fundamental efficacy have to adhere to the principle of uncertainty where the outcome of the comparison for two or more interventions is unknown. This presents surgeons, who without the trial might ordinarily offer the surgical procedure to patients, to accept that what they are about to do (in terms of surgery), may not be optimal or even worthwhile. Furthermore, introducing a placebo element requires one step further. Inside a placebo trial surgeons must be willing to complete the surgery without including the surgical element that is expected to provide the benefit. Such a conversation is >>



a tall order in front of a patient about to undergo invasive surgery and could potentially lead to substantial confidence erosion and undermining potential. To display uncertainty usually goes against a surgeon's natural instinct and everyone's expectation that they are cloaked as the 'bold decision maker'. There is no real solution except to provide greater familiarity with issues of equipoise and uncertainty in surgery by education and greater discussion with patients and the public about clinical research. But more of this dilemma in a later article.

The ethics of asking a patient to enter a trial where they have a balanced chance of having surgery (and all the risk) without the supposed 'good' bit (although at that stage the 'good' is by definition unproven), is also a substantial ask and has occupied the ethical space of placebo trials for a while, (but more of that in Charles Weijer's paper).

And lastly, what do we do if the placebo surgery is shown to have benefit? Either for the individual or in terms of trial results?

If, in a three-way trial comparing the full definitive surgery, a placebo surgical intervention and no treatment, both surgical procedures are better than no treatment but definitive surgery is no better than placebo, what do we do? Do we then discard the surgery in any form? Or do we offer a treatment that captures the benefit providing aspect, placebo or otherwise? After all, it might be cheaper than a definitive treatment. These are difficult questions to answer and also circle back to the risk arguments and ethical aspects of placebo control. How much benefit do we have to achieve to justify the risk of an essentially placebo surgical procedure? Again, we have no answers just yet, but are working hard to find out.

There is no question that placebo-controlled trials in surgery are useful and valuable, but they are demanding and complicated and certainly should not be considered for every surgical evaluation. Working with surgeons, ethicists, patients and researchers we have attempted to assist and guide those interested in the subject or who are setting up placebo-controlled trials with the publication of the ASPIRE guidelines[4]. This does not have all the answers though and whilst we have started the placebo-controlled surgical journey we have certainly not reached the end. All of us – surgeons, researchers, patients – are welcome to join us on that journey. ■

## References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