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CLINICAL EFFECTIVENESS OF ADDING INTRAVENOUS AZITHROMYCIN TO ROUTINE ANTIMICROBIAL PROPHYLAXIS FOR PRIMIGRAVIDA IN LABOR UNDERGOING CESAREAN DELIVERY AT TERM

Obstetrics & Gynaecology

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ABSTRACT

Background: Cesarean delivery is associated with a higher risk of postoperative infectious morbidity than vaginal delivery. Standard cephalosporin prophylaxis reduces post-cesarean infection, but adjunctive azithromycin may provide broader coverage in women undergoing nonelective cesarean delivery during labor. **Methods:** This randomized controlled study included 189 primigravida women in labor undergoing term cesarean delivery. Participants received either adjunct intravenous azithromycin 500 mg with standard cephalosporin prophylaxis (n=94) or standard cephalosporin prophylaxis alone (n=95), administered within 60 minutes before skin incision. The primary outcome was postoperative wound infection within 6 weeks. Secondary outcomes included endometritis, urinary tract infection, sepsis, composite postoperative infection, drug-related adverse effects, and neonatal outcomes. **Results:** Wound infection occurred in 7/94 (7.4%) women in the adjunct azithromycin group compared with 19/95 (20.0%) in the control group (RR 0.37, 95% CI 0.16-0.84; p=0.019). Composite postoperative infection was also lower with adjunct azithromycin (7.4% vs 22.1%; RR 0.34, 95% CI 0.15-0.75; p=0.007). Endometritis (1.1% vs 9.5%; p=0.018) and postoperative fever (4.3% vs 14.7%; p=0.023) were significantly reduced. NICU admission, neonatal sepsis, birth weight and Apgar scores were comparable between groups. Nausea was more frequent in the adjunct azithromycin group, while no arrhythmia, anaphylaxis, or neonatal death was recorded. **Conclusion:** Adjunct intravenous azithromycin added to routine cephalosporin prophylaxis was associated with a significant reduction in post-cesarean wound infection and composite postoperative infection without evidence of serious maternal or neonatal adverse outcomes.

KEYWORDS

Azithromycin, Antimicrobial Prophylaxis, Cesarean Delivery, Primigravida, Surgical Site Infection, Endometritis.

INTRODUCTION:

Cesarean delivery is one of the most commonly performed obstetric operations and is associated with clinically important postoperative infectious morbidity. Compared with vaginal delivery, cesarean delivery carries a substantially higher risk of surgical site infection, endometritis, urinary tract infection, febrile morbidity and, rarely, severe maternal infectious complications such as bacteremia and sepsis (1,4). These complications increase hospital stay, readmissions, antibiotic use and health-care costs (5).

Routine pre-incision antibiotic prophylaxis with a narrow-spectrum cephalosporin is recommended for women undergoing cesarean delivery and has consistently reduced post-cesarean infectious morbidity (1). However, women undergoing cesarean delivery after onset of labor or after rupture of membranes remain at higher risk because of polymicrobial genital tract exposure. The addition of azithromycin has been proposed to broaden antimicrobial coverage against ureaplasma and other organisms that may not be adequately covered by cephalosporins alone (1,3).

Previous studies have demonstrated that adjunctive azithromycin prophylaxis reduces postoperative infection among women undergoing nonelective cesarean delivery, and observational implementation studies have suggested reductions in surgical site infection even in routine practice settings (1-4). Data from Indian tertiary-care settings are still limited, particularly among primigravida women in labor undergoing term cesarean delivery.

The present study was therefore conducted to assess the clinical effectiveness of adding single-dose intravenous azithromycin 500 mg to routine antimicrobial prophylaxis for primigravida women in labor undergoing cesarean delivery at term. The primary objective was to compare postoperative wound infection rates, and secondary objectives were to compare other serious postoperative infections, adverse drug reactions and perinatal outcomes.

Materials and methods

Study design and setting:

This randomized controlled study was conducted in the Department of Obstetrics and Gynecology, Vijayanagar Institute of Medical Sciences, Ballari, Karnataka, India. The study period was from June 2025 to June 2026. Institutional Ethics Committee approval was obtained before commencement of the study [IEC number/date to be inserted]. Written informed consent was obtained from all participants.

Study population:

Primigravida women in labor undergoing cesarean delivery at term were eligible for enrolment. Women not in labor, women with pre-existing urinary tract infection or pyelonephritis, immunosuppressed patients, women in the second stage of labor and women with clinical chorioamnionitis were excluded. The study population was divided into two groups: women receiving adjunct intravenous azithromycin with routine cephalosporin prophylaxis and women receiving routine cephalosporin prophylaxis alone.

Intervention:

All participants received routine preoperative cephalosporin prophylaxis within 60 minutes before skin incision. In the study group, a single dose of intravenous azithromycin 500 mg was added to the routine cephalosporin prophylaxis within 60 minutes before skin incision. Antibiotic redosing was considered when the procedure duration exceeded 4.5 hours or when estimated blood loss exceeded 1500 mL. In patients with severe beta-lactam allergy, clindamycin and gentamicin were planned as alternate prophylaxis according to institutional practice.

Outcomes:

The primary outcome was postoperative wound infection within 6 weeks after cesarean delivery. Secondary maternal outcomes included postoperative fever, endometritis, urinary tract infection, pyelonephritis, bacteremia, sepsis, abdominopelvic abscess, pelvic septic thrombophlebitis, pneumonia/meningitis, acute kidney injury, composite postoperative infection, hospital stay and readmission within 6 weeks. Safety outcomes included nausea, diarrhea, headache, arrhythmia, tinnitus/vertigo and anaphylaxis. Neonatal outcomes included birth weight, Apgar scores, NICU admission, neonatal sepsis, neonatal death and overall perinatal outcome.

Sample size:

The sample size was calculated using an expected postoperative infection proportion of 50%, 95% confidence level and 7.5% absolute precision. The calculated sample size was 171; after adding 10% for non-response or follow-up loss, a final sample size of 189 women was included.

Statistical analysis:

Continuous variables were summarized as mean ± standard deviation and compared between groups using the independent samples t-test. Categorical variables were summarized as frequency and percentage and compared using the chi-square test or Fisher exact test, as appropriate. Relative risk with 95% confidence interval was calculated

for key binary outcomes. A p value <0.05 was considered statistically significant.

RESULTS

Baseline demographic and obstetric characteristics:

A total of 189 primigravida women undergoing cesarean delivery at term were included. Of these, 94 women received adjunct intravenous azithromycin with standard cephalosporin prophylaxis and 95 women received standard cephalosporin prophylaxis alone. The mean age was 24.85 ± 3.39 years in the adjunct azithromycin group and 24.89 ± 3.79 years in the control group (p=0.934). Gestational age, BMI, hemoglobin, rupture-to-delivery interval, labor duration and cervical dilatation at cesarean delivery were comparable between the groups. Residence distribution differed between groups, with a higher proportion of rural participants in the adjunct azithromycin group (p=0.020). The distribution of indications for cesarean delivery was not statistically different between groups (Table I).

Intraoperative and antibiotic-related characteristics:

The mean antibiotic-to-incision interval was 36.48 ± 12.54 minutes in the adjunct azithromycin group and 38.23 ± 14.34 minutes in the control group (p=0.372). Mean surgery duration was shorter in the adjunct azithromycin group (52.89 ± 10.57 vs 56.59 ± 10.63 minutes; p=0.018). Estimated blood loss and antibiotic redosing rates were similar between groups. Intraoperative complications occurred in 8 (8.5%) and 3 (3.2%) women, respectively (p=0.133) (Table II).

Maternal postoperative infectious outcomes:

The primary outcome, wound infection within 6 weeks, occurred in 7/94 (7.4%) women in the adjunct azithromycin group and 19/95 (20.0%) women in the control group (RR 0.37, 95% CI 0.16-0.84; p=0.019). Composite postoperative infection was significantly lower in the adjunct azithromycin group (7.4% vs 22.1%; RR 0.34, 95% CI 0.15-0.75; p=0.007). Postoperative fever was also lower with adjunct azithromycin (4.3% vs 14.7%; p=0.023). Endometritis occurred in 1.1% in the adjunct group and 9.5% in the control group (p=0.018). UTI was less frequent in the adjunct group but did not reach statistical significance by Fisher exact test (0 (0.0%) vs 5 (5.3%); p=0.059). No bacteremia, abdominopelvic abscess, pelvic septic thrombophlebitis, pneumonia/meningitis or acute kidney injury was recorded in either group. Maternal outcomes are shown in Table III and Figure 1.

Safety and neonatal outcomes:

Nausea was more common in the adjunct azithromycin group (14 (14.9%) vs 2 (2.1%); p=0.001). Diarrhea, headache and tinnitus/vertigo were infrequent and did not differ significantly between groups. No arrhythmia or anaphylaxis was recorded. Birth weight (2.84 ± 0.38 vs 2.87 ± 0.39 kg; p=0.554), Apgar score at 1 minute, Apgar score at 5 minutes, NICU admission (7 (7.4%) vs 8 (8.4%); p=1.000) and neonatal sepsis (3 (3.2%) vs 1 (1.1%); p=0.368) were comparable. No neonatal death occurred in either group (Table IV and Figure 2).

DISCUSSION:

In this randomized controlled study of 189 primigravida women in labor undergoing term cesarean delivery, adjunct intravenous azithromycin added to routine cephalosporin prophylaxis was associated with significantly lower postoperative wound infection and composite postoperative infection. The absolute reduction in wound infection was 12.6%, corresponding to an approximate number needed to treat of 8. The reduction in composite postoperative infection was 14.7%.

The findings are biologically plausible because cesarean delivery after labor or membrane rupture is associated with polymicrobial exposure from the lower genital tract. Standard cephalosporin prophylaxis provides important coverage, but adjunct azithromycin may broaden activity against organisms implicated in post-cesarean endometritis and wound infection (1,3). The present results are consistent with previous studies showing lower post-cesarean infectious morbidity when azithromycin is added to standard prophylaxis (1-4).

The reduction in endometritis and febrile morbidity in the adjunct azithromycin group supports the clinical relevance of expanded prophylaxis. Although urinary tract infection was numerically lower in the adjunct group, this difference did not reach statistical significance by Fisher exact test, probably because of the small number of events. Severe maternal complications such as sepsis, bacteremia, abdominopelvic abscess and acute kidney injury were rare or absent, limiting interpretation for these outcomes.

There was no significant difference in birth weight, Apgar scores, NICU admission or neonatal sepsis, and no neonatal death was observed. These findings support the short-term neonatal safety of a single pre-incision maternal dose, although larger studies with longer follow-up are required to evaluate rare neonatal outcomes and microbiome-related effects.

Nausea was significantly more frequent in the adjunct azithromycin group, but serious drug-related adverse events were not observed. No arrhythmia, anaphylaxis or neonatal death was recorded. Thus, the maternal tolerability profile was acceptable, but clinicians should remain vigilant for gastrointestinal intolerance and rare hypersensitivity reactions.

The study has limitations. First, it was a single-centre study and the findings may not be generalizable to all obstetric settings. Second, some rare secondary outcomes were underpowered because event rates were low. Third, residence distribution differed between groups, indicating a baseline imbalance despite random allocation; this should be considered while interpreting the findings.

In conclusion, adjunct intravenous azithromycin 500 mg given with routine cephalosporin prophylaxis within 60 minutes before cesarean skin incision significantly reduced postoperative wound infection and composite postoperative infection among primigravida women in labor undergoing term cesarean delivery. The intervention was not associated with serious maternal or neonatal adverse outcomes.

Conflict of Interest:

All authors declare no conflict of interest.

Funding:

Nil.

Table I: Baseline demographic and obstetric characteristics of the study groups.

Variables	Adjunct azithromycin (n=94)	Control (n=95)	p value
Age (years)	24.85 ± 3.39	24.89 ± 3.79	0.934
Gestational age (weeks)	39.09 ± 1.03	39.04 ± 0.88	0.718
BMI (kg/m²)	25.62 ± 2.76	25.26 ± 2.80	0.375
Hemoglobin (g/dL)	10.91 ± 1.12	10.85 ± 1.05	0.674
Residence			0.020
Rural	55 (58.5%)	39 (41.1%)	
Urban	39 (41.5%)	56 (58.9%)	
Booking status			0.426
Booked	64 (68.1%)	70 (73.7%)	
Unbooked	30 (31.9%)	25 (26.3%)	
Socioeconomic status			0.801
Lower	30 (31.9%)	34 (35.8%)	
Lower-middle	51 (54.3%)	47 (49.5%)	
Middle	13 (13.8%)	14 (14.7%)	
Membrane status			0.161
Intact	41 (43.6%)	29 (30.5%)	
Ruptured <4 h	22 (23.4%)	30 (31.6%)	
Ruptured ≥4 h	31 (33.0%)	36 (37.9%)	
Rupture-to-delivery interval (h)	4.41 ± 5.65	4.86 ± 5.53	0.579
Labor duration (h)	8.12 ± 2.93	8.20 ± 2.79	0.842
Cervical dilatation at CS (cm)	5.67 ± 1.51	5.37 ± 1.40	0.163
Preoperative temperature (°C)	37.07 ± 0.26	36.99 ± 0.22	0.016
Indication for cesarean delivery			0.409
Cephalopelvic disproportion	18 (19.1%)	24 (25.3%)	
Failed induction/failed progress	12 (12.8%)	16 (16.8%)	

Fetal distress	21 (22.3%)	25 (26.3%)	
Malpresentation	4 (4.3%)	5 (5.3%)	
Meconium-stained liquor	17 (18.1%)	12 (12.6%)	
Non-progress of labor	22 (23.4%)	13 (13.7%)	

Data are shown as mean ± SD or n (%). BMI: body mass index; CS: cesarean section.

Table II: Intraoperative and antibiotic-related characteristics.

Variables	Adjunct azithromycin (n=94)	Control (n=95)	p value
Antibiotic-to-incision interval (min)	36.48 ± 12.54	38.23 ± 14.34	0.372
Skin incision-to-delivery interval (min)	8.35 ± 2.28	7.64 ± 2.26	0.033
Surgery duration (min)	52.89 ± 10.57	56.59 ± 10.63	0.018
Estimated blood loss (mL)	634.89 ± 167.75	644.32 ± 131.95	0.669
Antibiotic redosing required	2 (2.1%)	2 (2.1%)	1.000
Intraoperative complication	8 (8.5%)	3 (3.2%)	0.133

Data are shown as mean ± SD or n (%).

Table III: Maternal postoperative infectious outcomes.

Variables	Adjunct azithromycin (n=94)	Control (n=95)	p value
Postoperative fever	4 (4.3%)	14 (14.7%)	0.023
Wound infection within 6 weeks	7 (7.4%)	19 (20.0%)	0.019
Composite postoperative infection	7 (7.4%)	21 (22.1%)	0.007
Endometritis	1 (1.1%)	9 (9.5%)	0.018
Urinary tract infection	0 (0.0%)	5 (5.3%)	0.059
Pyelonephritis	1 (1.1%)	0 (0.0%)	0.497
Maternal sepsis	0 (0.0%)	1 (1.1%)	1.000
Readmission within 6 weeks	2 (2.1%)	3 (3.2%)	1.000
6-week follow-up completed	93 (98.9%)	89 (93.7%)	0.118
SSI type			0.022
None	87 (92.6%)	76 (80.0%)	
Superficial incisional	7 (7.4%)	15 (15.8%)	
Deep incisional	0 (0.0%)	4 (4.2%)	
Hospital stay (days)	5.10 ± 1.06	5.31 ± 1.08	0.180

Composite postoperative infection includes wound infection, endometritis, UTI, pyelonephritis, bacteremia, sepsis, abscess, septic thrombophlebitis, pneumonia/meningitis or AKI. SSI: surgical site infection.

Table IV: Adverse drug effects and neonatal outcomes.

Variables	Adjunct azithromycin (n=94)	Control (n=95)	p value
Nausea	14 (14.9%)	2 (2.1%)	0.001
Diarrhea	5 (5.3%)	1 (1.1%)	0.118
Headache	4 (4.3%)	3 (3.2%)	0.721
Arrhythmia	0 (0.0%)	0 (0.0%)	NA
Tinnitus/vertigo	2 (2.1%)	1 (1.1%)	0.621
Anaphylaxis	0 (0.0%)	0 (0.0%)	NA
Birth weight (kg)	2.84 ± 0.38	2.87 ± 0.39	0.554
Apgar score at 1 min	7.18 ± 0.84	7.33 ± 0.95	0.267
Apgar score at 5 min	8.91 ± 0.70	9.03 ± 0.63	0.228
NICU admission	7 (7.4%)	8 (8.4%)	1.000
Neonatal sepsis	3 (3.2%)	1 (1.1%)	0.368
Neonatal death	0 (0.0%)	0 (0.0%)	NA
Perinatal outcome			0.581
Healthy live birth	84 (89.4%)	86 (90.5%)	
NICU admission	7 (7.4%)	8 (8.4%)	
Neonatal sepsis	3 (3.2%)	1 (1.1%)	

Data are shown as mean ± SD or n (%). NICU: neonatal intensive care unit.

Figure 1:

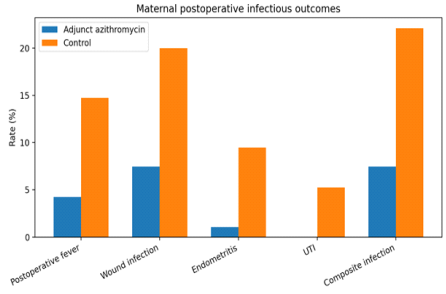

Figure 1: Rates of maternal postoperative infectious outcomes in the adjunct azithromycin and control groups. Wound infection, postoperative fever, endometritis and composite postoperative infection were lower in the adjunct azithromycin group.

Figure 2:

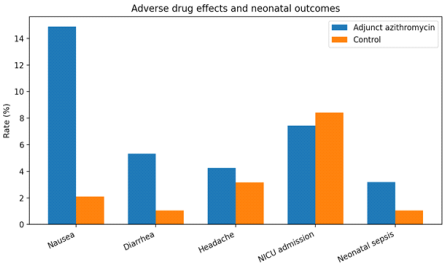

Figure 2: Rates of adverse drug effects and neonatal outcomes in the adjunct azithromycin and control groups. Nausea was more frequent with adjunct azithromycin, while neonatal outcomes were comparable.

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