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Comparison of Moxalactam and Cefazolin as Prophylactic Antibiotics During Cesarean Section

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Prophylactic antibiotics have been shown to be effective in decreasing the incidence of febrile morbidity associated with cesarean section after labor. However, the relative effectiveness of different single antibiotics has been studied infrequently, and these investigations have been limited by small patient samples. Several new, broad-spectrum antibiotics are now available, and any further benefit from more traditional antibiotics for surgical prophylaxis remains untested. A randomized prospective double-blind therapeutic trial was therefore undertaken to compare the value of a first-generation cephalosporin (cefazolin) with a new third-generation cephalosporin (moxalactam). Between July 1981 and June 1983, 254 qualifying women who underwent primary cesarean section after labor were randomly chosen for either of the two treatment groups. Although not statistically significant, the rates of febrile morbidity, wound infection, and endometritis were less for those treated with cefazolin (4.0, 3.2, and 0.8%, respectively) than for those treated with moxalactam (9.2, 7.7, and 1.6%, respectively). No serious adverse effects were apparent in the mother and newborn infant from short-term exposure to either drug. Although the newer, more expensive, and broader-spectrum cephalosporin, moxalactam, was associated with a low postoperative febrile morbidity rate and short postpartum hospitalization, it was no more beneficial than cefazolin.

Since the rates of cesarean section have increased threefold within the past decade, febrile morbidity, infections of the endometrium and wound, and prolonged hospitalizations are now more common on postpartum wards at most hospitals (3, 10). Attempts have been made to decrease postpartum infections by the perioperative administration of an antibiotic before a polymicrobial pelvic infection occurs. Recent reviews of the literature have confirmed that prophylactic antibiotics for women undergoing cesarean sections are effective in decreasing the incidence of febrile morbidity related to endometritis, wound infection, and urinary tract infection when compared with placebo-controlled groups (17, 18). The advantages of prophylatic antibiotic therapy in selected women include less risk for postpartum fever, patient discomfort and inactivity, and prolonged hospitalization. Labor has been considered by many investigators to be the most important condition predisposing to postpartum infection (1, 12, 15, 16, 21). Other factors contributing to postpartum endometritis or wound infection and in which patients may benefit most from remedial antibiotic therapy include ruptured amniotic membranes for 6 h or more, multiple vaginal examinations, and lower socioeconomic status (1, 4, 10, 12, 15, 16, 21).

When used prophylactically, a single antibiotic with broad-spectrum coverage against most pelvic pathogens appears to be as effective as a combination of two or more antibiotics and would be associated with fewer side effects (17). Examples of commonly used antibiotics include ampicillin and first-generation cephalosporins such as cefazolin and cephalothin (17). No single penicillin or cephalosporin preparation has been clearly shown to be more effective, but few studies have compared two different drugs in a randomized, double-blind manner. The small number of women in these studies has revealed neither antibiotic to be more effective, even though each was more useful than a placebo.

Moxalactam disodium is a new semisynthetic, oxa-beta-lactam compound with promising in vitro activity against a wide spectrum of pathogens similar to those isolated from women with pelvic infections (14). The bactericidal activity of this third-generation cephalosporin encompasses a wide range of anaerobes, gram-negative aerobes, and certain gram-positive aerobes. Because of the modification of the beta-lactam structure, moxalactam has a high degree of stability in the presence of beta-lactamases (2, 8). It is therefore more resistant to both penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria (19). *Bacteroides* sp. and other anaerobic organisms are also sensitive to this antibiotic. For these reasons, moxalactam has been reported to be helpful in eradicating serious infections (19, 20).

The goal of this randomized prospective drug trial was to determine whether moxalactam is more beneficial than cefazolin in diminishing postpartum febrile morbidity after surgical prophylaxis. Postpartum febrile morbidity rates and sites of infection for women at risk after cesarean section are reported from two university centers during a recent 2-year period.

MATERIALS AND METHODS

The study was undertaken between July 1981 and June 1983 at The University of Michigan Women's Hospital and the University of Iowa Hospitals and Clinics. Prior approval was obtained by the Human Investigations Committee at each institution. Those persons eligible for this study were to undergo primary cesarean section while in labor. Many had ruptured amniotic membranes for more than 6 h. Ineligible women included those who had signs of obvious infection, suspected renal impairment by history and laboratory evi-

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dence, known drug hypersensitivity to a penicillin or cephalosporin, or recent administration of antibiotics.

After the informed consent was obtained, each subject was randomly assigned to receive moxalactam or cefazolin based on a randomized table supplied by the sponsor (Eli Lilly & Co.). Laboratory studies sent before drug administration included a complete blood and platelet count, urinalysis, and chemistries (blood urea nitrogen, creatinine, serum glutanic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, bilirubin, alkaline phosphatase). No coagulation studies or cultures were obtained before therapy.

A 2-g dose of moxalactam or cefazolin was administered intravenously during the cesarean section in a blind manner. Second and third 2-g doses were given at 6 and 12 h postoperatively. The duration of surgery was recorded.

Each subject was examined daily for the remainder of her hospitalization. Evidence for febrile morbidity included a fever of 38°C or greater beyond the first 24 h after surgery on two occasions 6 h apart. If additional antibiotic therapy was necessary, appropriate cultures were obtained from the blood, catheterized urine, endometrium, or wound. Any wound infection, endometritis, pelvic cellulitis, peritonitis, pelvic thrombophlebitis, septicemia, or pelvic abscess was recorded. Endometritis was diagnosed on the basis of two or more of the following symptoms and signs: fever, uterine tenderness, and foul-smelling lochia. It was frequently a diagnosis of exclusion—i.e., an absence of factors indicating infection elsewhere. A wound infection was defined as drainage, purulence, dehiscence, or cellulitis (or a combination) in the wound of a febrile patient. An operative incision with purulent exudate was also deemed infected. The number of hospital days after surgery was also recorded.

Any adverse clinical or laboratory effects were monitored daily by the investigators. The drug was discontinued if any significant adverse effect occurred or if the woman asked to be removed from the study. A case report form was completed for each patient at the end of the study. The specific drug administered to each patient was not known until the data were collected and recorded. Statistical comparisons were made with Chi-square and Student's *t* testing. A difference was statistically significant if the *P* value was less than 0.05.

RESULTS

During the recent 2-year period, 290 patients were enrolled in this study. All had undergone labor, and 191 (75%) had ruptured membranes before surgery. Thirty-six were excluded because of any of the following reasons: subsequent antibiotic therapy within 24 h postoperatively (16), insufficient therapy (15), preoperative infection (4), concomitant antibiotic therapy (1), and vaginal delivery (1). Of the 254 qualifying patients, 141 (56%) were enrolled at The University of Iowa, and 113 (44%) were enrolled at The University of Michigan. The number of women given moxalactam versus cefazolin was distributed evenly at each hospital, with 130 women receiving moxalactam and 124 receiving cefazolin.

The profiles of qualifying women and indications for cesarean section are shown in Table 1. Fetal distress, breech presentation, and cephalopelvic disproportion were the most common indications for surgery and were similar in frequency between the two treatment groups. Other indications for cesarean section involved third-trimester bleeding from an apparent placental abruption or previa, space-occupying fetal malformation, medical complication with failed induction of labor, and active herpetic genital infection. The duration of surgery averaged approximately 1 h in each treatment group.

TABLE 1. Profiles of qualifying women and indications for cesarean section[a]

Patient profile	Treatment groups	
	Moxalactam (n = 130)	Cefazolin (n = 124)
Maternal age (years)	22 ± 4	22 ± 4
Indication for cesarean section (no. [%])		
Fetal distress	51 (39)	52 (41.9)
Breech	26 (20)	24 (19.4)
Cephalopelvic disproportion	19 (14.6)	13 (10.5)
Other	34 (26.2)	35 (28.2)
Duration of surgery (mean ± SD min)	66 ± 21	68 ± 23
Hospital days postpartum (mean ± SD)	5.2 ± 2.1	5.4 ± 1.7
Febrile morbidity (%)	12 (9.2)	5 (4.0)
Wound infection (%)	10 (7.7)	4 (3.2)
Endometritis (%)	2 (1.6)	1 (0.8)

[a] Differences between the two treatment groups were not statistically significant.

The overall febrile morbidity rate was 6.6% (17 of 254 cases). Rates were not significantly different between those persons receiving moxalactam or cefazolin therapy (9.2% versus 4.0%). The ability to detect a difference in rates between the two groups of at least 10% has a statistical power of approximately 75% (beta error no greater than 25%). The number of hospital days on the postpartum ward was similar between the two group. Although not statistically significant, wound infections and endometritis were also less common for women receiving cefazolin (1 [0.8%] and 4 [3.2%], respectively) than for those receiving moxalactam (2 [1.6%] and 10 [7.7%], respectively). No urinary tract infections were found. Occasional peptococcal, *Bacteroides* spp., group D streptococcal, and staphylococcal organisms were isolated on endometrial cultures, but no single gram-negative or anaerobic organism was found consistently.

No person asked to be removed from the study. Long-lasting clinical effects from exposure to either drug were not apparent, but each drug was discontinued on one occasion. A person receiving moxalactam had the drug discontinued after the first dose because of an apparent increase in body temperature from 37 to 38.6°C. The fever did not persist after stopping the antibiotic. In another case, a mother who had a severe headache and was weak and tired experienced relief after discontinuation of the cefazolin.

DISCUSSION

The traditional measure of effectiveness of an antibiotic used prophylactically is the subsequent presence or absence of postpartum febrile morbidity. Variations in study designs, patient populations, choices of antibiotics, and treatment schedules are obvious. Several new, broad-spectrum antibiotics are available, and in this randomized prospective investigation, a new third-generation cephalosporin was compared with a recognized first-generation cephalosporin. The 6.6% febrile morbidity rate with cefazolin (7.2% at University of Iowa and 5.8% at University of Michigan) is the lowest reported rate compared with an average of 25% in six other reports examining cefazolin with placebo (6, 9, 14, 15, 22). In two of these prior reports, the duration of

cefazolin therapy was longer than the 12 h reported here (6, 9).

Features of this study include a larger number of subjects (254) in contrast to an average of 78 subjects (range, 55 to 97) in the other six cefazolin studies. This study further emphasizes that low febrile morbidity rates may be obtained with the prophylactic use of a single antibiotic for 12 h or less postoperatively. This was particularly true for a group of women at greatest risk for infection, namely, those undergoing labor with most having ruptured amniotic membranes. Those few persons who had infectious morbidity postoperatively developed endometritis or a wound infection that required a longer hospitalization and often two or three antibiotics given simultaneously for broader antimicrobial coverage.

Moxalactam has been recognized to be an effective third-generation oxa-beta-lactam compound for treatment of serious infections due to multiresistant organisms. The only other reports of moxalactam use late in pregnancy were by Gibbs et al. (11) and Cunningham et al. (5), in which moxalactam was used to treat endomyometritis after cesarean section. Moxalactam alone was equally effective or superior to this other combination of antibiotics (11). However, no known report exists looking at the effectiveness of moxalactam as a prophylactic antibiotic during cesarean section. The low febrile morbidity rate reported here is quite encouraging, but this rate is no better than that reported with a comparable group of women being treated with cefazolin. Moxalactam has been found to be associated with prolonged bleeding, which is thought to result from reduced vitamin K-dependent clotting factors and platelet function (7, 13; FDA Drug Bull. **13**:17, 1983). Clinical signs of a coagulopathy were not found during the present study, perhaps because the drug was prescribed for such a short interval in healthy, reproductive-aged women.

Findings from this investigation support a prior impression that first-generation cephalosporins are as helpful as and perhaps better than third-generation cephalosporins for surgical prophylaxis (19). Although activity against gram-negative bacilli apparently increases from first- to third-generation drugs, the use of first-generation agents may prevent bacterial resistance to newer cephalosporins and be less costly.

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