Original Article

Randomized controlled trial of cefazolin monotherapy versus cefazolin plus azithromycin single dose prophylaxis for cesarean deliveries: A developing country's perspective

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Abstract

Aim: To compare the efficacy of pre-incision intravenous single doses of cefazolin versus cefazolin plus azithromycin as an antibiotic prophylaxis in cesarean delivery (CD). **Methods:** This was a single-center, double blind, randomized controlled trial conducted in the PGIMER, Chandigarh. 200 women undergoing elective/emergency cesarean section were randomized. Group A received single dose of cefazolin plus placebo while Group B received single dose of cefazolin plus azithromycin. Primary outcome evaluated was occurrence of surgical site infections (SSI); secondary outcomes included incidence of febrile morbidity, UTI, endometritis, neonatal outcome, total cost of antibiotics, and duration of hospital stay in both the study arms. Descriptive statistics and χ^2 tests were used for analysis of the data. **Result:** There was an overall significant reduction in the incidence of SSI (15% vs 3%; $P = 0.03$), endometritis (8% vs 2%; $P = 0.048$), and post-operative febrile morbidity (17% vs 3%; $P = 0.001$) with the addition of azithromycin to cefazolin. Duration of hospital stay was almost two days lesser for the cefazolin plus azithromycin group. Subgroup analysis of patients with SSI showed the age, duration of ruptured membranes, and type of anesthesia as important predictors of infection rate. Study observed statistically significant reduction in requirement of additional post operative antibiotics, phototherapy for neonates, hospital stay and cost of therapy in cefazolin plus azithromycin group ($P < 0.05$). **Conclusion:** Tertiary care hospitals in developing countries such as India can opt for the cefazolin plus azithromycin as antimicrobial prophylaxis during CD to maximize the efficacy as well as for decreasing the cost burden of postoperative infections.

Keywords: Antimicrobial prophylaxis, azithromycin, cefazolin, cesarean delivery

Introduction

How can the so called "evidence-based" antimicrobial prophylaxis guidelines be the same in different geographic regions when patient and hospital hygiene practice differ from region to region? Questions such as these have remained unanswered till date.[1] From the primary care and obstetrics practice point of view, the infectious complications following cesarean delivery (CD) are almost 20-fold higher the cause of maternal mortality and morbidity when compared to the complications in women who have had vaginal delivery.[2] Maternal mortality and morbidity following CD may result from a number of infections, including surgical site infections (SSI),

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endometritis, and urinary tract infections; rarely, pelvic abscess, septic pelvic phlebitis, and pneumonia are also observed.[2]

Postcesarean infections are polymicrobial, involving aerobes, anaerobes, and ureaplasma. The main source of postpartum infection after CD is the lower genital tract, particularly if the membranes are ruptured. The most commonly isolated pathogens are anaerobes (*Bacteroides spp*, *Clostridium spp*, and *Fusobacterium spp*.) and gram-negative aerobes (*Escherichia coli*, *Klebsiella spp, Enterobacter spp,* and *Proteus spp)*. Rarely, exogenous bacterial contamination may occur through skin flora (such as *Staphylococcus aureus*) as a result of a break in sterile technique, especially following a difficult surgery.[3]

Hospitals in many countries currently use single-dose cefazolin as prophylaxis for a cesarean section, as recommended by most international bodies. However, in several low-resource settings like India, antibiotics are used very liberally and irrationally due to concerns about higher incidence of infection even though there is no concrete data to support this.[4] There have been no randomized controlled trials from developing countries clarifying their choice of antibiotics. Cefazolin provides activity against ureaplasma and mycoplasma but may cause an increase in resistant organisms, such as anaerobes.[5] Hence, adding agents, such as metronidazole, clindamycin, or azithromycin may have a role in an extended cover, especially in low-resource settings with suboptimal asepsis and patient hygiene. Azithromycin is active against aerobes, anaerobes as well as ureaplasma.[6] Till date, no studies from developing or underdeveloped countries have addressed this specific issue. The study took into consideration the developing country's characteristics, such as suboptimal asepsis, level of patient hygiene and dearth of primary care or obstetric care providers. The background incidence of hospital-acquired infections, especially in the tertiary-care government hospitals of India remain high due to more number of patients with increased complications and/or co-morbidities.[7,8] The study aimed at evaluating the prophylaxis efficacy of azithromycin as an add on in routine cefazolin for cesarean deliveries.

Methodology

Trial design

Prior approval was obtained from the ethics committee of the institute before initiating the enrolment (No. NK/2212/MD/9929-30 dated 28-12-2016). The trial was a double-blind, single center interventional study conducted at the Department of Obstetrics and Gynecology, PGIMER, Chandigarh. The study population consisted of 200 consecutive, eligible pregnant women who were admitted in the labor ward or obstetric ward and underwent elective or emergency cesarean section.

Women undergoing elective or emergency cesarean section and consenting to participate in the study were enrolled. Exclusion criteria were inability to give consent, hypersensitivity history for azithromycin, eligibility for vaginal delivery, azithromycin use in past 7 days before randomization, chorioamnionitis, or other infection warranting, postpartum antimicrobial use, fetal death, or major congenital anomaly. The exclusion criteria for study population also included fever of of ≥38ºC within one week before cesarean section, having had prolonged or obstructed labor, prolonged rupture of membranes (>18 hours), active liver disease (cirrhosis or aminotransferase level at least three times the upper limit of the normal range), a serum creatinine level of more than 1.2 U/L or with a need for dialysis, any comorbid medical illness making patient more susceptible to infections, i.e. during immunosuppressive therapy, heart disease, diabetes mellitus, retrovirus positive, or pulmonary edema, use of drugs with the ability to produce QT prolongation, and electrolyte imbalance.

Screening, Randomization, Recruitment, and Allocation Concealment

Consent was obtained from the patient or legally acceptable relative accompanying the patient at the time of enrollment. All pregnant women, irrespective of their enrolment in the study, received the same standard of care as per the unit's existing protocol. An information sheet (in Hindi/English) furnishing details of the study was provided to the patients and the relatives.

Randomization code was prepared in sufficient number for potential participants using Microsoft Excel 2016 program installed in the computer. Pharmacology faculty who was not involved in the study drug administration or the outcome evaluation performed the block randomization with variable block sizes (2,4,6, and 8), where group labels A or B were allocated to each consecutive study patient, and the concerned doctor received opaque, sealed A4 size envelopes containing the freshly prepared azithromycin in normal saline and normal saline without any drug in it for administration in the potential study participants.

All consecutive pregnant women satisfying the inclusion/exclusion criteria were randomized into either of the two arms. The study arm i.e. "Group A" participants received a single dose of 2-gram cefazolin intravenously over 30–60 minutes followed by a placebo 250 ml normal saline infusion over 15–20 minutes before the skin incision, whereas the study arm i.e. "Group B" participants received 2-gram intravenous cefazolin intravenously over 30–60 minutes followed by 500 mg intravenous azithromycin in 250 ml normal saline over 15–20 minutes, prior to skin incision.

The pharmacology faculty and the residents were available round the clock. Each envelope was opened only after enrollment in the study and provided the envelope containing the normal saline solution based on their respective allocation group. The identity of the study medication was concealed using uniformly packed opaque envelopes of azithromycin added in normal saline and normal saline alone.

Procedure

The cesarean section was performed by a consultant/senior resident according to the predecided routine protocol. Both

groups received similar postoperative care. Complete blood count (CBC) and urine culture were performed on postoperative day 2 as per protocol. On postoperative day 2, occlusive dressing applied at the time of surgery was changed, the wound was assessed, and the findings were recorded. All women were asked to return for stitch removal after 1 week. The next follow-up was done on the sixth week. Surgical site infection (SSI) was defined according to the published criteria by Mangram *et al.*[9]

Statistical analysis

SPSS version 25 (SPSS, Chicago, IL) software was used for the statistical analysis of data. Descriptive statistics were presented as percentages. Chi square test and unpaired T test were used for assessment of variables in two groups . Significance was set at $P < 0.05$.

Results

The baseline parameters of two study arms were similar [please see Table 1]. There was no statistical significance in both the study groups with respect to the indications and the characteristics [please see Table 2], except postoperative total leukocyte count (TLC), which was higher in the cefazolin plus placebo group ($P < 0.05$). The primary outcome evaluation in both the groups is presented in Table 3. SSI was higher in the cefazolin plus placebo group as compared to cefazolin plus azithromycin ($P = 0.03$). *E. coli* was observed in the wound culture of three patients in the cefazolin plus placebo group, whereas none of the patients in the cefazolin plus azithromycin group tested positive for the *E. coli* on wound culture. The secondary outcome evaluation between the study arms showed statistically significant differences with respect to the overall febrile morbidity ($P = 0.001$) and fever plus endometritis ($P = 0.048$). Cefazolin plus placebo group had more number of events as compared to cefazolin plus azithromycin [please see Table 4]. The UTI due to *E. coli* were significantly higher in the cefazolin plus placebo group ($P < 0.05$). The duration of the hospital stay was significantly prolonged in the cefazolin plus placebo group due to the requirement of additional antimicrobials in the post-operative period, increasing the cost burden on the patient. Upon evaluation of the neonatal outcomes, no statistically significant difference was observed between the study arms with respect to birth weight, Apgar scoring at 1 min and 5 min, neonatal sepsis, and neonatal intensive care unit (NICU) admission requirement. Neonates born to mothers in the cefazolin plus placebo group required more phototherapy as compared to those born to mothers in the cefazolin plus azithromycin group ($P < 0.004$).

Parameters that correlated with the development of SSI were duration of rupture of membranes (ROM), type of anesthesia administered, and age. Those who received general anesthesia showed a significant increase in the incidence of SSI ($P = 0.017$). The mean age and duration of rupture of membranes were significantly higher in women who developed SSI compared to those who did not developed SSI ($P < 0.005$ and $P < 0.001$ respectively). Pregnancy-registered or not, BMI, the number of vaginal examinations, urgent or nonurgent cesarean section, and duration of surgery did not affect the incidence of SSI [please see Table 5].

No women in either of the groups in our study developed allergies or showed any other side effects due to the injection of cefazolin or azithromycin.

Discussion

Research studies conducted in the western world or developed nations generally form the backbone of guidelines, which are followed or replicated as national guidelines in developing countries regardless of the ethnicity differences, drug response, or resistance issues.[10] A judicious selection of antimicrobials is the need of the hour, especially in developing countries such as India.[8] The present study is the first randomized controlled trial

Table 1: Baseline variables of the study population and pregnancy details

Parameters	Group A (*n*=100)	Group B (*n*=100)	*P*
Age (years)	27.39±3.03	26.42±2.65	0.17
Parity	2.02±1.26	2.05±1.19	0.863
BMI	25.49±3.18	24.88±2.9	0.160
Registered pregnancies	92	91	0.8
Previous cesarean	30	27	0.638
POG (weeks)	36.75±2.71	36.41±2.77	0.389
No. of vaginal examinations	1.53±1.70	1.51±1.70	0.934
Duration of rupture of membranes (hours)	4.34±4.01	4.48±3.87	0.852
Complication of pregnancy			
1. Placenta previa	10	11	0.818
2. Abruption	5	5	1
3. Breech	15	12	0.535
4. Rh isoimmunized	2	1	0.561
5. Hypothyroidism	11	7	0.323
6. Multiple pregnancy	5	4	0.733
7. HDP	27	34	0.389
8. Fetal complications (IUGR, abnormal Doppler or liquor)	25	39	0.421

Table 2: The Indications of caesarean delivery and characteristics of surgery

Indication/characteristic	Group A (*n*=100)	Group B (*n*=100)	*P*
Fetal distress	39	37	0.814
Previous cesarean delivery			
(i) Not willing for VBAC	10	10	1.0
(ii) Previous 2 cesarean	4	3	0.7
(iii) Short interconception interval	2	1	0.561
(iv) SScar dehiscence	0	2	0.155
(v) Previous CS with poor Bishop	0	1	0.316
Breech	15	12	0.535
Placenta previa	10	11	0.818
REDF/AEDF	5	5	1.0
Abruption	5	5	1.0
Other indications	10	13	0.541
Type of cesarean			
Emergency	73	71	0.753
Elective	27	29	0.753
Type of anesthesia			
Spinal	91	87	0.366
General	9	13	0.366
Approx. blood loss (cc)	391±120.06	377±114.45	0.417
Duration of surgery (hours)	1.095±0.26	1.06±0.22	0.331
Women requiring intraoperative blood transfusion (*n*)	11	15	0.4
Uterine closure in single layer	10	17	0.147
Uterine closure in double layer	90	83	0.147
Preoperative hemoglobin	11.14±1.39	10.92±1.52	0.284
Postoperative hemoglobin	10.480±1.41	10.425±1.46	0.788
Postoperative TLC	11205.00±3012.48	10189.00±2891.85	0.016*

*Indicates *P*<0.05

Table 3: The main outcome evaluation in between the study groups

Primary outcome	Group A (*n*=100)	Group B (*n*=100)	*P*
SSI	15	3	0.003*
Superficial SSI	12	3	0.016*
Deep SSI	3	0	0.081
Organ space involvement	None	None	
Wound culture sterile	9	2	0.829
Positive wound culture			
(i) *E. coli*	3	0	0.396
(ii) Acinetobacter	1	0	0.645
(iii) Klebsiella	0	1	0.356
(iv) Pseudomonas	2	0	0.502

*indicates *P*<0.05.

from a developing country evaluating the maternal and neonatal outcomes in women undergoing either planned or emergency cesarean section and receiving the single versus combination of antimicrobial agents as prophylaxis regimen.

In the present study, the overall incidence of SSI was nine percent with a statistically significant difference between the groups. Women receiving cefazolin plus placebo (15%) developed more SSI as compared to those receiving the combination of cefazolin plus azithromycin regimen (3%). The infectious morbidity in the form of fever with or without endometritis was also significantly higher in the cefazolin plus placebo group when compared to the cefazolin plus azithromycin group. Similar findings were earlier reported by Tita *et al.* from Birmingham, where the addition of azithromycin single dose to cefazolin led to a decreased number of endometritis cases from 6.1—3.8% and wound infection rate (from 6.6% to 2.4%) in a study involving more than 48,000 CDs.[11] Our study included both emergency and elective CDs and the numbers of emergency cesarean sections were more in present study than the elective cesarean sections, unlike the study by Tita *et al.*, where only elective cases of CDs were considered. The strength of the present study was that the two study arms were comparable in terms of the known risk factors of infection after the caesarean section, i.e. maternal age, BMI, duration of labor and rupture of membranes, number of vaginal examinations prior to surgery, previous scars, and comorbidity such as hypertension. The prolonged rupture of membranes and increasing number of vaginal examinations are well-recognized risk factors in the development of infectious morbidity associated with cesarean section.[8] However, in the present study, analysis of all women who developed SSI showed that nearly one-third of women had ruptured membranes for more than 12 h when compared to only 1.6% of those who did not develop SSI. Other risk factor for developing SSI in addition to these include chorioamnionitis, premature rupture of membranes, prolonged labor (particularly prolonged second stage), large incision length, subcutaneous tissue thickness more than three cm, subcutaneous hematoma, lack

Table 4: The secondary outcome evaluation in between the study groups

Secondary outcomes	Group A (*n*=100)	Group B (*n*=100)	*P*
Febrile morbidity (total)	17	3	0.001*
1. Fever alone	4	1	0.174
2. Fever + UTI + endometritis	1	0	0.316
3. Fever + endometritis + septic shock	1	0	0.316
4. Fever + endometritis	8	2	0.048*
5. Fever + SSI	3	0	0.081
Urinary tract infection			
1. Total	12	3	0.156
2. *E. coli*	6	1	0.054
3. Klebsiella	2	1	0.561
4. Pseudomonas	1	1	1.0
5. Enterococcus fecalis	3	0	0.08
Endometritis (defined by CDC)	10	2	0.015*
Microbiological pattern in cervical culture			
E. coli	4	1	0.174
Klebsiella pneumonia	4	1	0.174
Pseudomonas	2	0	0.228
Sterile	8	1	0.017*
Average Antibiotic cost (Rs)	136.25±187.52	312.40±49.85	<0.001**
Duration of hospital stay (days)	7.03±4.86	5.44±2.68	<0.001**
Requirement of additional antibiotics	26 (25+1 for incidental scabies)	9	0.002*
Neonatal outcome			
1. Birth weight (mean±SD)	2.46±0.66	2.34±0.64	0.189
2. Apgar score at 1 min	7±1	8±1	0.143
3. Apgar score at 5 min	9±0	9±0	1.0
4. Neonatal sepsis	7	5	0.552
5. Requirement of phototherapy	24	9	0.004*
6. Neonates requiring NICU admission	9	4	0.152
Microbiological pattern of neonatal sepsis	*n*=7	*n*=5	*P*
Sterile	3	2	0.921
Blood culture			
a) Burkholderia cepacia	2	1	0.735
b) Acinetobacter baumani	1	1	0.793
c) Stool culture for Clostridium difficile	1	1	0.793

* indicates *P*<0.05. **indicates *P*<0.01

Table 5: Analysis of risk factors among women with SSI vs without SSI

Risk factor	Women who developed SSI (*n*=18)	Women who did not developed SSI (*n*=182)	*P*
Unregistered pregnancy (%)	1 (5.5%)	16 (8.7%)	0.639
Age (years)	28.72±3.01	26.73±2.8	0.005*
BMI	26.37±25.07	25.07±3.04	0.088
Duration of ROM >12 h	6	3	<0.001**
No. of vaginal examination	1.33±1.28	1.54±1.74	0.539
Type of cesarean section			
(i) Emergency	14	130	0.567
(ii) Elective	4	52	
Type of anesthesia			
(i) spinal	13	165	0.017*
(ii) general	5	13	
Duration of surgery in hours	1.07±0.28	1.08±0.24	0.871

*indicates *P*<0.05. **indicates *P*<0.01

of antibiotic prophylaxis, emergency delivery, excessive blood loss, preeclampsia, and diabetes mellitus.[12]

The present study showed a significant difference in the infection rates in the women who received general anesthesia as compared to spinal anesthesia. General anesthesia is sometimes given in patients with ominous fetal distress to save time. Also, in such cesarean sections, a complete adherence to all aseptic precautions may take a back-seat, keeping in view the need for urgent fetal delivery for optimal neonatal outcomes. Tsai *et al.* compared

the odds ratio (OR) of surgical site infection within 30 days after operation with general anesthesia (GA) versus neuraxial anesthesia (NA), in Taiwanese women who had underwent CD. In more than 3 lakh Taiwanese women, the multivariate-adjusted OR of having post caesarean SSIs (up to 30 days) in the GA group was 3.73 as compared with the NA group.[13] In the present study, a majority of patients were given spinal anesthesia (91% in group A and 87% in group B), and both groups of women were comparable in this aspect. However, amongst all the women who developed SSI (of both study groups), 27.8% had received general anesthesia when compared to the 7.1% of those who were operated under spinal anesthesia, which supports the findings of Tsai *et al.* i.e. increased association of SSI with general anesthesia. Neonatal outcome evaluation in present study showed no difference in two groups except for the duration of phototherapy required. Multiple etiologies - physiological or pathological, play an important role in neonatal jaundice, one being over the counter use of antibiotics during pregnancy due to older ABCDX drug categorization diluting risk benefit assessment for primary care provider and obstetrician.[14]

The present study was planned to evaluate the efficacy of adding a single dose of broad spectrum antimicrobial—azithromycin to cefazolin as antibiotic prophylaxis—for CDs in a randomized controlled trial design. The rationale for adding another broad spectrum agent, such as metronidazole, clindamycin, or azithromycin to extend the cover is very well elucidated in the literature but sufficiently evaluated only in developed countries.[5] The broad spectrum antibiotics that have been evaluated are mainly single-agent extended-range penicillin or second or third generation cephalosporin (β-lactams) that showed no advantage. However, four RCTs compared the use of narrow-range antibiotic prophylaxis (first generation cephalosporins or ampicillin) with broad-spectrum regimens, which had an addition of agents from different classes of antibiotics such as gentamicin, metronidazole, or azithromycin. Broad-spectrum antibiotics were associated with a statistically significant reduction in infection rates, endometritis, and wound infection when compared to a narrow range.[6,15-17]

UTIs account for 40% of all nosocomial infections, and 80% of these are associated with the use of urinary catheters.[18] In the present study, all women had undergone urinary catheterization for about 24 h, as is the routine practice. There was no significant difference in the occurrence of UTI between the two groups of women, although *E. coli* was the most frequent isolate accounting for UTI in the group of women who received the cefazolin plus placebo pre-operatively. Studies are also required to confirm a change in the practice of routine urinary catheterization during the cesarean section. Though the initial cost of preoperative antibiotic was significantly more in the cefazolin plus azithromycin group, additional antibiotics were required more frequently in the cefazolin plus placebo group for various infectious/febrile morbidity indications. These antibiotics were either empirical or based on culture sensitivity reports. These additional antibiotics, along with a longer duration of stay for the women, in the cefazolin plus placebo group proved the cost-effectiveness of the addition of azithromycin. Janssen *et al.* had also reported cost effectiveness of antimicrobial prophylaxis in CDs in Orebro county.[19] The current study could not define how the use of azithromycin helps in reducing SSI. It may be possible that the azithromycin acts by extending its effect beyond the coverage of the ureaplasma organisms.

A single dose of preincision cefazolin (narrow range first-generation cephalosporin) is recommended prior to all CDs by most guidelines, and this practice is followed in different corners of the world.[2] However, a detailed analysis of the microbiology of the causative organisms and the pharmacology of the antibiotics used, instigated many institutions to add broad spectrum antibiotics with good anaerobic coverage such as metronidazole or azithromycin. The outcomes of such an evaluation can help to decide whether extended spectrum antibiotics should be added to narrow spectrum antibiotic (cefazolin) in all women undergoing cesarean section or in selected cases only. There is a need to evaluate other variables that can affect the outcomes with respect to SSI, such as surgical technique (the use of drainage of wounds or type of suture material used for closure). Finally, each hospital has the opportunity to create its own CD surgical bundle to decrease the surgical site infection.

Declaration

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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