Placebo Surprisingly Effective

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efficacy end points was reached in the company's pivotal clinical trial. Due to a lack of specific data on women undergoing procedures in which they would not be expected to require adhesiolysis, the committee narrowed the scope of the indication the company originally sought, which would have also included the product's use for primary adhesion prevention.

"I support approval based on the fact that there is no currently available way to prevent adhesion reformation, and the safety data are reassuring," said panel member Dr. Marcelle I. Cedars, director of reproductive endocrinology at the University of California, San Francisco. Fellow panelist Dr. Jonathan W. Weeks, director of the Maternal-Fetal Medicine Center at Norton Suburban Hospital, Louisville, Ky., noted, "The safety data are convincing. I'm not as convinced about efficacy. I wouldn't have supported it if we hadn't limited it to procedures requiring adhesiolysis."

The committee's evaluation of the product's efficacy was complicated by two unforeseen issues relating to Innovata's pivotal U.S. study, in which 449 women undergoing laparoscopic peritoneal cavity surgery for gynecologic procedures requiring adhesiolysis were randomized to receive either Adept or lactated Ringer solution (LRS) as both intraoperative irrigant and postoperative instillate.

One issue was that the LRS, which was intended as a control, also turned out to be somewhat effective in reducing adhesions. The second was that the FDA's predetermined statistical threshold for defining clinical "success" may have been too stringent, the company argued—and several panel members agreed. The committee also grappled with the relative significance of the numerous secondary end points included in the company's submission.

Elizabeth Peers, Ph.D., Innovata's director of clinical development, presented the findings of the 16-center, double-blind, randomized, controlled clinical trial in adhesion reduction. Surgical indications among the 449 patients included pelvic pain, infertility, adhesions, and endometriosis; some had more than one diagnosis.

All patients had at least three available surgical sites with adhesions and had at least three adhesion sites lysed during the procedure. They were randomized to receive either Adept (227) or LRS (222) as intraoperative irrigations of 100 mL every 30 minutes, followed by a postoperative instillate of 1,000 mL. This is not an FDA-approved use of LRS, Dr. Peers noted.

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Adverse events were largely related to the surgical procedure or underlying condition, with the most common in both groups being postprocedural pain (83%-87%), headache (32%-34%), nausea (16%-17%), and port-site leakage (13%-14%). Vaginal/vulvar/labial swelling was the only event that occurred significantly more often in the Adept group (6% vs. 0.4%). Most cases were mild to moderate and resolved within a few days without intervention, she noted.

For the first primary efficacy end point, the reduction in adhesions from the first surgery to a second-look procedure conducted 4-8 weeks later, "success" rates were 45.4% for the Adept group, compared with 35.6% for LRS. Although statistically significant, this difference did not qualify as "success" according to the FDA's definition, which required that the lower bound of the confidence interval exceed 5%. This is more stringent than what is normally required in clinical trials, according to biostatistician Steven Piantadosi, M.D., Ph.D., of Johns Hopkins University, Baltimore, who spoke on behalf of Innovata. "It's an unreasonable clinical and regulatory boundary for a company to have to meet," Dr. Piantadosi told this news organization.

Dr. Julia Carey-Corrado of the FDA's Office of Device Evaluation, explained that the threshold had been determined based on earlier data. "We wanted to set a high boundary to be sure of a real clinical benefit." However, panel voting consultant Dr. Keith Isaacson, medical director of the Center for Minimally Invasive Gynecologic Surgery at Newton-Wellesley Hospital in Newton, Mass., was one of several panel members who sided with Innovata: "I agree with the sponsor that the 5% bar in retrospect doesn't make a lot of sense."

The high success rate for LRS—the study's intended control—contributed to the problem. "These were remarkably good results for LRS, but we still see additional benefit for Adept," Innovata's Dr. Peers commented.

The second primary end point—the reduction in the number of sites with adhesions at second look compared with the first procedure in the group receiving Adept—was significant and did meet the FDA's success criteria, dropping from 10.3 to 7.9, a mean reduction of 23%. The third primary end point, the proportion of patients having fewer sites with dense adhesions at the second vs. the first surgery, was 50% with Adept and 49% with LRS, not significantly different.

The results, Dr. Peers remarked, showed "a meaningful clinical result overall for the study population. … The surprise wasn't that Adept did well, but that LRS worked as well as it did." Indeed, among patients presenting with pelvic pain, 80% in both groups had a reduction in pain at 2 months post surgery, she reported.

Pain score was 1 of 13 secondary clinical end points in the trial, a majority of which did significantly favor Adept when factored individually. Once the data were adjusted for multiplicity, however, only the reduction in American Fertility Society score in the group with infertility (odds ratio 2.72 in favor of Adept) remained significant.

The proportion of patients who were free of de novo adhesions at second look was also significantly lower in the Adept group, with an odds ratio of 1.59. That was the piece of data the company hoped would gain it the primary prevention indication in patients undergoing procedures not expected to require adhesiolysis, such as diagnostic laparoscopy or tubal ligation. Some panel members agreed, but the group ultimately sided with those who expressed discomfort in expanding the indication beyond what was studied.

"If we're doing our jobs, we should stick to what we have good evidence for," said panel voting consultant Dr. Russell Snyder of the gynecology department at the University of Texas, Galveston, but he added that "in practice, that won't necessarily influence off-label use."

The panel also decided that Adept should not be used in "contaminated cases," such as those with bowel perforation or a breach in the bladder or vaginal epithelium. That was based on European postmarketing registry data on Adept that showed an adverse event rate of 28.4% (including 2.5% with infection) during general laparotomy procedures in 1,469 patients vs. just 5.5% among 2,069 patients undergoing gynecologic laparoscopic procedures.

Voting consultant Dr. Hugh S. Miller, a perinatologist in private practice in Tucson, Ariz., summed up the panel's overall view: "With clear efficacy and no safety concern in a market with no competitors, this [represents] a clear benefit to women." ■

Many Adhesion Mysteries Unraveled, but Questions Remain

BY BETSY BATES
Los Angeles Bureau

PASADENA, CALIF. — Adhesion formation probably occurs within the first 3-5 days following surgery, when hypoxia triggers a cascade of cytokines, growth factors, and clotting factors that form a fibrinous, clotlike mass, Dr. Michael P. Diamond said at a meeting of the Obstetrical and Gynecological Assembly of Southern California.

Unless a high level of tissue plasminogen activator (TPA) in relation to plasminogen activator inhibitor-1 (PAI-1) can break up the mass, conditions become ripe for uniquely equipped fibroblasts to proliferate and amass at the site of injury.

Angiogenesis follows, and resilient adhesive bands of tissue are formed that are exceedingly difficult to permanently eradicate through adhesiolysis.

The scenario, based on years of research into the unique properties of adhesion tissue, explains why adhesions are so likely to recur after they are lysed. It also offers guidance in the quest for antiadhesion barriers or medications, since these evidently require only short-term action to prevent long-term problems, said Dr. Diamond, professor and associate chair of obstetrics and gynecology at Wayne State University in Detroit.

The fibroblasts in adhesion tissue and fibroblasts in normal peritoneal tissue differ in fundamental ways. Those differences are exaggerated in the face of hypoxia, Dr. Diamond said. "Years later, there are still molecular and biological differences in these tissues that predispose [patients with adhesions] to further adhesion formation."

Adhesions form after about 60%-80% of laparotomies or laparoscopies, with no meaningful differences seen between the two. "They are not something unique to the work we do as obstetrician gynecologists. Name a surgical specialty and they will have a problem with adhesions," said Dr. Diamond, who also directs the division of reproductive endocrinology and infertility at his university.

Compared with normal tissue, fibroblasts in adhesions have higher basal levels of collagen, fibronectin, transforming growth factor (TGF)-β1, TGF-β2, and PAI-1. Hypoxia—a result of tissue injury during surgery—heightens the disparity in most of these cytokines. Basal TPA levels, critical to breaking up early adhesion formation, are higher in fibroblasts in normal tissue. In adhesion tissue, they plummet to near zero with hypoxia.

Furthermore, fewer cytokines involved in programmed cell death are produced in adhesion tissue. "These cells are in a revved-up position to heal," said Dr. Diamond.

In the face of further injury, such as adhesiolysis, the cells are preprogrammed to heal again, with even more vigor than when they first evolved in response to hypoxia.

Dr. Diamond said these studies may shed light on why patients with chronic pelvic pain may obtain significant pain relief following adhesiolysis, but often find that their pain returns to near-baseline levels within several months.

Roughly 10%-20% of patients do experience lasting pain relief following adhesiolysis, but no one has been able to distinguish them from other patients, he said.

Still other questions persist about the connection between adhesions and chronic pelvic pain. For example, Dr. Diamond noted that men develop adhesions at the same or higher rates as women after surgery, trauma, hemorrhage, and other hypoxic events. But the literature contains no studies about adhesions causing pelvic pain in men. He noted that the two approved products designed to prevent adhesions—Interceed and Seprafilm—consistently reduce adhesion formation about half the time. "Each of these help, but neither is a panacea," he said. Importantly, neither device is approved for use in laparoscopic surgery.

Because hypoxia seems inexorably tied to adhesion formation, any surgical tool that causes injury—scalpel, laser, or coagulation device—is as likely as the others to cause adhesions, according to Dr. Diamond.

More promising than new adhesiolysis techniques may be new preventive agents, perhaps barriers infused with medications, liquids, or gels designed to stay in place at the site of injury for the 3-5 critical days after surgery. One intriguing possibility might be the use of cyclooxygenase-2 (COX-2) inhibitors, since COX-2 is expressed only in the context of hypoxia in fibroblast tissue, he said. ■