ORIGINAL ARTICLE

Antibiotic Prophylaxis Before Surgery vs After Cord Clamping in Elective Cesarean Delivery

A Double-blind, Prospective, Randomized, Placebo-Controlled Trial

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Context: Perioperative antibiotic prophylaxis during elective cesarean delivery at term to reduce postoperative maternal infectious morbidity is generally used but may not be effective on the basis of the available data. Also, the optimal timing of prophylactic antibiotic administration is unclear.

Objective: To compare the effectiveness of cefazolin administered before skin incision vs cefazolin administered after umbilical cord clamping vs placebo in a 3-arm randomized trial. The primary objective of the study was to compare postoperative infectious morbidity, defined as wound infection, endometritis, or urinary tract infection (primary end point), in women with cefazolin vs placebo. The comparison between the 2 arms administering cefazolin before skin incision vs after umbilical cord clamping was a secondary end point.

Design: Double-blind, prospective, randomized, placebo-controlled trial.

Setting: The Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria.

Patients: We recruited 1112 women undergoing elective cesarean delivery at term from March 1, 2004, through January 31, 2010.

Interventions: In group 1, cefazolin (2 g) was administered 20 to 30 minutes before skin incision. In group 2, cefazolin (2 g) was administered immediately after clamping of the cord. In group 3, placebo was administered before skin incision.

Results: The primary outcome was observed in 18 of 370 women in group 1 (4.9%) and in 14 of 371 women in group 2 (3.8%), whereas it was noted in 45 of 371 women in group 3 (12.1%) ($P<.001$ for group 1 plus group 2 vs group 3). The number needed to treat to avoid 1 primary outcome was 13 (95% CI, 9 to 24). Between groups 1 and 2, there was no statistically significant difference regarding postoperative infectious morbidity ($P=.60$).

Conclusion: We were able to demonstrate the usefulness in elective cesarean delivery of prophylactic cefazolin vs placebo in reducing postoperative maternal infectious morbidity.

Trial Registration: clinicaltrials.gov Identifier: NCT01248078

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CESAREAN DELIVERY IS THE most common risk factor for postpartum maternal infections, which occurs at a rate of 18% to 38%.[1] The potential of antibiotic prophylaxis during cesarean delivery to reduce the number of postpartum maternal infections was studied in detail and summarized in 2 meta-analyses[2,3] of the Cochrane Library. On the basis of these data, antibiotic prophylaxis reduces the incidence of endometritis after cesarean delivery by 66% to 75%. Hence, it may be concluded that further placebo-controlled studies regarding the issue of antibiotic prophylaxis during cesarean delivery are not needed.

See Invited Critique at end of article

These meta-analyses, however, cover a period of more than 20 years and include studies[4] dating back to 1988, which may no longer be representative. In addition, several authors[3,5,6] have clearly questioned the therapeutic efficacy of prophylactic antibiotics during elective cesarean delivery. In a Cochrane meta-analysis,[3] average incidences of endometritis between 9% and 29% have been reported for women undergoing elective and emergency cesarean deliveries, respectively.

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These figures seem to be high for modern standards and may no longer be representative. The most common substances used in previous studies were aminopenicillins (eg, ampicillin), acylaminopenicillin (eg, mezlocillin), first-generation cephalosporins (eg, cefaclor), and metronidazole. In fact, circumstances may have improved regarding the surgical technique of cesarean delivery, operation time, quality of antibiotics, and the spectrum of bacteria involved. The updated version of the aforementioned Cochrane Review by Smaill and Gyte[7] again comprised studies mostly published before 2001. One of the more recent trials of this review, a study published by Bagratee et al[8] in 2001, investigated 480 women and showed no benefit of antimicrobial prophylaxis during elective cesarean delivery. Therefore, new studies are needed to confirm or refute the generally accepted practice of antibiotic prophylaxis during cesarean delivery.

Another point of interest is the timing of antibiotics application. In this regard, a "single-shot" prophylaxis has been generally accepted, which may be administered 30 minutes before skin incision or after umbilical cord clamping. Before 1978, prophylaxis during cesarean delivery was given before skin incision. After 1978, antibiotic administration immediately after clamping of the umbilical cord has been generally used, as in almost all published studies investigating this issue.[2,3] This change in the timing of administration was caused by the publication of a prospective, randomized, placebo-controlled study involving 114 patients. In this study, the administration of ampicillin before skin incision compared with such administration after umbilical cord clamping demonstrated no statistically significant differences in maternal morbidity (ie, wound breakdown and fever).[9] Hence, the practice of antibiotic prophylaxis after umbilical cord clamping was generally adopted to avoid a possible selection pressure on intestinal bacteria of the neonate. Of note, this approach is in clear contrast to the usual procedure of antibiotic prophylaxis for other surgical procedures, which is administered 30 minutes before skin incision. It has been shown that the lowest risk of surgical wound infection after elective clean or clean-contaminated surgical procedures is associated with antibiotics administered in the preoperative period.[10] Regarding cesarean section, the effectiveness of the administration of antibiotics before skin incision compared with that after umbilical cord clamping on the rate of postpartum infections has been the subject of 2 recently published randomized clinical trials. The first trial, published in 2005, assessed 303 women and found no difference in the rate of maternal infectious morbidity in relation to the timing of antibiotic administration.[11] The other trial was published in 2007 and randomized 357 women. The results of this trial supported the effectiveness of the "before skin incision" approach.[12] Specifically, the administration of prophylactic cefazolin before skin incision resulted in a decrease in both endomyometritis and total postcesarean infectious morbidity compared with the administration at the time of cord clamping. More studies with greater power are needed to resolve this clinically important question.

Therefore, in the present study, we compared the effectiveness of cefazolin, a first-generation cephalosporin, administered before skin incision vs after umbilical cord clamping vs placebo in a 3-arm randomized trial of women undergoing elective cesarean delivery. The results of the present work meet the main recommendations for further research in this area postulated by the Cochrane Library's review.[3]

METHODS

This randomized, double-blind, placebo-controlled trial was approved by the institutional review board of the Medical University of Vienna. The primary outcome was total postoperative infectious morbidity according to Cochrane Collaboration criteria (ie, endometritis, wound infection, and urinary tract infection).[3]

Women undergoing cesarean delivery at term from March 1, 2004, through January 31, 2010, at the Department of Obstetrics and Gynecology of the Medical University of Vienna were recruited. Inclusion criteria were a gestational age of at least 37 weeks and reassuring fetal heart traces. Rupture of membranes and labor contractions were allowed. Exclusion criteria included fever greater than 38°C, cephalosporin allergy, age younger than 18 years, and exposure to any antibiotic agent within 1 week before delivery. Following written informed consent, patients were randomized into 3 study arms by using a computer-generated randomization list. Randomization was done in permuted blocks of 5. After inclusion of the patient, a study nurse checked the randomization list and handed the appropriate infusion bag to the anesthesiologist. The study nurse, but not the patient, the surgeon, or the anesthesiologist, was aware of the allocation. Infusion bags were of identical appearance and were prepared according to randomization and labeled as A, B, or C. Bags A and B contained 2 g of cefazolin mixed with 100 mL of saline solution. Bag C contained only 100 mL of saline solution. Bag A was administered 20 to 30 minutes before skin incision (group 1) and Bag B was administered immediately after clamping of the cord (group 2). Bag C was administered 20 to 30 minutes before skin incision (group 3). All infusions were prepared and administered by the anesthesia staff. Patients and surgeons were masked to the administration schedule. All cesarean deliveries were performed by residents (ie, physicians in training) under the supervision of fully trained attending physicians using a modified Misgav Ladach technique.

Patient-specific data elements, such as age, body mass index (BMI), and gestational diabetes mellitus, were collected using medical charts. Evaluation of the infectious morbidity was performed by 2 residents who were masked to the group assignments of the study patients. Endometritis was diagnosed if the patient had fever, defined as an axillary temperature of at least 38°C for at least 48 hours, along with uterine tenderness and malodorous lochia. Wound infection was diagnosed if there was purulent discharge or erythema (>1 cm in diameter) and induration of the incision site. Urinary tract infection was diagnosed if there were clinical symptoms (ie, polyuria and dysuria) and a positive urine dipstick nitrite test result. The duration of hospital stay and the need for therapeutic antibiotics were recorded. Neonatal data (ie, respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, sepsis, and neonatal death) were collected by neonatology staff members who were masked to the group assignments of the neonates' mothers. Patients were followed up during the hospital stay. Thirty days after hospital discharge, all patients were contacted by telephone and interviewed. They were rescheduled for a clinic visit if they reported signs and symptoms of the primary end point as described previously.

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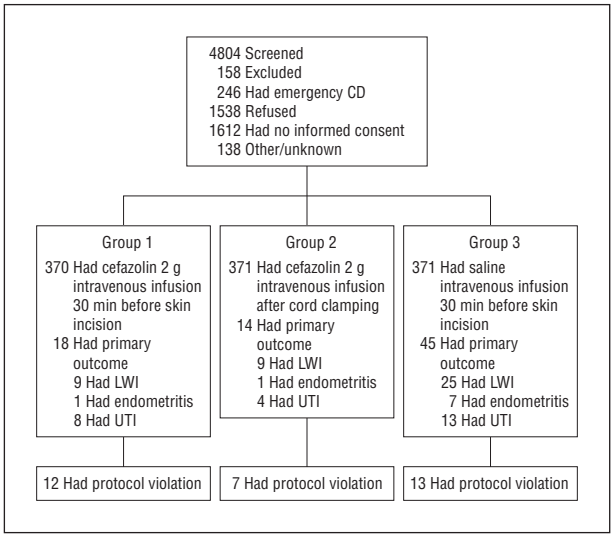

Figure. Consolidated Standards of Reporting Trials diagram of the patient flow through the study. CD indicates cesarean delivery; LWI, local wound infection; and UTI, urinary tract infection.

The null hypothesis of this trial was that there is no difference in the comparison of a combined antibiotic group with the placebo arm regarding the primary outcome. If the null hypothesis were rejected, we planned a secondary analysis comparing the 2 antibiotic-containing arms. We assumed that the rate of the primary outcome (ie, postoperative infection) would be 10% in the placebo group and 5% in the combined antibiotic-containing arms against the null hypothesis of equivalent rates of 10% in all arms. A power calculation demonstrated that, with a sample size of 360 per arm, this study had a power of 90% to detect an absolute reduction of 5% in the primary outcome (ie, postoperative infection according to Centers for Disease Control and Prevention criteria) in the 2 antibiotic-containing arms compared with the placebo arm at a significance level of .05. This calculation was based on published incidence rates of the primary outcome of 10% and on published efficacy rates of antibiotics of 50% in women undergoing cesarean delivery.[2,3] For primary and secondary outcome analysis, we calculated the risk difference and associated 95% CIs. Descriptive statistics (means, SDs, and ranges) were calculated for demographic data. One-way analysis of variance on ranks was used on means. The χ^2 test, or Fisher exact test in cases of expected cell frequencies below 5, was used for comparisons of frequencies and cross-tabulations. The Bonferroni correction was used for multiple comparisons—that is, a null hypothesis was evaluated with significance set at $P \leq .05$, followed by pairwise comparisons. We performed a multivariable logistic regression model on the intention-to-treat population with postoperative infection as the dependent variable and antibiotic therapy (groups 1 plus 2 vs group 3), patient age (as a continuous variable), BMI (as a continuous variable), gestational diabetes (yes vs no), and immunosuppressive therapy during pregnancy (yes vs no) as independent variables. Given the number of events (n=77), we restricted the number of variables to 5, selected for their potential to affect infectious complications. Aside from antibiotic therapy as the tested intervention, patient age, BMI, gestational diabetes, and immunosuppressive therapy can be expected to potentially affect the risk of developing infectious complications. The adequacy of the multiple logistic regression model was assessed by a test for goodness of fit.[13] We used the statistical software R, version 2.12 (R Development Core Team) for statistical analyses.

RESULTS

In this prospective randomized trial, we screened 4804 women and randomized 1112 women from March 1, 2004, through January 31, 2010. Of these 1112 women, 370 women were randomized in group 1 (cefazolin [2 g] intravenous infusion 30 minutes before skin incision), 371 women were randomized in group 2 (cefazolin [2 g] intravenous infusion after clamping of the cord), and 371 women were randomized in group 3 (saline intravenous infusion 30 minutes before skin incision). The **Figure 1** shows a Consolidated Standards of Reporting Trials diagram of the patient flow through the study. During randomization, 32 women were lost to follow-up, protocol violations, or withdrawal from the study; their occurrence was similar in the 3 groups (group 1: n=12, group 2: n=7, group 3: n=13; P=.37). Thus, 1112 women were eligible for the intention-to-treat analysis.

Table 1 shows patient characteristics of the study participants (intention-to-treat population). The 3 groups were balanced with regard to age, BMI, prevalence of gestational diabetes, personal history of allergy, immunosuppressive therapy during pregnancy, and anticoagulation therapy during pregnancy.

In the intention-to-treat population, the primary outcome of postoperative infection occurred in 77 of 1112 women (6.9%). Specifically, local wound infections, endometritis, and urinary tract infections were noted in 43 cases (3.9%), 9 cases (0.8%), and 25 cases (2.2%), respectively. The primary outcome was observed in 18 of 370 women (group 1; 4.9%) and in 14 of 371 women (group 2; 3.8%) in the 2 groups who were administered antibiotics, whereas the primary outcome was noted in 45 of 371 women (group 3; 12.1%) in the control group. According to the principal hypothesis of this trial, a comparison of the 2 antibiotic-containing groups and the placebo group showed a statistically significant difference regarding the primary outcome ($P < .001$ for group 1 plus group 2 vs group 3) with a risk difference of 7.8% (95% CI, 4.2% to 11.4%). Comparing the number of events in the antibiotic-containing groups 1 and 2 with the placebo group (group 3), the number needed to treat to avoid 1 case of postoperative infectious morbidity, as defined in this trial, was 13 (95% CI, 9 to 24). After rejection of the null hypothesis, a comparison of the 2 antibiotic-containing arms showed no statistically significant difference regarding the primary outcome (P=.60 for group 1 vs group 2) with a risk difference of 1.1% (95% CI, −1.8% to 4.0%).

The distribution of primary outcome events between 2 observation periods (hospital stay vs postdischarge period until 3 weeks postpartum) was evenly distributed among the 3 groups (group 1: 13 vs 5 events; group 2: 13 events vs 1 event; group 3: 33 vs 12 events, respectively; $P > .99$ for group 1 plus 2 vs 3). **Table 2** shows the distribution of specific primary outcome events (ie, local wound infection, endometritis, and urinary tract infection) in the 3 groups during hospital stay as well as after discharge to home up to 3 weeks postpartum. Of note, each component of the composite end point was less common in each antibiotic arm than in the placebo arm. Table 2 demonstrates that most events occurred dur-

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Table 1. Patient Characteristics of 1112 Women Undergoing Cesarean Delivery With or Without Antibiotic Prophylaxis

Variable	Group 1: Cefazolin (2 g) 30 min Before Skin Incision (n = 370)	Group 2: Cefazolin (2 g) After Cord Clamping (n = 371)	Group 3: Saline Infusion 30 min Before Skin Incision (n = 371)
Patient age, mean (SD), y	31.3 (6.3)	32.2 (5.8)	31.2 (5.7)
BMI, mean (SD)	28.3 (5.4)	28.3 (4.9)	28.1 (4.9)
GDM, yes vs no, No. (%)	39/370 (10.5)	33/371 (8.9)	37/371 (10.0)
History of allergy, yes vs no, No. (%)	27/370 (7.3)	30/371 (8.1)	26/371 (7.0)
Immunosuppression, yes vs no, No. (%)	4/370 (1.1)	2/371 (0.5)	4/371 (1.1)
Anticoagulation, yes vs no, No. (%)	9/370 (2.4)	12/371 (3.2)	6/371 (1.6)
Length of stay, mean (SD)	5.5 (1.6)	5.5 (1.9)	5.7 (2.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GDM, gestational diabetes mellitus.

Table 2. Distribution of the Primary Outcome Parameters

Variable	Group 1: Cefazolin (2 g) 30 min Before Skin Incision (n = 370)	Group 2: Cefazolin (2 g) After Cord Clamping (n = 371)	Group 3: Saline Infusion 30 min Before Skin Incision (n = 371)	*P* Value[a]
LWI	**9**	**9**	**25**	.001
Hospital stay	6	8	18	
3 wk PP	3	1	7	
Endometritis	**1**	**1**	**7**	.008
Hospital stay	0	1	7	
3 wk PP	1	0	0	
UTI	**8**	**4**	**13**	.05
Hospital stay	5	4	8	
3 wk PP	3	0	5	
Total	**18**	**14**	**45**	<.001

Abbreviations: LWI, local wound infection; PP, postpartum; UTI, urinary tract infection.
[a]Fisher exact test (group 1 plus group 2 vs group 3).

ing the patients' hospital stay throughout the 3 groups. Methicillin-resistant *Staphylococcus aureus* infection was not noted in the study population. There were 2 cases of pelvic abscess (1 in group 1 and 1 in group 2) and 1 case of sepsis (in group 3).

In a multivariable logistic regression model with the primary outcome of postoperative infection as the dependent variable and antibiotic prophylaxis (groups 1 plus 2 vs group 3), patient age (as a continuous variable), BMI (as a continuous variable), gestational diabetes (yes vs no), history of allergy (yes vs no), immunosuppressive therapy during pregnancy (yes vs no), and anticoagulation therapy during pregnancy (yes vs no) as the independent variables, we found that antibiotic prophylaxis (odds ratio, 0.31; 95% CI, 0.19-0.50), but not patient age (0.94 per decade; 0.64-1.37), BMI (1.01; 0.97-1.05), gestational diabetes (1.27; 0.62-2.62), or immunosuppressive therapy (1.38, 0.17-11.35) were significantly associated with the primary outcome. A test for goodness-of-fit did not indicate any evidence of lack of fit ($P=.33$). **Table 3** demonstrates the results of the univariable and multivariable regression models for antibiotic therapy, patient age, BMI, gestational diabetes, and immunosuppressive therapy during pregnancy as predictors for postoperative infection.

We address the problem of changes in patient characteristics during 2 time periods, that is, March 2004 to June 2007 and July 2007 to January 2010. Median age, median BMI, ethnic background (Austrian vs non-Austrian), gestational diabetes (yes vs no), and indications for cesarean delivery (breech presentation vs repeat cesarean delivery vs no medical indication vs others) did not change significantly during the 2 periods ($P=.20$, $P=.30$, $P=.10$, $P=.60$, and $P=.30$, respectively). Infection rates (ie, endometritis, wound infection, and urinary tract infection) were comparable between the two 3½-year periods and on a yearly basis ($P=.40$).

Neonatal outcome, as recorded in the hospital discharge record, showed no statistically significant differences between the 3 treatment groups regarding respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, sepsis, and neonatal death (data not shown).

COMMENT

In the present prospective, randomized, placebo-controlled trial, we were able to demonstrate the usefulness of prophylactic cefazolin in elective cesarean delivery vs placebo regarding maternal postoperative infectious morbidity. In patients who received prophylactic cefazolin during cesarean delivery, infectious episodes postpartum were reduced by two-thirds. Therefore, we recommend the use of cefazolin as a single-shot antibiotic prophylaxis before or during elective cesarean delivery.

In this study, we defined the primary outcome as postoperative infectious morbidity, comprising endometri-

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Table 3. Univariate and Multivariable Regression Models of Patient Characteristics as Predictors of Postoperative Infection After Cesarean Delivery

Characteristic	Postoperative Infection OR (95% CI)	
	Univariate Regression	Multivariable Regression
Antibiotic prophylaxis, groups 1 and 2 vs group 3	0.33 (0.20-0.52)	0.31 (0.19-0.50)
Patient age, per decade[a]	0.90 (0.62-1.30)	0.94 (0.64-1.37)
BMI[a]	1.01 (0.97-1.05)	1.01 (0.97-1.05)
GDM, yes vs no	1.32 (0.66-2.64)	1.27 (0.62-2.62)
Immunosuppression, yes vs no	1.46 (0.18-11.70)	1.38 (0.17-11.35)

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; OR, odds ratio.
[a]Continuous variable.

tis, wound infection, and urinary tract infection. Specifically, this primary outcome was observed in the 2 active groups in 4.9% and in 3.8% of women, whereas it was noted in the control group in 12.1% of women. These incidence rates of infectious morbidity are in agreement with the recent literature,[11,12] confirming that the study population was representative of a common low-risk population.

In a multivariable regression model, administration of cefazolin, but not age of the patient, BMI, a diagnosis of gestational diabetes, or immunosuppression, affected the primary outcome. Interactions between the antibiotic effect and other variables were not tested. Therefore, we cannot rule out that variables such as age or BMI might modulate the antibiotic effect of cefazolin. However, we can say that the investigated variables do not have an independent effect on maternal postoperative infectious morbidity as defined in this study.

We observed no statistically significant difference regarding the protective effect of cefazolin comparing 2 administration schedules, that is, before skin incision vs after umbilical cord clamping. These data suggest that antibiotic prophylaxis during elective cesarean delivery can be administered after umbilical cord clamping without compromising the prophylactic efficacy. It has to be acknowledged, however, that the comparison between the 2 antibiotic-containing arms of the study was a secondary end point. As such, the results of this comparison are exploratory. Although previous studies[11,12] have demonstrated no increase in neonatal morbidity when prophylactic antibiotics were given preoperatively compared with after umbilical cord clamping, others[14] have found that the administration of antibiotics before incision was associated with decreased rates of maternal infection.

In our study, only 1 antibiotic substance, cefazolin, was investigated and found to be effective. A possible future research area is the use of extended-spectrum antibiotics during cesarean delivery on the basis of the growing importance of *Ureaplasma urealyticum* in wound infections.[14] These studies should focus primarily on cesarean deliveries in case of preterm delivery.[15] With regard to elective cesarean deliveries at term, cefazolin, administered before skin incision or after cord clamping, appears adequate.

Our study has strengths and weaknesses. One strength is the large sample size and the homogeneous sample comprising women with elective cesarean deliveries at term. On the other hand, the results of our study are not useful to guide clinical practice in women with preterm cesarean deliveries, those with premature rupture of membranes, and those with signs and symptoms of chorioamnionitis. Also, only a single antibiotic preparation was studied, which increases the internal validity of this study but limits the external validity to the use of cefazolin. Other antibiotics or antibiotic combinations may be less or more effective.

In addition, the long study duration of almost 6 years has to be acknowledged. Patient characteristics, elements of care, or unknown factors potentially affecting outcomes may have changed over time. To address this problem, we have compared selected characteristics, such as age, BMI, ethnic background, gestational diabetes, and indications for cesarean delivery, during 2 time periods. We did not find significant changes over time, providing reassurance that patient characteristics did not change over time in a significant manner. Also, infection rates, that is, endometritis, wound infection, and urinary tract infection, were comparable between the two investigated time periods and on a yearly basis. Elements of care, such as cesarean delivery technique and anesthesia procedures, did not change during the study. However, there was a turnover of residents who work in the labor ward for 12 months during their rotation. Faculty did not change during the study period. In addition, it should be acknowledged that the method of follow-up may have affected the number of infections identified. Thus, comparisons with other studies regarding postdischarge infection rates should take follow-up protocols into account.

We did not observe cases of oral thrush or other potential adverse outcomes associated with infant exposure to antibiotics during the study period. It has to be acknowledged, however, that infant follow-up was limited to the stay in the well-baby nursery.

In summary, we found that prophylactic cefazolin during elective cesarean delivery administered before skin incision or after umbilical cord clamping reduces postoperative infectious morbidity by two-thirds. The number needed to treat to avoid 1 woman reaching the primary outcome was 13. On the basis of this significant reduction of postoperative morbidity, we recommend the routine administration of cefazolin during elective cesarean delivery.

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Author Contributions: *Study concept and design:* Witt, Döner, Petricevic, Berger, Germann, and Tempfer. *Acquisition of data:* Witt, Döner, Petricevic, Berger, and Germann. *Analysis and interpretation of data:* Witt, Döner, Petricevic, Berger, Germann, Heinze, and Tempfer. *Draft-*

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INVITED CRITIQUE

History and Comparative Effectiveness Research

Those who cannot remember the past are condemned to repeat it.
George Santayana

Comparative effectiveness research is a potentially useful tool to identify value in health care. The current report by Witt et al[1] is an excellent example of this concept. This prospective, randomized trial of perioperative antimicrobial prophylaxis for women undergoing cesarean section followed recommended clinical trial guidelines, was adequately powered to demonstrate statistical significance (more than 1100 women were enrolled), and had an amazing 97% follow-up at 30 days, likely accounting for all measured outcomes. No study is flawless; here, there is the inherent bias of unstated practice patterns in a trial limited to a single institution. We also must assume that all other preventive measures necessary to minimize the number of surgical site infections were properly performed.

Why was this subject controversial in spite of proof for more than 40 years that antimicrobial prophylaxis works?[2] A number of recent reports that were not as well structured as the current one questioned the principles of prophylaxis. This is not a debate specific to this operation; this issue has been raised recently by others in different circumstances.[3,4]

There are important lessons to be learned from this study. First, properly administered perioperative antibiotic prophylaxis reduces the number of surgical site infections in selected operations (in this situation, by two-thirds) despite a greater understanding of the many additional factors contributing to these infections. Second, first- and second-generation cephalosporins remain the agents of choice for prophylaxis, even though newer antibiotics are available. Third, dose matters. Patients in this study received 2 g of cefazolin, which provides greater tissue levels of drug. Fourth, preincisional and post–cord clamping groups had *identical* results, suggesting that they achieve similar antibiotic concentration at the site of contamination, which is a key element for efficacy.[5]

Although more research may be needed to validate and refine some of the empirical practices in medicine, we do not need to validate all of the well-conducted studies of previous investigators. The most critical lesson we should learn is to remember these past accomplishments.

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