
Addition of Parenteral Cefoxitin to Regimen of Oral Antibiotics for Elective Colorectal Operations

A Randomized Prospective Study

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The efficacy of cefoxitin, a perioperative parenteral antibiotic, combined with mechanical bowel preparation and oral antibiotics to prevent wound infections and other septic complications in patients undergoing elective colorectal operations, was examined in a prospective randomized study. All 197 patients who completed the study received mechanical bowel preparation and oral neomycin/erythromycin base. In addition a perioperative parenteral antibiotic was given in three divided doses to 101 patients. The other 96 patients received no parenteral antibiotics. The overall incidence of intra-abdominal septic complications was 7.3% (7 of 96) in the control group (no cefoxitin) and 5% (5 of 101) in the treatment group (cefoxitin). This difference was not statistically significant. The incidence of abdominal wound infection was 14.6% in the control group and 5% in the treatment group, a statistically significant difference ($p = 0.02$). The addition of perioperative parenteral cefoxitin greatly reduced the incidence of wound infections in patients undergoing elective colorectal operations who had been prepared with mechanical bowel cleansing and oral antimicrobial agents.

PREPARATION TECHNIQUES OF the large intestine for elective operations of the colon and rectum have evolved so that the current standard of surgical care mandates the use of mechanical cleansing combined with antimicrobial agents. Some debate exists regarding the relative importance of the preoperative administration of oral antibiotics compared with the use of parenteral antibiotics in the perioperative period.¹ Specifically the addition of parenteral antibiotics to the regimen of mechanical cleansing and the use of oral antibiotics has not consistently reduced the number of septic complications associated with elective colorectal procedures.^{2,3} As a result of these inconsistencies and in light of increased pressures for cost containment, surgeons are being asked to reassess the common clinical practice of combining oral and parenteral antibiotics as prophylaxis in this situation.

Materials and Methods

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Our aim was to determine the efficacy of the addition of a second-generation cephalosporin, cefoxitin (Mefoxin; Merck Sharp & Dohme, West Point, PA), to the regimen of mechanical cleansing and the use of oral antibiotics in a randomized prospective study. Cefoxitin is an antibiotic with activity against gram-negative aerobes and anaerobes, the most common pathogens isolated from infections associated with colorectal procedures.⁴ This feature makes it one of the most commonly used prophylactic antibiotics in colorectal procedures. Our study compares the rates of wound infection with the rates of intra-abdominal infections in two groups of patients. One group received cefoxitin in addition to mechanical preparation and oral antibiotics, and the other group did not.

The study population consisted of 197 patients who underwent elective colorectal operations at the Lahey Clinic Medical Center between January 4, 1985, and March 25, 1988. Prior approval for the study was obtained from the Institutional Review Board of the Lahey Clinic Medical Center.

All patients 18 years of age and older who were undergoing elective operations on the colon or rectum by the abdominal route were potentially eligible. Previous penicillin or cephalosporin allergy, use of oral or parenteral antibiotics within 72 hours before operation, use of probenecid within 1 week before operation, and evidence of colonic obstruction that would preclude adequate mechanical bowel preparation were criteria for exclusion. In addition patients requiring parenteral antibiotic prophylaxis for cardiac valve disease and patients having *in situ* foreign material, such as vascular grafts, prosthetic valves or joints, and cardiac pacemakers, were not eligible.

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Accepted for publication October 30, 1989.

This study was conducted as an open-label randomized observer-blinded trial. Randomization was achieved by means of a multiplicative congruent linear method of pseudorandom number generation using a Hewlett Packard Series 41 program SSTI-04A (Rockville, MD). Blocks consisted of 10 patients randomized to cefoxitin and 10 patients to no cefoxitin. Sealed opaque envelopes were used and were prepared in the Department of Research, where they were numbered consecutively. Consent for entrance into the study was obtained in writing from the patient by physicians in the Department of Colon and Rectal Surgery and the Department of General Surgery. Four of five attending surgeons (JAC, JJM, DJS, and MCV) and all patients were not informed of the results of randomization.

All patients received a standard mechanical bowel preparation and oral antibiotics in a schedule as outlined in Table 1. The control group received no parenteral antibiotics. The treatment group received three doses of cefoxitin, 2 g each, with the first dose administered within 60 minutes before incision, the second dose in the recovery room at 6 hours, and the third dose 6 hours thereafter.

Shaving of the abdomen was performed within 60 minutes before the incision was made. The skin was prepared with povidone-iodine (Betadine; Purdue Frederick Co., Norwalk, CT) solution. Paper drapes were used in all instances. Adhesive skin barriers and wound protectors were used for patients without a pre-existing stoma. Fascial closures were accomplished with a single layer of absorbable monofilament sutures using a continuous mass closure technique. Subcutaneous sutures were not used, and the skin was closed with stainless steel clips. No attempt was made to standardize operative technique.

Wounds were inspected daily. For purposes of this study, wound infection was defined as purulent wound drainage; the exudate either spontaneously drained or was expressed after removal of skin staples over a clinically suspect area of the wound. Cultures were obtained whenever possible.

Other complications of infection were recorded and managed appropriately according to the clinical circumstance. Intra-abdominal sepsis was diagnosed in patients who had a fever after operation and for whom no other

TABLE 2. Comparison of Control and Treatment Groups

| Factor | Control (No Cefoxitin) n = 96 | Treatment (Cefoxitin) n = 101 |
|----------------------------|-------------------------------------|-------------------------------------|
| Sex (male:female) | 62:34 | 64:37 |
| Age, median (range) | 54 (18-96) | 56 (22-80) |
| Disease* | | |
| Carcinoma | 43 | 48 |
| Inflammatory bowel disease | | |
| Chronic ulcerative colitis | 20 | 16 |
| Crohn's disease | 11 | 6 |
| Indeterminate disease | — | 1 |
| Diverticular disease | 14 | 20 |
| Polyp | 6 | 8 |
| Familial polyposis | 4 | 2 |
| Miscellaneous | 1 | 2 |
| Patients taking steroids | 30 | 17 |

* Five patients had two diagnoses.

source of infection could be demonstrated on complete investigation or a documented intra-abdominal source by radiographic investigation, such as in the case of abscesses within the peritoneal cavity or anastomotic leakage.

Records were reviewed by one of the authors (PLR). Follow-up was obtained by office visits 1 and 4 months after operation. Late complications of infection were recorded.

The randomization code was broken after data had been compiled. Statistical analysis was carried out by paired two-tail t test (program BMDP-3D) and Miettinen's modification of the Fisher exact test and the Mantel-Haenszel chi test described by Rothman and Boice⁵ using a CALC41 System (Tacit Logic Systems, Inc., Tigard, OR) in a microcomputer with 80287 coprocessor. Differences at the level of two-tail $p < 0.05$ were considered statistically significant.

Results

Of the 225 randomized patients, 28 were withdrawn from the study: because of improper dose of study drug, 10 patients; because of change in operative strategy, 9 patients; because of ineligibility that was not recognized, 7 patients; and due to patient request, 2 patients. Data from the remaining 197 patients (126 men and 71 women) were analyzed. The median age was 55 years (range, 18 to 96 years). The control group (no cefoxitin) included 96 patients, and 101 patients received cefoxitin. Comparisons between the groups and the indications for operation are given in Table 2. The actual operative procedures are summarized in Table 3 for both groups. Carcinoma was the most common indication for operation in this series. Data for septic complications directly attributable to the colorectal nature of the operation are presented in Table 4.

Wound infection occurred in 14 patients in the control group (14.6%) and in 5 patients in the treatment group

TABLE 1. Bowel Preparation

| Day | Preparation |
|-----|---|
| 1 | Clear liquids Citrate of magnesia, 10 fluid oz.—Afternoon Saline enemas until clear—Evening |
| 2 | Clear liquids Citrate of magnesia, 10 fluid oz.—Morning Neomycin 1 g, erythromycin base, 1 g— Orally at 1 P.M., 2 P.M., 11 P.M.* |
| 3 | Operation at 8 A.M. |

* Times amended for later operation.

TABLE 3. Operations Performed

| Operation | Control (No Cefoxitin) | Treatment (Cefoxitin) | Total |
|---|---------------------------|--------------------------|-------|
| Abdominoperineal resection | 6 | 3 | 9 |
| Anterior resection | 4 | 11 | 15 |
| Low anterior resection | 7 | 15 | 22 |
| Total colectomy, ileorectal anastomosis | 7 | 5 | 12 |
| Colostomy closure | 2 | 3 | 5 |
| Descending colectomy | 1 | — | 1 |
| Ileocolic resection | 3 | 2 | 5 |
| Left hemicolectomy | 4 | 6 | 10 |
| Ileoanal reservoir | 16 | 12 | 28 |
| Right hemicolectomy | 12 | 12 | 24 |
| Sigmoid colectomy | 21 | 22 | 43 |
| Transverse colectomy | 1 | — | 1 |
| Total colectomy, ileostomy | 7 | 5 | 12 |
| Loop colostomy | 2 | 1 | 3 |
| Hartmann resection | 1 | — | 1 |
| Total proctocolectomy | 2 | 3 | 5 |
| Small bowel and colon resection | — | 1 | 1 |
| Total | 96 | 101 | 197 |

(5%). This difference is statistically significant ($p = 0.02$). Because the number of patients taking steroids at the time of operation was substantially higher in the control group, this specific issue was addressed by analyzing data with the Mantel-Haenszel chi test, controlling for steroid use as a confounding variable. Again the incidence of wound infection was significantly higher in the control group ($p = 0.045$).

Anastomotic leakage occurred in 4 of 78 (5.1%) anastomoses in the control group and in 3 of 89 (3.4%) anastomoses in the treatment group. This difference is not statistically significant ($p = 0.67$). Of the seven instances of leakage, four occurred in patients undergoing low anterior resection for either carcinoma of the rectum or villous adenoma; the other three occurrences were in patients undergoing anastomosis for Crohn's disease.

Intra-abdominal sepsis was recognized in two different forms. Pelvic cellulitis, characterized by fever, leukocytosis, lower abdominal pain, and purulent drainage from the ileal reservoir, occurred in two patients undergoing construction of an ileoanal reservoir; one patient was in the control group and the other patient was in the treatment group. Cultures from the abdominal drain revealed

Escherichia coli in one patient and *Staphylococcus aureus* and *Pseudomonas* in the other patient. Based on these cultures, specific antimicrobial therapy was administered for 7 days without the need for operative intervention. Pelvic abscesses occurred in two patients in the control group (2%) and in one patient in the treatment group (1%). Two patients required surgical intervention, and in the third patient, the abscess resolved after spontaneous drainage from a Hartmann pouch. The difference between the two groups in overall rates of the incidence of intra-abdominal sepsis is not statistically significant ($p = 0.68$).

No patient experienced substantial adverse effects from either the oral antibiotics or the cefoxitin.

The results of bacteriologic study are outlined in Table 5.

Discussion

Mechanical cleansing of the colon before elective colorectal operations has long been recognized as an essential part of preoperative preparation.⁶ Because the colon is a rich reservoir of bacteria, purgation of fecal contents substantially reduces the number of potentially pathogenic bacteria.

With the advent of antimicrobial agents, oral preparation was added to mechanical cleansing in an attempt to reduce further the incidence of septic complications. In 1953 Poth⁷ reviewed the data on available drugs and concluded that neomycin was an excellent oral agent because of its poor absorption from the gastrointestinal tract and consequent low toxicity. He noted overgrowth of yeast in the intestine with its use. Studies by Cohn and Rives⁸ demonstrated that the addition of intraluminal neomycin and tetracycline decreased the incidence of septic and anastomotic complications in an experimental model. Nichols and associates⁹ documented appreciable reduction in intraluminal bacteria by the use of oral antibiotics. In fact, as a result of this study, the authors⁹ demonstrated the need for drugs directed at both aerobes and anaerobes. Based on their results, a combination of neomycin and erythromycin base in the dosage schedule depicted in Table 1 was studied retrospectively¹⁰ and applied prospectively,¹¹ and a meaningful reduction in the number of septic complications resulted when these antibiotics were used with mechanical cleansing.

Despite the fact that the neomycin/erythromycin base

TABLE 4. Operation and Specific Septic Complications

| Complication | Control (No Cefoxitin) | | Treatment (Cefoxitin) | |
|------------------------------------|------------------------|-----------------|-----------------------|-----------------|
| | Total | Taking Steroids | Total | Taking Steroids |
| Wound infection | 14 | 6 | 5 | 2 |
| Anastomotic leakage | 4 | 1 | 3 | 1 |
| Intra-abdominal abscess/cellulitis | 3 | 2 | 2 | 0 |

TABLE 5. Bacteriology of Infected Wounds

| Complication | Number |
|--|--------|
| Control (no cefoxitin): 9 of 15 wounds | |
| <i>E. coli</i> | 3 |
| Enterococcus | 3 |
| <i>S. aureus</i> | 3 |
| Gram-negative rods (other) | 5 |
| Alpha-hemolytic streptococcus | 1 |
| Treatment (cefoxitin): 5 of 5 wounds | |
| <i>E. coli</i> | 3 |
| Enterococcus | 2 |
| <i>S. aureus</i> | 2 |
| Other | 1 |

(the Nichols-Condon prep) has become the most widely used oral antibiotic regimen, any nonabsorbable combination or single agent that is highly effective against both aerobic gram-negative rods and anaerobes has also been shown to be effective for colorectal cleansing before operation.¹²

With the development of parenteral antibiotics, attempts were made to substitute these agents for oral agents. Results of studies up to 1983, as reviewed by Guglielmo and associates,¹³ were mixed. Antimicrobial agents with a spectrum limited to either aerobes or anaerobes alone are usually ineffective in reducing septic complications of colorectal operations when administered parenterally as a substitute for oral antibiotics.

Crucial to our study was the question of the benefit of combining parenteral and oral antibiotics to confer additional protection against septic complications compared with the benefit of either regimen alone. In recent analyses of available studies, the majority conclusion has been that 'combining oral and parenteral drugs should be unnecessary in most patients.'¹³ Unfortunately most of the antibiotics administered parenterally were not active against both aerobes and anaerobes, and, consequently, the conclusions of these analyses are questionable.

Cefoxitin is a second-generation cephalosporin that is bactericidal against a wide range of potential colonic pathogens, including gram-positive cocci, gram-negative bacilli, and anaerobes.⁴ Hoffmann and associates¹⁴ reported a small series in which cefoxitin was randomly added to one half of a group of patients undergoing mechanical preparation and oral kanamycin (Kantrex; Bristol Laboratories, Syracuse, NY) therapy. They¹⁴ demonstrated appreciable reduction in rates of wound infection with the addition of parenteral cefoxitin. A potential weakness of this study¹⁴ was the deletion of an oral antianaerobic agent in the control group. Consequently the favorable results may have been the result of this omission rather than because of the addition of cefoxitin.

Our study was designed to compare numbers of septic complications in two groups of patients undergoing elective colorectal operations by means of the abdominal

route. Specifically cefoxitin was added in a randomized prospective manner to the most widely used oral antibiotic combination that has been proved highly effective. Results indicate that the addition of cefoxitin confers appreciably more protection against the development of wound infection (5% versus 14.6%; $p = 0.02$). On the other hand, anastomotic leakage and intra-abdominal sepsis were not affected by addition of cefoxitin. The former is usually the result of a technical failure and would not be expected to be altered substantially by prophylactic antibiotics; the latter might be expected to be affected, but the number of occurrences in the two groups is too small to draw statistically valid conclusions.

Our data support the addition of perioperative parenteral cefoxitin to the regimen of mechanical cleansing and the use of oral neomycin/erythromycin base to reduce the risk of abdominal wound infection in patients undergoing elective colorectal operations.

Acknowledgments

The authors thank Elton Watkins, Jr., M.D., Sias Surgical Research Unit at the Lahey Clinic, for randomization and data analysis.

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