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Choice of Antibiotic in Nonelective Cesarean Section

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The use of antibiotics for prophylaxis against infection among women undergoing nonelective cesarean section has become the standard of care in the United States. Many different antibiotics have been used successfully. Single-dose regimens administered after the cord is clamped have proven just as effective as multiple-dose regimens. Although the most frequently used class of antibiotics is the cephalosporin family, the single best agent has not been determined. This study was a double-blind, randomized trial in which we compared a narrow-spectrum cephalosporin (cefazolin; *n* = 63) with an expanded-spectrum cephamycin (cefoxitin; *n* = 66) and with a broad-spectrum cephalosporin (cefotaxime; *n* = 60) used as a single-dose prophylaxis in patients undergoing a nonelective cesarean section. Of the 194 patients enrolled in the study, 189 were evaluable. There was no significant difference between the groups in mean age, gravidity, parity, duration of labor, duration of ruptured membranes, number of vaginal examinations, or socioeconomic status (socioeconomic status was defined by third-party coverage). There was no significant difference among the antibiotics in the incidence of immediate or delayed postoperative infections. These data indicate that a less expensive, narrow-spectrum cephalosporin is as effective as more expensive, broader-spectrum cephamycins and cephalosporins as prophylaxis for patients undergoing nonelective cesarean section.

The efficacies of the antibiotics used prophylactically to reduce the incidence of postoperative infectious morbidity in obstetrics and gynecology have been well documented. The incidence of infection among women undergoing nonelective cesarean sections who did not receive antibiotic prophylaxis varies from 27% (9) to 86% (3), depending upon the population studied. Reviews of the evaluable studies in the literature have concluded that antibiotics administered prophylactically can significantly reduce the incidence of infectious morbidity among women undergoing nonelective cesarean section (4).

Previous reports have concluded that a short course of prophylaxis is as effective as a longer course (12) and that administering the antibiotic after the cord is clamped is as effective as doing so before cord clamping (8). More recent studies have shown that a single-dose regimen is as effective as two-dose (10) and three-dose (7) regimens.

The causative organisms isolated from patients with postcesarean section endomyometritis are mixed aerobic and anaerobic bacteria (1). We have reported that bacteria cultured from patients in whom antibiotic prophylaxis fails are frequently resistant to the antibiotic type used (9). On the other hand, Hemsell et al. (11) have shown that the antibiotic used does not necessarily need to be effective in vitro against the organism cultured to be effective in vivo.

Numerous antibiotics have been used in studies evaluating prophylaxis in patients undergoing cesarean section. The most frequently used agents include the penicillins, cephalosporins, and cephamycins. Most studies have shown a significant difference between the use of an antibiotic and a placebo but no significant difference between the various antibiotics that were used (4). Stiver et al. (13) have reported that a three-dose regimen of cefoxitin is significantly better than a three-dose regimen of cefazolin in women undergoing nonelective cesarean section. Faro et al. (5) recently reported that ampicillin (2 g), cefazolin (2 g), piperacillin (4 g), and cefotetan (1 g) are superior to six other regimens in cesarean section prophylaxis. Carlson and Duff (2) recently reported no significant difference between a narrow-spectrum and an expanded-spectrum cephalosporin used prophylactically in a single dose.

Although prophylaxis has become a standard of care in nonelective cesarean section, the ideal choice of an antibiotic has not been identified. The most frequent group of antibiotics used is the cephalosporins. There are no studies in the literature in which only narrow-spectrum, expanded-spectrum, and broad spectrum cephalosporins were compared in one study. We desired to determine, then, whether there was a significant difference between the effects of a narrow-spectrum, expanded-spectrum, and broad spectrum cephalosporin-type antibiotic in reducing infectious morbidity among this population of patients. The infectious morbidity rate without antibiotic prophylaxis in this patient population is 27%.

MATERIALS AND METHODS

The study was designed as a prospective, randomized, double-blind comparison of cephalosporin antibiotics with three spectra of activity used prophylactically in women undergoing nonelective cesarean section at the obstetrical service at University Hospital, University of Kentucky School of Medicine. Patients were eligible if they were 18 years of age or older, had no history of allergy to cephalosporins, were in active labor or had ruptured membranes requiring induction of labor, and had signed an informed consent. Patients were excluded if they were undergoing elective cesarean section, if they were receiving antibiotics for a current infection, if they had chronic renal or hepatic disease, or if they refused to sign an informed consent. The protocol was approved by the human investigation committee of the University of Kentucky Medical Center.

Eligible patients were randomly assigned to receive a

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single dose of 1 g of cefazolin, 2 g of cefoxitin, or 1 g of cefotaxime intravenously after the infant's umbilical cord was clamped. Before the patients received the antibiotic, laboratory studies were obtained, including a complete blood count, platelet count, liver and renal function tests, and urinalysis.

All patients were evaluated each postoperative day for symptoms or signs of infection. Patients who had a temperature of ≥38°C on two occasions at least 6 h apart after the first postoperative 24 h or who had a single elevation of ≥38.3°C within the first 24 h were evaluated for infection by obtaining a complete blood count with differential, a catheterized urine culture, endometrial cultures obtained by double-lumen swab or aspirate, and blood cultures. Patients were classified as infected on the basis of the following criteria. Patients with endomyometritis had temperature elevation, uterine tenderness, foul smelling or purulent lochia, and a leukocyte count of ≥15,000. Urinary tract infection was defined by a positive catheterized urine culture that grew ≥50,000 colonies of a pathogenic microorganism per cm^3. Wound infection was classified as purulent drainage from an abdominal incision with a positive culture.

All culture specimens were processed immediately and were evaluated by using standard techniques reported previously (9). All patients were given 2- and 6-week follow-up appointments in the obstetrical postpartum clinic. Data were analyzed by using the chi-square test or the Fisher exact test.

The average hospital costs of the infected patients in each arm of the study were calculated in order to determine whether there were significant differences in the cost-effectiveness of the antibiotics used.

RESULTS

A total of 194 patients were enrolled in the study, with 189 patients being evaluable. Four patients had vaginal deliveries after being enrolled in the study but prior to cesarean section, and in one patient, there was no documentation that the study antibiotic was administered. A total of 63 patients received cefazolin, 66 received cefoxitin, and 60 received cefotaxime.

There was no significant difference between patients in mean age, gravidity, or parity. Evaluation of risk factors for infection indicated no significant difference between the study groups in the duration of labor, duration of ruptured membranes, number of vaginal examinations, or socioeconomic status. Socioeconomic status is described as the presence of independent third-party insurance coverage in the numerator versus no insurance or the presence of medical assistance in the denominator. The use of intrauterine pressure catheters could not be ascertained satisfactorily from the records to allow evaluation of these as a risk factor. Twenty-nine patients were infected in the postoperative period, before hospital discharge. A total of 9 of 63 patients (14.3%) treated with cefazolin, 12 of 66 patients (18.2%) treated with cefoxitin, and 8 of 60 patients (13.3%) treated with cefotaxime became infected. There were no significant differences in the infectious morbidity rates between the three groups. ($P > 0.05$) The majority of infections were classified as endomyometritis ($n = 18$), although urinary tract infections ($n = 6$), bacteremia ($n = 3$), and wound infections were also seen. Five of the six urinary tract infections were cystitis, and one was a pyelonephritis. Samples were obtained for culture from patients with endomyometritis, and the patients were then treated with ampicillin, gentamicin, and clindamycin. Urinary tract infections were treated with ampicillin alone or gentamicin. The patients with bacteremia were treated with ampicillin, gentamicin, and clindamycin.

TABLE 1. Infections by site and drug

Infection	No. of infected patients treated with:		
	Cefazolin	Cefoxitin	Cefotaxime
Bacteremia	2	1	0
Endomyometritis	4	9	5
Urinary tract	1	2	3
Wound	2	0	0

The sites of infection according to the prophylactic antibiotic used are indicated in Table 1. No patient had infections at multiple sites. Although the numbers are small, there was no significant difference between the study groups for site of infection. The larger number of cases of endomyometritis in the cefoxitin group ($n = 9$) versus the cefazolin group ($n = 4$) approached significance ($P = 0.06$).

The most frequently isolated bacteria are listed in Table 2; *Bacteroides* species were the most frequent isolates and were all *Bacteroides bivius* or *Bacteroides disiens*. There were no *Bacteroides fragilis* isolates. Although several studies have reported that cephalosporin prophylaxis predisposes patients to enterococcal infection, we had only four patients each infected with one enterococcal isolate. Samples from four patients with clinical endomyometritis were negative on culture.

The clinical follow-up data on the study patients revealed no follow-up in 30% of the cefazolin-treated group, 35% of the cefoxitin-treated group, and 25% of the cefotaxime-treated group (Table 3). Three patients in the cefazolin-treated group and one in the cefotaxime-treated group had temperature elevations after discharge, with no site of infection identified, no treatment, and spontaneous resolution of fever. The open wounds were seromas, which were drained and packed and which did not require antibiotic therapy. All the wound infections occurred in patients with prior endomyometritis or urinary tract infections; all the patients were managed as outpatients and were treated with drainage and packing. There were no delayed chlamydial infections. There was no significant difference in delayed morbidity rates between the groups. There were no adverse reactions to any of the antibiotics. There was no significant difference in the duration of hospital stay between the groups.

In this study, the average hospital costs of the cefazolin-treated group who became infected were $4,450.75, those for

TABLE 2. Most frequently isolated bacteria

Organism	No. of patients with:			
	Bacteremia	Endomyometritis	Urinary tract infection	Wound infection
Staphylococcus aureus				1
Group B streptococci	2	3	1	
Enterococcus spp.		1	2	1
Escherichia coli	1		3	
Klebsiella sp.		1		
Lactobacillus spp.		2		
Peptostreptococcus sp.		1		
Bacteroides spp.		8		

TABLE 3. Follow-up of cesarean section study patients

Antibiotic	Total no. treated	No. (%) followed up	No. with:			
			Late infection	Postoperative morbidity	Open wound	Wound infection
Cefazolin	63	19 (30)	39	3	0	2
Cefoxitin	66	23 (35)	39	0	2	2
Cefotaxime	60	15 (25)	42	1	2	0

the cefoxitin-treated group were $5,431.07 and those for the cefotaxime-treated group were $4,295.00. The infected cefoxitin-treated patients had significantly higher mean hospital costs ($P = 0.001$) than those of the other groups. This was true even though there were two patients with bacteremias in the cefazolin-treated group. The bacteremias were caused by group B streptococci ($n = 2$) and *Escherichia coli* ($n = 1$). They were treated and responded readily to antibiotic therapy.

DISCUSSION

The purpose of antibiotic prophylaxis is to reduce the incidence of infectious morbidity, not febrile morbidity. The ideal agent to be used prophylactically has not been identified, although a cephalosporin antibiotic appears to be the one most frequently chosen in published studies (4). We desired to determine whether there was any significant difference between the cephalosporins with different spectra of activity that are used prophylactically in patients undergoing nonelective cesarean section.

In this study, the reduction in infectious morbidity in each of the groups was significantly better than the 27 to 86% incidence reported in the literature for patients not receiving prophylaxis (3, 9). There was no significant difference between the three groups in the incidence of immediate or delayed infectious morbidity. As with most studies with limited numbers of patients, the chance of a type II statistical error must be kept in mind. We calculated that to reduce the type II or beta statistical error to a P value of 0.2, assuming there is a difference of 10% in infection rates, we would have needed to study over 500 patients in each antibiotic treatment group. We feel that the exacting techniques used in this study add validity to the lack of a significant difference between the regimens.

Since there was no difference in morbidity between the groups and no difference in adverse reactions to the medication, the cost of the antibiotic becomes very important. At the University Hospital, the pharmacy cost of 1 g of cefazolin is $2.15, that of 2 g of cefoxitin is $13.96, and that of 1 g of cefotaxime is $8.15. Cefazolin is four to six times less expensive than the other agents.

Another way to look at cost-effectiveness is to compare the average hospital costs of the patients who were infected in each group. Even if a narrow-spectrum cephalosporin is equally effective in prophylaxis of postoperative infection and is cheaper, if the patients who do become infected have severe infections resulting in expensive hospital bills, the benefits are outweighed by these costs. Not only was the narrow-spectrum cephalosporin equally effective in preventing postoperative infection, but the average hospital costs for those patients who became infected while they were on this antibiotic were significantly less than the costs for the cefoxitin-treated group and were not significantly greater than the costs for the cefotaxime-treated group.

Although Faro et al. (5) have recently reported an evaluation of 10 different antibiotics used for prophylaxis, the patients in that study were not all entered into a single investigation. We compared narrow-, expanded-, and broad-spectrum cephalosporins in a single study and found no significant differences in efficacy among the three.

Since the narrow-spectrum cephalosporin was as effective as the broader-spectrum agents, when they are used prophylactically, is cheaper for the patient, and is not associated with significantly higher hospital costs among those who develop postoperative infections, we recommend its use as the prophylactic antibiotic of choice in women undergoing nonelective cesarean section.

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