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# Role of First-generation Cephalosporin (Cefazolin) Versus Combined First-generation Cephalosporin and IV Metronidazole in Prevention of Postcesarean Section Site Infection

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## Abstract

**Background:** Cesarean section (c-section) is the biggest postpartum infection risk factor. Cesarean births increase the risk of infection and infectious morbidity. Post-c-section complications include fever, infection of the incision, endometritis, and urinary tract infection. Occasionally, pelvic abscess, bacteremia, septic shock, necrotizing fasciitis, and septic pelvic vein thrombophlebitis manifest. First-generation cephalosporins kill Gram-positive bacteria. Metronidazole injection treats severe bacterial infections.

**Aim and objectives:** This study aims to compare first-generation cephalosporin (cefazolin) versus combined first-generation cephalosporin and intravenous metronidazole in prevention of postoperative surgical site infection following c-section.

**Patients and methods:** This was a double blinded comparative study that was carried out at the obstetrics and gynecology departments of Al Azhar University Hospitals, El Hussein, and Alexandria maternity hospital - Ministry of health. This Randomized prospective double blinded study included 300 pregnant women  $\pm$  38 weeks opting for an elective C-section. Patients divided into two groups, group 1: 150 patients had been treated with first-generation cephalosporin and group 2: 150 patients had been treated with combined first-generation cephalosporin I.V metronidazole.

**Results:** The weight and gestational age ranges were not significant difference between the cefazoline and cefazoline with metronidazole groups. However, there was a significant increase in hospital stays for the cefazoline group compared with the metronidazole group. The cefazoline-only group had significantly higher rates of endometritis, purulent wound discharge, and wound infection compared with the cefazoline-plus-metronidazole group.

**Conclusion:** Cefazolin plus metronidazole is superior for C-section antibiotic prophylaxis, according to this study. Cefazolin plus metronidazole may minimize postoperative infection morbidity and hospital costs.

**Keywords:** Cephalosporin, Cesarean section, Metronidazole

## 1. Introduction

Cesarean delivery poses a higher risk than any other type of delivery for maternal infection in the postpartum period. Infection and infectious morbidity are 5–20 times more common in women who have a cesarean section than in those who give birth the traditional way. The OECD reports that between 12.9 and 33.3 % of Western live

deliveries are assisted by cesarean section, while in underdeveloped nations the number ranges from 12 % to 40 %.<sup>1</sup>

Cesarean section infection problems are a major reason for maternal mortality and are linked to significantly longer hospital stays. Urinary tract infections, surgical wound infections, and pelvic organ infections are all possible.<sup>1</sup>

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Fevers, wound infections, endometritis, and urinary tract infections are all examples of infectious problems that can arise after a cesarean delivery. Maternal mortality has been linked to significant infection consequences like pelvic abscesses, bacteremia, septic shock, necrotizing fasciitis, and septic pelvic vein thrombophlebitis. A low-grade fever after a cesarean birth may not always be indicative of infection, but fever can occur after any operational surgery. Endometritis is said to occur in 20 %–85 % of women without prophylaxis, and wound infection and significant infectious consequences can occur in as many as 25 % of women.<sup>2</sup>

Postoperative intravenous antimicrobial prophylaxis with anaerobic and aerobic coverage was suggested for adult colorectal surgery procedures in the 2013 AHSP Therapeutic Guidelines on Antimicrobial Prophylaxis in Surgery. When it comes to first-line treatment, the guidelines recommend cephalosporin-containing regimens. Nonetheless, 'the optimal choice of antimicrobial agent has not been fully resolved,' they note.<sup>4</sup>

Against Gram-positive bacteria, first-generation cephalosporins do exceptionally well. Injections of metronidazole are also used to treat life-threatening bacterial infections in many parts of the body. Some people take it before and after surgery to keep their digestive tracts healthy and free of infection. Combining two medications may be more effective than using a first-generation cephalosporin alone in preventing surgical site infection after a cesarean section.<sup>3</sup>

This work aimed to compare between first-generation cephalosporin (cefazolin) versus combined first-generation cephalosporin and intravenous metronidazole in prevention of postoperative surgical site infection following cesarean section.

## 2. Patients and methods

This was a double blinded comparative study that had been conducted at obstetrics and gynecology department of Al Azhar University Hospitals, El Hussein and Alexandria maternity hospital - Ministry of health, study was conducted from December 2020 to November 2022.

At the obstetrics and gynecology division of Al Azhar University Hospitals, El Hussein, and Alexandria maternity hospital - Ministry of health, 300 pregnant women +38 weeks who chose to have an elective Caesarean section were enrolled in this randomized prospective case-control research.

Patients had been selected after their consent and separated into a pair of groups: group 1: 150 patients had been treated with intravenous first-generation

cephalosporin (cefazolin) [Zinol, Al Hekma Company] (A single 2 gm dosage of cefazolin was administered intravenously within half to an hour prior to skin incision (Preoperative). Postoperatively patients received 1 gm of cefazolin twice daily for 5 days) and group 2: 150 patients had been treated with combined first-generation cephalosporin [Zinol, Al Hekma Company] and intravenous metronidazole [Flagyl, Sanofy Affents Company] (Receiving 2 gm intravenous cefazolin intravenously followed by 500 mg intravenous metronidazole 30–60 min before the skin incision (Pre-operative). Postoperatively patients received 1 gm intravenous cefazolin twice daily for 5 days plus Metronidazole 500 mg IV bid for 5 days).

**Inclusion Criteria** for study group: Patients consented to participate in the study. Patients between the ages of 21 and 45, pregnant women with a gestational age of  $\pm$  38 weeks, and women undergoing elective cesarean section. No medical conditions including Diabetes and/or Hypertension, There are no dermatological conditions like Psoriasis or Scleroderma. 10. No autoimmune disease, such as SLE, or drug intake, such as corticosteroids and chemotherapy, effecting wound-healing.

**Exclusion Criteria** for groups: Histopathology of drug hypersensitivity, Eligibility for vaginal delivery, Metronidazole use within the previous seven days prior to randomization, Chorioamnionitis, or other infection requiring treatment, fever of greater than or equal to 38 °C within 1 week before cesarean section, fetal mortality, or significant congenital anomaly.

Participants were randomly assigned to one of the groups using a computer-generated randomization schedule.

### 2.1. Methods

Patients underwent a comprehensive history and physical examination (General examination and abdominal and local clinical examination).

### 2.2. Statistics and statistical analysis

The sample size was determined using epi info STATCALC (Statistical calculator that gives summary epidemiologic information) with the following assumptions in mind: a two-sided confidence of 95 % and an 80 % power. A 5 % margin of error yields an odds ratio of 1.115. The Epiinfo result was used to determine a maximum sample size of 142. Because of this potential for dropouts during follow-up, the sample size was expanded to 150 participants each group.

SPSS (Version 25) for Windows will be used for coding, processing, and analysis of the obtained data. Means, medians, ranges, and percentages will be computed in addition to other descriptive statistics. Comparisons of means for continuous variables will be conducted using independent *t*-tests, comparisons of medians for non-normally distributed data will be conducted using Mann–Whitney *U* tests, and comparisons of means and frequencies for categorical variables will be conducted using  $\chi^2$  tests.

### 3. Results

**Table 1.**

This table shows that Weight distribution among study sample ranged from 51 to 157 with  $91 \pm 20.202$  for Mean  $\pm$  SD in cefazoline group and ranged from 56 to 147 and  $92 \pm 20.374$  for mean in cefazoline and metronidazole group. There was insignificant difference between both groups as regard weight [Table 2](#).

Gestational Age among study group ranged from 27 to 46 with  $36.5 \pm 4.75$  for Mean  $\pm$  SD in cefazoline group and ranged from 28 to 47 and  $37.5 \pm 4.75$  for Mean  $\pm$  SD in cefazoline and metronidazole group. There was insignificant difference between both groups as regard Gestational Age [Table 3](#), [Fig. 1](#).

This table shows that Hospital stay distribution among study groups among study groups ranged from 0 to 24 with  $12 \pm 6$  for Mean  $\pm$  SD in cefazoline group and ranged from 1 to 4 and  $2.5 \pm 0.75$  for mean in cefazoline and metronidazole group. There was highly significant difference between both groups as regard Hospital stay [Table 4](#).

This table shows that postoperative infectious morbidity was detected in 27 (18 %) cases in the cefazoline group compared with 24 (16 %) cases in the Cefazoline plus metronidazole group. Neither group was significantly different from the other [Table 5](#).

This table shows that Endometritis percentages in Cefazoline only group was 2 (1.4 %) cases compared with 0.0 % positive in the Cefazoline plus metronidazole group. There was nonsignificant difference between the studied groups [Table 6](#).

This table shows that Purulent wound discharge frequency among study groups. 2.7 % showed positive Purulent wound discharge in Cefazoline only group, 1.4 % positive Purulent wound discharge in Cefazoline plus metronidazole group. When comparing the groups, there was no discernible difference [Table 7](#).

This table shows that wound infection frequency among study groups. 3.4 % showed positive wound

*Table 1. Weight distribution among study sample.*

	Cefazoline only group (n = 150)	Cefazoline plus metronidazole group (n = 150)	Test of Significance	P
Weight (kg)				
Mean $\pm$ SD	$91 \pm 20.202$	$92 \pm 20.374$	t = -0.175	0.860
Median (IQR)	85 (78–100)	90 (75.575–105.62)		
Range (Min-max)	106 (51–157)	91 (56–147)		

*Table 2. Gestational age among study group.*

	Cefazoline only group (n = 150)	Cefazoline plus metronidazole group (n = 150)	Test of Sig.	P
Gestational Age				
Mean $\pm$ SD	$36.5 \pm 4.75$	$37.5 \pm 4.75$	t = -0.7056	0.240495
Median (IQR)	37 (36–40)	38 (35–40)		
Range (Min-max)	19 (27–46)	19 (28–47)		

*Table 3. Hospital stay distribution among study groups among study groups.*

	Cefazoline only group (n = 150)	Cefazoline plus metronidazole group (n = 150)	Test of Sig.	P
Hospital stay				
Mean $\pm$ SD	$12 \pm 6$	$2.5 \pm 0.75$	t = 13.1530	<0.0001
Median (IQR)	8 (4.25–12)	3 (2.25–3)		
Range (Min-max)	24 (0–24)	3 (1–4)		

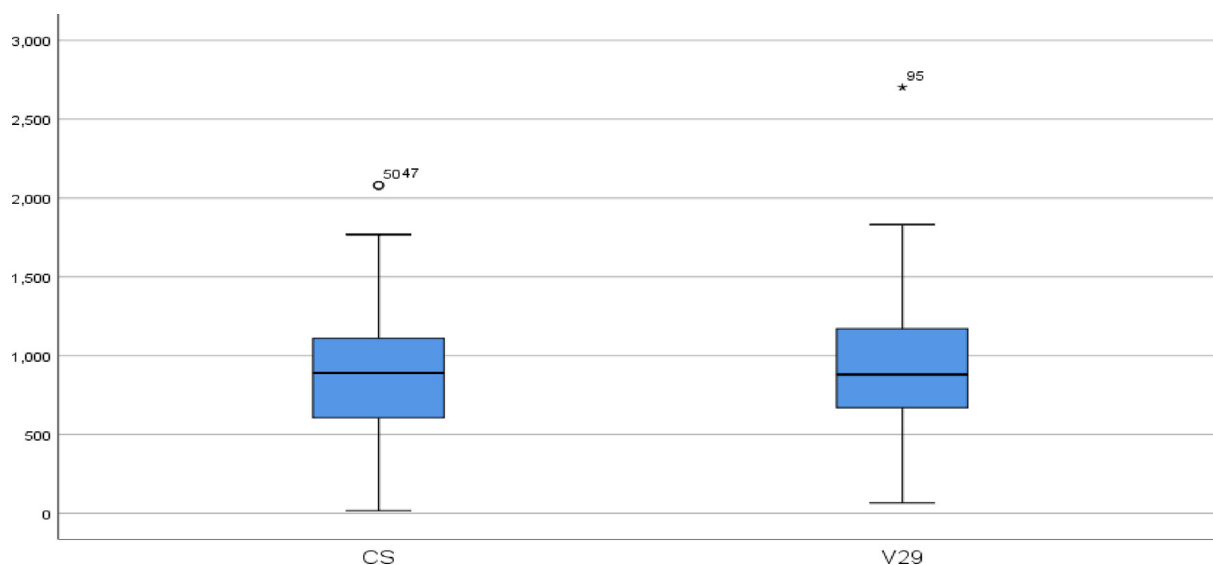


Fig. 1. Box-plot showing population data regarding surgical time.

Table 4. Postoperative infectious morbidity distribution between study groups.

	Cefazoline only group (n = 150)		Cefazoline plus metronidazole group (n = 150)		P-value
	+ve	-ve	+ve	-ve	
Postoperative infectious morbidity					0.645
N (%)	27 (18)	123 (82)	24 (16)	126 (84)	

Table 5. Endometritis percentages among study groups.

	Cefazoline only group (n = 150)		Cefazoline plus metronidazole group (n = 150)		P-value
	+ve	-ve	+ve	-ve	
Endometritis					0.562
N (%)	2 (1.4)	148 (98.6)	0	150 (100)	

Table 6. Purulent wound discharge frequency among study groups.

	Cefazoline only group (n = 150)		Cefazoline plus metronidazole group (n = 150)		P-value
	+ve	-ve	+ve	-ve	
Purulent wound discharge					0.409
N (%)	4 (2.7)	146 (97.3)	2 (1.4)	148 (98.6)	

Table 7. Wound infection frequency among study groups.

	Cefazoline only group (n = 150)		Cefazoline plus metronidazole group (n = 150)		P-value
	+ve	-ve	+ve	-ve	
wound infection					0.099
N (%)	5 (3.4)	145 (96.6)	1 (0.7)	149 (99.3)	

infection in Cefazoline only group, 0.7 % positive wound infection in Cefazoline plus metronidazole group. Differences across groups were not significant.

#### 4. Discussion

Polymicrobial postcesarean infections include aerobes, anaerobes, and ureaplasma. If membranes

rupture, the lower vaginal tract is the major source of postpartum infection after CD. Gram-negative aerobes and anaerobes (*Bacteroides*, *Clostridium*, and *Fusobacterium*) are the most commonly isolated pathogens (*Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp, and *Proteus* spp). A breach in sterile method might cause skin flora (such as *Staphylococcus aureus*) to contaminate, especially after a difficult surgery.<sup>4</sup>

Postoperative intravenous anaerobic and aerobic antimicrobial prophylaxis for adult colorectal surgery was recommended by the 2013 ASHP Therapeutic Guidelines. The guidelines recommend cephalosporin-containing regimens as firstline, although 'the best choice of antimicrobial drug has not been fully resolved'.<sup>5</sup>

There were insignificant difference between both groups as regard weight.

The current study was in agreement with Jääskeläinen et al. who showed that women having cesarean deliveries were randomly assigned to receive either 2 g of cefazolin ( $n = 81$ ) or 1 g of cefazolin +500 mg of metronidazole ( $n = 79$ ) as prophylaxis. We compared the two groups' post-operative infection morbidity and hospitalization times. They showed that women in both groups did not differ significantly from one another in terms of body mass index or weight.

This study showed that there were insignificant difference between both groups as regard Gestational age.<sup>6</sup>

The current study was in agreement with Dominguez and colleagues who showed that Gestational ages of the women in the study did not differ significantly between the two groups.<sup>7</sup>

The current study was in agreement with Ribeiro et al. who showed that Gestational age was comparable between the cephalexin-metronidazole and placebo groups.<sup>8</sup>

This study showed that there were insignificant difference between both groups as regard Surgical time.

Furthermore, our results were in harmony with Zang et al. who found that There were no discernible differences in operative time between the two groups.<sup>9</sup>

This study found a substantial variance between the two groups in terms of hospital stay.

The current study was in agreement with Zang et al. who found that Patients who received the combination prophylaxis spent significantly less time in the hospital after surgery (3.12 0.8 d vs. 4.46 4.7 d) and required fewer antibiotic treatments (1.98 5.2 d vs. 0.4 1.04 d) than those who received cefazolin alone.<sup>9</sup>

In Cefazoline only group, there were 18 % positive postoperative infectious morbidity. In Cefazoline plus metronidazole group, there were 16 % positive.

In a recent study by Till and colleagues however, the expense of the antibiotics did not justify the use of the extended-spectrum antibiotic regimen, and 2 gm of the broad-spectrum antibiotic cefotetan was not any more effective than the conventional 2 gm

dose of cefazolin in preventing postoperative febrile morbidity.<sup>10</sup>

This results were in line with Tharpe et al. who found that Each group had a lower rate of infectious morbidity than the 27–86 % reported in the literature for patients who did not get prophylaxis. The rates of either acute or chronic infectious morbidity did not differ significantly across the three groups.<sup>11</sup>

In Cefazoline group, there were 1.4 % positive Endometritis, in Cefazoline plus metronidazole group, there were 0 % positive.

This results were in line with Jyothi et al. who found that the 26 patients who developed post-partum endometritis after prophylactic cefazolin were compared with the 11 patients who developed endometritis after prophylactic cefazolin plus metronidazole.<sup>12</sup>

The current study was in disagreement with Betran et al. (2016) who showed that women who got either a single dosage or a course of antibiotics had similar rates of bacterial infection and endometritis.<sup>13</sup>

In Cefazoline group, there were 2.7 % positive Purulent wound discharge, in Cefazoline plus metronidazole group, there were 1.4 % positive.

Smaill and colleagues conducted a meta-analysis of RCTs and found that first-generation cephalosporins reduced the risks of wound infections (Relative Risk (RR) 0.38; 95 % confidence interval (CI) 0.28, 0.53) and endometritis (RR 0.42; 95 % CI 0.33, 0.54) when compared with no antibiotics.<sup>14</sup>

In Cefazoline group, there were 3.4 % positive wound infection, in Cefazoline plus metronidazole group, there were 0.7 % positive.

Valent and colleagues showed that In the study population, the overall risk of SSI was 10.9 % (95 % CI, 7.9%–14.0 %), with 13 (6.4 %) of 202 women receiving a postoperative course of cephalexin-metronidazole compared with 31 (15.4 %) of 201 women receiving a placebo (difference, 9.0 %; 95 % CI, 2.9%–15.0 %;  $P = 0.01$ ). In comparison to the placebo group, the antibiotic group's RR of SSI was 0.41 (95 % CI, 0.22–0.77).<sup>15</sup>

#### 4.1. Conclusion

Antibiotic prophylaxis before a cesarean section may be more effective when cefazolin is combined with metronidazole. The current findings need to be confirmed by additional, larger-scale studies. Metronidazole should be injected intravenous only this may be lead to complications from long term cannulations versus cefazolin can be taken intravenous and intramuscular.

## Disclosure

The authors have no financial interest to declare in relation to the content of this article.

## Authorship

All authors have a substantial contribution to the article.

## Conflicts of interest

The authors declared that there were no conflicts of interest.

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