

Reduction of postoperative adhesions by N,O-carboxymethylchitosan: a pilot study

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Objective: To examine the logistics, safety, and efficacy of N,O-carboxymethylchitosan (NOCC) in reducing adhesions in women.

Design: Multicenter, prospective, randomized, reviewer-blinded clinical trial.

Setting: Gynecologic practices.

Patient(s): Thirty-four patients were enrolled; 17 in each group were available for the safety analysis and 16 for the efficacy analysis.

Intervention(s): Adhesion reduction by administration of NOCC vs. Ringer's lactate at the conclusion of the initial surgical procedure, as assessed at second-look laparoscopy. The NOCC was applied as 200 mL of a 1% NOCC gel that was tamped in place, followed by 100 mL of 2% NOCC solution. Efficacy was assessed by covariate analysis.

Main Outcome Measure(s): Safety and postoperative adhesion formation.

Result(s): Groups did not differ in age, ethnicity distribution, height, weight, or body mass index. No deaths or serious adverse events were attributable to NOCC, and no adverse events were definitively or probably related to NOCC administration. Adhesions recurred at 61% of sites in controls and 38% of sites in NOCC recipients. De novo grade 1a and 1b adhesions tended to occur more commonly in controls than NOCC recipients. Adhesion extent and severity at second look were also less in NOCC recipients.

Conclusion(s): Intraperitoneal use of NOCC gel and solution appears to be safe. Despite the small sample, strong trends were identified for reduction of occurrence, extent, and severity of adhesion recurrence and de novo adhesion formation. (Fertil Steril® 2003;80:631-6. ©2003 by American Society for Reproductive Medicine.)

Key Words: Adhesions, N,O-carboxymethylchitosan, laparoscopy

The sequelae of postoperative adhesion development can be multifaceted, lifelong, and pronounced. Such adhesions are found in 55% to 97% of men and women undergoing intra-abdominal surgery, and adhesions result in variable clinical manifestations (1). In a report from Scotland, women undergoing an initial abdominal surgery had a 5% likelihood of being rehospitalized because of adhesions over the next 10 years, and adhesions may have contributed to rehospitalization in an additional 20% of patients (2).

Adhesions involving the tubes and ovaries are a well-recognized cause of infertility and contribute to the occurrence of ectopic pregnancies (3). Postsurgical adhesions, which can

occur days to decades after the initial surgery, are the leading noncancerous cause of bowel obstruction (4). Abdominopelvic pain is frequently attributed to adhesions and can persist years after definitive surgery for the initial pathologic condition (3).

Among approximately 25,000 laparoscopic surgeries in the Netherlands in 1994, more than half of the complications occurred during entry into the abdominal cavity; many of these complications were due to adhesions of the bowel and other structures to the anterior abdominal wall (5). The financial cost of adhesions is estimated to be \$1.2 to \$1.3 billion yearly in the United States alone (6, 7).

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Despite an unquestionable clinical need (8), limited options are available over and above good surgical technique for reduction of postoperative adhesions. The U.S. Food and Drug Administration approved three products for reduction of postoperative adhesions after intraabdominal surgery. Two of these methods, Intercede (Gynecare, Somerville, NJ) and Seprafilm (Genzyme, Cambridge, MA), are barriers that provide efficacy only at the anatomic sites where placed and are approved for use only at laparotomy, not after laparoscopy (9, 10). The third method (Intergel; Lifecore, Canasta, MN) is a solution that is also only approved for use after laparotomy (11). While beneficial, its use resulted in a reduction of only fewer than one site per patient. Thus, more efficacious agents that are proven to be effective in laparoscopic procedures are needed.

N,O-carboxymethylchitosan (NOCC) is a purified derivative of chitin obtained from the exoskeleton of shrimp (12). The molecule has structural similarities to hyaluronic acid and carboxymethylcellulose, which have been shown to be beneficial in adhesion reduction both in its native and derivative forms. N,O-carboxymethylchitosan is effective in reducing adhesions in rats and rabbits and has a high level of safety in cardiac and bowel anastomosis models (12–15).

We present findings from the first human pilot trial of NOCC after laparoscopic surgery for the purpose of reduction of postoperative adhesion development.

MATERIALS AND METHODS

Study Design

This prospective, randomized multicenter placebo-controlled parallel group, reviewer-blinded was conducted at four clinical sites. The aim was to assess the safety of intraabdominal instillation of NOCC in humans and to obtain preliminary evidence of the effectiveness of NOCC in reducing development of postoperative adhesions. Approval was obtained from the institutional review boards of the participating surgeons' clinics. All participants provided informed written consent.

To qualify for participation, women had to be at least 18 years of age and scheduled to undergo laparoscopic surgery with a planned second-look laparoscopy. Indications for the initial surgery included infertility, pelvic pain, a pelvic mass, uterine fibroids, or endometriosis. Women were excluded if they were pregnant or lactating; had previously undergone salpingectomy, oophorectomy, or hysterectomy; had a known cancer; had active pelvic inflammatory disease; or had received hormonal therapy within 1 month of the initial surgery.

At completion of the initial surgery, once hemostasis was achieved (as evidenced by inspection after deinsufflation and reinsufflation) and just before closure, patients were randomized to undergo instillation of 300 mL of Ringer's lactate (controls) or 200 mL of NOCC gel plus 100 mL of NOCC

solution (total volume, 300 mL). The NOCC gel was placed at sites of adhesiolysis and at surgical sites by extrusion from a laparoscopic irrigation instrument. The NOCC gel was tamped in place by using the laparoscopic instrument. Subsequently, the NOCC solution was placed at the same sites; excess flowed to the dependent portions of the abdominal cavity.

Participants returned for a follow-up office visit 2 to 9 days later and underwent second-look laparoscopy 2 to 10 weeks after the initial surgery. This time frame for second-look studies was chosen because adhesion development does not appear to vary over this time interval (9, 16–19).

At the conclusion of each surgical procedure, the surgeon scored each of 23 anatomical sites by using a previously validated scoring system. Each site was scored for the presence or absence of adhesions, adhesion severity, extent of involvement of each site, and raw surface area at each site. Adhesion severity was scored as follows: 0, no adhesions; 1, filmy, vascular adhesions; 2, dense or vascular adhesions; or 3, cohesive adhesions. Adhesion extent was scored as follows: 0, no adhesions; 1, up to 25% of total area of site; 2, 26% to 50% of total area of site; or 3, 50% of total area of site.

Each surgical procedure was videotaped in its entirety. After editing to remove application of the test or study agent, the video of each procedure was reviewed by an evaluator who was blinded to group assignment. The reviewer applied the same scoring system as the surgeons. The data presented in this report are those from this single-blinded evaluator.

Surgery

The attending surgeon determined surgical procedures conducted at each operation and used their own standard surgical care and practices. To minimize variation in the conduct of the surgeries, the investigators agreed to use lactated Ringer's solution for all intraoperative irrigation, to limit sutures in contact with the peritoneal cavity to 2-0 to 4-0 polydioxanone surgical (PDS), and to place patients in the reverse Trendelenberg position for suctioning of fluids from the abdominal cavity before confirmation of hemostasis.

Statistical Analysis

Clinical data were double entered by using an SAS database (SAS Software, Inc., Cary, NC). Statistical analysis was performed by using SAS software for PC. Safety and efficacy variables were summarized by descriptive statistics, including number, mean, median, SE, and range for continuous variables and the number and percentages for categorical variables. Baseline characteristics were compared by using the Student *t*-test for continuous variables and the Fisher exact or χ^2 test for categorical variables.

All comparisons were two-tailed. Data are expressed as means (\pm SE). $P < .05$ was considered significant. Because of baseline and demographic variations between the study