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First Cut

Sham Surgery Is Used To Test Effectiveness Of Novel Operations

Idea Is to Match the Rigor Of Placebo Drug Trials, But It's Controversial

Drilling Holes in the Skull

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As a Parkinson's disease sufferer, Judy Ruth Ashley eagerly agreed to take part in a study of an experimental form of surgery to treat the debilitating condition. She flew from her New Jersey home to Denver, where surgeons at the University of Colorado put her under sedation and local anesthesia and drilled four holes through her skull.

A year later, her doctor gave her some bad news: She hadn't gotten the therapy, which involves implanting human fetal tissue in the brain. She had been part of a control group that got "sham surgery"— just the holes but no implant — for the purpose of serving as a scientific comparison.

"I was crushed," says the 66-year-old, whose hopes had soared when she perceived small improvements in her condition following the operation. She knew there was a 50-50 chance she hadn't gotten the real surgery, but "I really thought I had," she says. "I thought I couldn't be fooled. But I was."

The trial paved the way for other trials involving placebo surgery, a development that has startled some doctors and touched off a medical debate.

In Search of Rigor

In assessing drugs, placebo-controlled tests have long been the gold standard. One group gets the drug, while another gets a sugar pill. Neither group knows which is which, and neither do the doctors running the test, until the code is broken later and patients' outcomes prove how well, if at all, the new drug really works.

With therapy involving surgery, this long was ruled out. Doctors couldn't justify harming a person, even if only slightly, for the sake of unknown future patients who might benefit someday from the information gathered. One attempt at testing surgery for the pain of angina against a fake procedure in the 1950s provoked a backlash.

But things are changing. A proliferation of innovative biomedical techniques, coupled with medical cost-containment pressures, has altered the calculus. Sham surgeries have been used in at least five recent or current trials of therapies: three for Parkinson's, one for cancer pain and one involving the knee.

Cost Factor

One force driving this is the federal government. The National Institutes of Health and the Food and Drug Administration are eager to get decisive research on controversial new operations that involve implanting human or animal cells.

Also, in recent years a number of surgical procedures have been discredited or shown to be overused, such as efforts to prevent stroke through brain-artery bypass. Advocates of control-group trials say such tests might help prevent some kinds of surgery from being done needlessly year after year, at potential harm to patients. And insurers that are asked to pay for costly new surgeries sometimes refuse on the ground that the procedures haven't been subject to the same rigorous proof as drugs must be.

Even sham surgery, however, doesn't necessarily make surgical testing the equal of drug tests. In some cases, it is impossible to keep the surgeons in the dark about who is getting the placebo and who isn't, and sometimes the doctors go only part way in faking surgery. The Colorado doctors, for instance, drilled into the skull put didn't insert needles into the brain or implant anything there.

Some doctors and medical ethicists remain firmly opposed to sham surgery. "This is going to extremes to worship at the altar of placebo controls," says Arthur Caplan, director of the University of Pennsylvania's Center for Bioethics.

Climate Change

Still, the Colorado trial of Parkinson's disease surgery signaled a shift in thinking. The NIH started funding it in 1994 and later paid for a similar trial, which began in 1996. And the FDA suggested that two Massachusetts companies pursuing implants of pig fetal cells for Parkinson's ought to measure the therapy against sham surgery, the companies say. "At first we thought they were crazy," says Henri Termeer, chief executive of Genzyme Corp., which is working with Diacrin Inc. on the therapy. He says he gave his approval after determining that surgical drilling in the skull wasn't as dangerous as it sounds.

Thomas Freeman, associate professor of neurosurgery at the University of South Florida in Tampa, says he searched his soul before beginning the second NIH-funded placebo-controlled trial of human fetal-cell brain implants, in which a third of the 36 Parkinson's patients got sham surgery. "Ultimately, I decided it's more ethical to put 12 patients through an imitation operation than have thousands go through operations, claimed to be efficacious, that actually kill more people than they help," he says.

The FDA has no authority over surgical techniques per se, and traditionally hasn't ruled on their efficacy or safety. But a

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growing number of proposed therapies require surgical implantation of animal cells or re-engineered human tissues. The FDA regards these tissues as akin to drugs, and thus subject to its approval. And for drugs, the agency almost invariably requires strict placebo comparisons.

The FDA approved the use of sham surgery in testing the pig-cell implants. The agency says it will decide on a case-by-case basis whether to require a placebo control for new surgical implantation therapies.

Cytotherapeutics Inc., of Lincoln, R.I., decided on its own that the unusual nature of its new cancer-pain treatment—tiny implanted capsules filled with cow cells that release a natural analgesic—made placebo testing necessary. It is doing clinical trials involving sham surgery in Europe and plans to apply for approval here. "The weirder it is, the more the medical community has a reason to doubt it," says Moses Goddard, director of the company's cancer-pain research.

Placebo Effect

Overall in medicine, an estimated 30% of patients report improvement after placebo treatment, for complex reasons that science continues to explore. Patients with Parkinson's, a debilitating illness involving loss of muscular control, have been especially prone to showing placebo effects. One reason may be that a more-positive attitude can cause patients to be more active and this lessens stiffness, says J. William Langston, founder of the Parkinson's Institute in Sunnyvale, Calif.

Dr. Langston notes that in the 1980s, a procedure involving implanting crushed adrenal glands in the brain spread rapidly in the U.S. after it was pioneered by a Mexican surgeon. But many people died after the surgery, and it turned out not to be effective, he says. "We learned a lot from that experience, none of it very pretty," Dr. Langston says. So he supports limited placebo testing to make sure surgery really works.

The Colorado trial that Mrs. Ashley took part in was spearheaded by Curt Freed, a professor at the medical school who had long done fetal-cell implants, had seen promising initial results and was itching to do a well-controlled trial to find out if they really helped. A ban on use of aborted tissue cut off his funding during the Reagan and Bush years, but the ban was lifted in the Clinton administration, and Dr. Freed won NIH funding for a trial in which some patients would get fake surgery.

Their operations didn't mimic the real thing in every detail. Some scientists say the test would have been truer if it had included not just hole-drilling but placebo injections as well. But that was deemed too dangerous because up to 2% of patients who undergo brain-invasive neurosurgery die or have serious complications. Dr. Freed and his team decided to drill into the skulls of control-group patients but stop before penetrating the brain.

The consent form estimated the risk of serious complications from the procedure, done under local anesthesia, at "less than 1%." It said the risks included skin or bone infections, complications from a sedative, and bleeding into the skin or skull. All test subjects also had to have brain scans, involving a dose of radiation equal to about a quarter of the maximum allowed by the FDA per person per year. And besides drilling, doctors anchored screws in the skull to hold a metal scaffolding to immobilize the head.

'Double Standard'

The NIH committee that reviewed the grant proposal was initially concerned about danger to placebo patients. But it also was delighted that someone had challenged the surgery/drug "double stan-dard," says the panel's chairwoman, Anne Young. "Too many surgeries are done on the basis of anecdotal evidence and not put to the same sort of rigorous tests that drug therapies are," says Dr. Young, chief of neurology at Massachusetts General Hospital.

About the time the NIH authorized $8 million for the trial, it rejected two proposals to test similar therapies, one by Dr. Freeman's group in Florida and one by a team at Yale. One apparent reason was that they didn't involve placebos, say Dennis Spencer, chairman of neurosurgery at the Yale School of Medicine, and Jeffrey H. Kordower, a researcher in Dr. Freeman's group.

The Yale group submitted a second application, but, following an internal debate, again didn't include a plan for sham surgery. The Yale team felt that drilling holes in a patient's head without giving treatment would be ethical only if further animal and human tests proved inconclusive, Dr. Spencer says. The NIH again rejected Yale's funding application.

The Freeman group reapplied with a new plan that included a placebo control group, and the NIH funded it. That Parkinson's disease trial, which began in early 1996, involved drilling a hole about the size of a dime in the skulls of all patients—under general anesthesia.

General anesthesia carries a distinct risk. "If something goes wrong, even in a good place, even with a healthy patient, the ultimate risk is that you may not survive, or may have a permanent brain injury for life," says John Neeld, head of the American Society of Anesthesiology. Dr. Langston in Sunnyvale doesn't support sham surgery that requires general anesthesia. But John Eichhorn, chairman of anesthesiology at the University of Mississippi, says recent improvements have cut the risk of the most serious ill effects to about one in 250,000 patients.

Spinal Tap

Another risk involves antibiotics. Genzyme and Diacrin, in their trial of fetal-pig-cell implants for Parkinson's, felt they had to give even sham-surgery subjects real antibiotics. This kept Columbia Presbyterian Medical Center in New York from participating. Donald Kornfeld, chairman of its institutional review board, says the board felt sham surgery was acceptable, but antibiotics added unnecessary risk. "If a patient wants to beat the system, they can do it in any trial," he says. "The whole thing gets a little ridiculous." But several other universities cleared their researchers to conduct the trial, and surgery has begun.

Meanwhile, in the trial of a therapy for cancer pain, Cytotherapeutics and partner Astra AB of Sweden have wrestled with how far placebo surgery should go. The therapy involves inserting capsules that contain natural bovine analgesic into the fluid-filled space at the base of the spine through a spinal tap. Investigators make an inch-long incision in the small of the back and use a needle for insertion. The device is anchored with a plastic tether tied to the connective tissue in the back.

The procedure causes a "fierce" headache that can last a day or two in about 10% of patients, says Cytotherapeutics' Dr. Goddard. In addition, there is a small chance it could cause permanent nerve injury or paralysis.

Initially, the companies decided to spare placebo patients the spinal tap and insert only the tether. But they decided that would put the surgeon in the position of knowing which patients got the medicine and which didn't. Ideally, people administering therapies are blind to that distinction so they can't tell patients or evaluators, which could in turn bias their assessments of effectiveness.

The companies stopped the initial trial of 10 patients and started a larger one, of 100 to 200 patients, in which the placebo patients will have a capsule containing a useless gel implanted. Only Cytotherapeutics will know which capsules are which.

In the Parkinson's tests, the surgeons do know who gets the real surgery, but according to Dr. Freed, they go to great lengths to keep this secret. For instance, during surgery they ask, "Are you ready for the implant now?" even if they don't plan to insert it. "We thought it might be difficult to maintain a poker face," he says. "In fact, it has worked very well."

But an unanticipated controversy arose. In February, after all 40 original surgeries—20 real, and 20 sham—were done, an NIH-appointed oversight committee stepped in because of concerns of a higher incidence of death and other "adverse events" in patients that had the real surgery.

Long Wait

Before the trial, the patients had been told that if they ended up getting sham surgery, they could get the actual therapy after waiting a year for assessments. But after the deaths, the trial's managers decided these patients should wait two more years, until final results were in. Several patients were outraged, saying they might not have taken part if they had known they would have to wait that long.

Patients perused a list of the adverse events and decided that some didn't seem related to the transplants. One woman had died while driving in a hurricane, and another had had a hysterectomy. "My husband's risk of hysterectomy is exactly zero," notes Barbara Yankee, whose husband, Mike, had the sham surgery in September 1996. "We felt we were double-shammed." The NIH eventually delegated the decision to review boards at universities where the patients were treated, and the placebo patients soon began getting the real surgery.

Mrs. Ashley and others have now had the fetal-cell brain implant and are waiting to see if it works. Getting a sham was "dreadful," says Mrs. Ashley, but she would do it again to get access to the real surgery. "It's given me hope," she says.