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Original Research Article

Safety and efficacy of adding single dose adjunctive azithromycin prophylaxis for emergency cesarean delivery

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Abstract

Background: Cesarean sections are on the rise globally, with a higher risk of surgical site infections compared to vaginal deliveries. Recent research suggests adding azithromycin to standard antibiotic prophylaxis may help reduce post-cesarean infections. However, a more comprehensive study is needed to evaluate the safety and efficacy of this approach in emergency cesarean sections.

Materials and Methods: In this randomized prospective observational study, 520 pregnant women at ≥28 weeks gestation underwent emergency cesarean section at B.M. Patil Medical College and Research Centre, Vijayapura. They were split into two groups: Group A received azithromycin and standard cephalosporin prophylaxis, while Group B received only ceftriaxone. Exclusion criteria and medical assessments were conducted, and Group A received intravenous azithromycin before the procedure. Post-operative monitoring continued for six weeks, and statistical analysis was performed using JMP-SAS Software.

Results: Group A had lower postoperative complication rates than Group B. Group A had 1.5% abnormal cases on the 7th-day follow-up versus 4.6% in Group B (p=0.041). By the 14th day, Group A had 1.14% abnormal cases compared to 3.8% in Group B (p=0.023). Group A also showed lower rates of induration (18.6% vs 29.9%), erythema (10.6% vs 20.3%), NICU admission (7.98% vs 14.2%), and secondary suturing (1.14% vs 3.8%). The mean hospital stay was slightly shorter in Group A (7.67 days vs 7.75 days) but not statistically significant (p=0.477).

Conclusion: Adding azithromycin before a cesarean section can improve postoperative outcomes and reduce NICU admissions, but decision-making should be guided by local protocols and individual patient factors.

Keywords: Azithromycin, Ceftriaxone, Postoperative complications, Post-cesarean infections.

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1. Introduction

Cesarean sections (C-sections) are the most commonly performed surgery for childbirth worldwide, with rates steadily increasing over the past few decades. In India, C-sections rose from 17.2% to 21.5% between 2016 and 2021,[1] reflecting a global trend that has seen cesarean rates climb from 7% in 1990 to 21% today. This surge surpasses the World Health Organization's recommended rate of 10-15% and is projected to reach 29% by 2030.[2]

While C-sections can be lifesaving for both mother and child in certain circumstances, they also carry risks, including a higher rate of surgical site infections (SSI) compared to vaginal deliveries.[3,4] SSIs are a significant concern, particularly in emergency cesarean sections, with a prevalence of 5-10% in India. These infections can lead to extended hospital stays, reduced quality of life, and, in severe cases, sepsis and maternal mortality.[5]

Antibiotic prophylaxis has been a standard practice to prevent SSIs in cesarean deliveries.[6] Traditionally, first-generation cephalosporins have been the recommended prophylactic agents. However, recent research has explored the potential benefits of adding azithromycin, a macrolide antibiotic, to the standard prophylactic regimen.[7] The effectiveness of this prophylactic has been attributed to its ability to provide coverage against Ureaplasma species, often linked to infections after cesarean delivery. In September 2018, the American College of Obstetricians and

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Gynecologists (ACOG) approved the inclusion of azithromycin in the standard antibiotic treatment for non-elective C-sections.[8-10]

Emergency cesarean deliveries, with their higher risk of post-operative infection compared to vaginal deliveries, underscore the need for impactful research.[11] Standard care involves administering prophylactic antibiotics like cefazolin before surgery, but post-cesarean infections like wound infection, endometritis, and urinary tract infections persist.[12] Azithromycin, a broad-spectrum macrolide antibiotic, has shown efficacy in reducing infectious complications when combined with standard prophylactic antibiotic regimens.[13] However, existing evidence has limitations, including small sample sizes and varying dosing regimens. A randomised controlled trial is needed to evaluate the safety and efficacy of adding a single dose of azithromycin, with the potential to impact post-cesarean infection rates significantly. Hence, we undertook this study to assess whether adding azithromycin to standard antibiotic prophylaxis before skin incision would reduce the incidence of surgical site infection after cesarean section.

2. Materials and Methods

This randomized prospective observational study was conducted in the Department of Obstetrics and Gynaecology of B.M. Patil Medical College and Research Centre, Vijayapura. The research included 520 pregnant women with singleton pregnancies and gestational age of 28 weeks or more who were experiencing labour and seeking care at the Department of Obstetrics and Gynaecology, as long as they expressed a willingness to participate. They satisfied the specified inclusion and exclusion criteria. The inclusion criteria were carefully chosen to ensure that the study focused on pregnant women who were most likely to benefit from the administration of azithromycin. In contrast, the exclusion criteria were designed to minimise potential risks and ensure patient safety.

2.1. Inclusion criteria

1. Singleton pregnancy,
2. Gestational age of 28 weeks or more,
3. Patients undergoing emergency cesarean section
4. After membrane rupture within 12 hours or premature rupture of membranes (PROM).

2.2. Exclusion criteria

1. Patients who are unable to provide consent.
2. Known allergy to azithromycin.
3. Use of azithromycin within seven days before randomisation.
4. Chorioamnionitis, fever, urinary tract infection requiring antibiotic treatment.
5. Liver diseases, serum creatinine level exceeding 2.0mg/dl.
6. Patients in need of dialysis.
7. Cardiomyopathy, pulmonary oedema, known case of electrolyte abnormalities.
8. Pre-eclampsia, or premature rupture of membranes lasting more than 12 hours.

Criteria-satisfied patients were divided into groups A and B: Group A received azithromycin as an adjunctive therapy, and Group B received ceftriaxone along with NS as a placebo therapy.

The data collection methodology was meticulously designed, Randomisation done by Computer-based randomisation underscoring the research process's thoroughness and attention to detail. This involved providing patients with a detailed explanation of the research and obtaining written consent. Initial assessments included Complete Blood Count, Peripheral Blood Smear, Random Blood Sugar, HIV test, HBsAg test, Urine routine, and Obstetric U.S.G. Additional investigations were carried out based on suspected medical issues. Each patient was given a predefined medical treatment plan based on their diagnosis, ensuring a comprehensive and reliable data collection process.

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A comprehensive medical history and examination were conducted upon admission to the hospital. After deciding to perform an emergency cesarean section, patients were prepared and given a single dose of intravenous azithromycin in addition to standard cephalosporin prophylaxis. A combination of ceftriaxone and intravenous azithromycin was administered within 30 to 60 minutes before making skin incisions. After childbirth, patients were closely followed up for six weeks to detect conditions such as endometritis, wound infection like erythema, wound discharge, cellulitis of skin, redness, sepsis, fever, and more. The infants were also carefully monitored to promptly identify any issues and ensure the safety and well-being of the patients throughout the study.

Advanced statistical analysis was conducted using JMP-SAS Software, a powerful tool that ensures the accuracy and reliability of the study's findings. Results were presented as mean ± S.D., counts and percentages, and graphs. An independent t-test was used to compare normally distributed continuous variables between two groups, while Chi-square tests were used to compare categorical variables. A p-value less than 0.05 was considered statistically significant, demonstrating the scientific rigor and reliability of the study's findings.

3. Results

The study compared two groups of patients undergoing cesarean sections: Group A, which received azithromycin as an adjunctive therapy along with routine antibiotics, and Group B, which received ceftriaxone along with Normal saline as placebo therapy. Both groups showed similar age distribution, with most participants falling within the 21-25- and 26-30-year age ranges. The ceftriaxone group had a slightly higher percentage of participants below 37 weeks gestational age, but this difference was not statistically significant. Gravida distribution was similar between the groups, with first-time pregnancies accounting for 40.68% in the azithromycin adjunctive group and 32.6% in the ceftriaxone group. The most common complaint in both groups was abdominal pain, with 70.3% reporting it in the azithromycin adjunctive group and 69.3% in the ceftriaxone group. Other complaints, such as vaginal leakage and bleeding, were also similar. Both groups were composed mainly of full-term pregnancies, with the ceftriaxone group showing a slightly higher percentage of preterm pregnancies. Hemoglobin levels were also comparable between the groups.

Group B consistently shows a higher prevalence of symptoms across almost all categories, especially in inflammatory responses. For example, 29.9% in Group B experience induration compared to 18.6% in Group A, and 20.3% of Group B show erythema compared to 10.6% of Group A. Wound-related issues also occur more frequently in Group B, such as higher rates of gaping (4.2% vs 2.7%) and wound discharge (5% vs 1.5%). Minimal differences are observed in fever and rashes between both groups. In Group A, only 3 cases (1.14%) required secondary suturing, while the majority, 260 cases (98.86%), did not. Group B showed a higher incidence of secondary suturing, with 10 cases (3.8%) requiring the procedure and 251 cases (96.2%) not needing it. (**Table 2**)

During the first follow-up on the third day, Group A and Group B showed 100% expected results with no abnormal cases observed. In the first week, a significant difference was seen, with Group A having 98.5% normal cases and Group B having 98.4% normal and 4.6% abnormal cases. The second week showed Group A with 98.86% normal cases and Group B with 96.62% normal and 3.8% abnormal cases. Both groups returned to 100% of the expected results in the sixth week, indicating strong reliability. (**Table 3**)

Table 1: Demographic data, complaints, the gestation period of pregnancy, and haemoglobin levels of the study population

	Azithromycin adjunctive Group A (Cases)	**Ceftriaxone Group B (Controls)**	**p-value**
Age (yrs)			0.295
< 20	17 (6.5)	19 (7.3)	
21-25	133 (50.6)	127 (48.7)	
26-30	79 (30)	75 (28.7)	
31-35	22 (8.4)	34 (13)	
> 35	12 (4.6)	6 (2.3)	
Gestational Age			0.407
< 37 Weeks	45 (17.11)	52 (20.1)	
> 37 Weeks	218 (82.89)	209 (79.9)	
Gravida			0.492
G1	107 (40.68)	85 (32.6)	
G2	80 (30.42)	92 (35.2)	
G3	55 (20.91)	56 (21.4)	
G4	15 (5.70)	20 (7.6)	
G5	5 (1.90)	5 (2)	
G6	1 (0.38)	2 (0.8)	
G7	0	1 (0.4)	
Complaints			0.506
Pain Abdomen	185 (70.3)	181 (69.3)	
Pain Abdomen, PV Leak	22 (8.4)	20 (7.7)	
PV Bleed	3 (1.1)	5 (1.9)	
PV Leak	17 (6.5)	25 (9.6)	
Decreased Fetal Movements	2 (0.8)	0	
Oligohydramnios	1 (0.38)	0	
Safe Confinement	33 (12.5)	30 (11.5)	
Term			0.269
Full Term	225 (85.6)	214 (82)	
Preterm	38 (14.4)	47 (18)	
Haemoglobin	11.12±1.26	11.17±1.23	0.383

Table 2: Comparison of the maternal outcomes between Group A and Group B

Maternal Outcome	Group A	Group B	p-value
Fever	2 (0.8)	5 (1.9)	0.249
Rashes	0 (0)	1 (0.4)	0.315
PV discharge	0 (0)	0 (0)	-
Erythema	28 (10.6)	53 (20.3)	0.002
Induration	49 (18.6)	78 (29.9)	0.003
Gaping	7 (2.7)	11 (4.2)	0.329
Wound discharge	4 (11.5)	13 (5)	0.025
Secondary suturing	3 (1.14)	10 (3.8)	0.048

Table 3: Comparison of normal and abnormal findings in Group A and Group B across different follow-up periods

	Group A	Group B	p-value
1st Followup 3rd day			
Normal	263 (100)	261 (100)	-
Abnormal	0	0	
2nd Followup 7th day			
Normal	259 (98.5)	249 (98.4)	0.041
Abnormal	4 (1.5)	12 (4.6)	
3rd Followup 14th day			
Normal	260 (98.86)	251 (96.62)	0.023
Abnormal	3 (1.14)	10 (3.8)	
4th Followup 6th week			
Normal	263 (100)	261 (100)	-
Abnormal	0	0	

Table 4: Duration of hospital stays between Group A and Group B

Duration of Stay (Days)	Group A	Group B
Mean	7.67	7.75
SD	1.98	3.31
p-value	0.477	

Table 5: Comparison of the maternal outcomes between Group A and Group B

Neonatal outcome	Group A	Group B	p-value
Fetal Sex			
Male	150 (57.03)	137 (52.5)	0.296
Female	113 (42.97)	124 (47.5)	
Fetal Weight	2.75±0.45	2.67±0.51	0.041
NICU Admission	21 (7.98)	37 (14.2)	0.024

The duration of hospital stays between Group A and Group B, Group A had a mean stay of 7.67 days, while Group B had a slightly longer mean stay of 7.75 days but a higher standard deviation of 3.31 days. The p-value for this comparison is 0.477, indicating that the difference in duration is not statistically significant. (**Table 4**)

In Group A, 57.03% are male fetuses, and 42.97% are female. In Group B, 52.5% are male and 47.5% are female. Group A has a slightly higher proportion of male fetuses, while Group B shows a more even distribution. Group A's mean fetal weight is 2.75, slightly higher than Group B's 2.67, with a difference of 0.08 units. The graph visually emphasizes this difference, suggesting that fetuses in Group A are heavier. In Group A, 7.98% of cases resulted in NICU admission, while 92.02% did not require NICU care. Group B showed a higher rate of NICU admissions, with 14.2% of

cases requiring NICU care and 85.8% not needing admission (**Table 5**).

4. Discussion

The current standard care involves administering prophylactic antibiotics, such as cefazolin, before surgical incision. However, after a cesarean section, infectious morbidities such as wound infections, endometritis, and urinary tract infections continue to occur. Azithromycin, a broad-spectrum macrolide antibiotic, effectively reduces infectious complications when combined with standard prophylactic antibiotic regimens.

The present study and Tita ATN et al.'s[3] research on azithromycin's effectiveness in preventing post-cesarean infections found similar results, suggesting that azithromycin significantly reduces endometritis and wound infections, irrespective of population and study design.

Pierce et al.[14] and Huang D et al.[15] found that the average maternal age for cases is 30.0 years, slightly lower than the 30.4 years for controls. Similarly, in our study, cases have an average maternal age of 24.5 years, compared to 24.8 years for controls. Our study's younger mean maternal age could reflect a population with different reproductive behaviours, possibly due to cultural, social, or economic factors. The differences in maternal age may be due to demographic variations, potentially affecting the generalizability of the findings to other populations with varying maternal age distributions and cultural practices, including early age at marriage.

Huang et al.'s[15] study found that most Group A and Group B participants were in their first pregnancy, with percentages decreasing as the number of pregnancies increased. Our study showed fewer cases and controls in G1, with higher percentages in G2 and G3. Both studies did not show statistically significant differences in pregnancy distributions, possibly due to demographic variations or selection criteria.

Our research and studies by Lingam KR et al.[16] and Huang D et al.[15] revealed consistent patterns and differences in cesarean section indications. Breech presentation prevalence ranges from 2.5% to 4.5% across populations. Our study found that 3.42% of Group A and 2.68% of Group B had a breech presentation. Additionally, 11.4% of Group A and 19.92% of Group B experienced fetal distress, differing from Huang D et al.'s[15] findings. These variations may prompt changes and further research to improve patient care. Also, our study observed a higher prevalence of cephalopelvic disproportion (CPD) in both groups compared to the findings of Lingam KR et al.[16] and Huang D et al.[15]

Our study shows notable differences in cesarean section indications compared to the research by Lingam KR et al.[16] and Huang D et al.[15] While the incidence of failed induction is relatively similar across all studies, our research reports a slightly lower percentage of controls (6.13%) experiencing this outcome. This difference could be due to variations in induction protocols or patient characteristics.

Our study shows a significantly higher prevalence, with 40.4% of cases and 27.20% of controls having had a prior cesarean, compared to lower rates in the other studies by Lingam KR et al.[16] and Huang D et al.[15] The significant increase indicates a higher incidence of C-sections among our participants, potentially influenced by factors like maternal age, parity, and specific obstetric complications prevalent in our population.

Furthermore, our study reports that 27.2% of cases had a history of two previous C-sections, a rate higher than those found by Lingam KR et al.[16] and Huang D et al.[15] This trend indicates that our study population may have a greater tendency towards repeat C-sections, highlighting a potential area for targeted intervention and management.

Our study found mean haemoglobin levels of 11.2 ± 12.6 g/l for cases and 11.7 ± 12.3 g/l for controls. Huang D et al.[15] found that the mean haemoglobin level for cases is 13.0 ± 12.7 g/l, and for controls, it is 12.8 ± 12.2 g/l. Both studies show minimal differences in haemoglobin levels between cases and controls, indicating consistent outcomes across different populations.

Our study shows significantly lower fever occurrence in cases (0.8%) than in controls (1.9%), indicating consistent fever rates across groups. Lingam KR et al.[16] found similar post-operative fever rates in both cases (4.42%) and controls (4.12%). The lower incidence in our study, especially among cases, may point to the added advantage of azithromycin reducing postoperative infections.

Our study found lower rates of hospital stays (7.67 days for cases, 7.75 days for controls) than Lingam KR et al.'s study.[16] Our secondary suturing rates were also lower (1.14% for cases, 3.8% for controls) compared to Lingam KR et al.[16]

The results demonstrated significantly improved postoperative outcomes in group A, including lower rates of postoperative symptoms, abnormal follow-up findings, NICU admissions, and secondary suturing. These findings suggest that incorporating azithromycin into the antibiotic prophylaxis regimen may help reduce postoperative morbidity and enhance maternal and neonatal outcomes. While promising, these results require further research to confirm their validity and assess generalizability across diverse populations and healthcare settings. This study contributes to the growing evidence supporting expanded antibiotic prophylaxis in emergency cesarean sections and highlights the potential benefits of including azithromycin in clinical practice. However, implementation should be subject to additional validation and careful consideration of local guidelines and patient-specific factors.

5. Conclusion

Adding azithromycin to standard antibiotic prophylaxis for emergency cesarean sections significantly improved postoperative outcomes, reducing complications and NICU admissions. This study contributes to growing evidence supporting expanded antibiotic prophylaxis in cesarean deliveries. While promising, the implementation should consider local guidelines and patient-specific factors. Further research is needed to validate these findings and assess their broader applicability across diverse populations and healthcare settings.

6. Source of Funding

None.

7. Conflict of Interest

None.

8. Ethical Committee Approval

Ethical committee approval was obtained. BLDE (DU)/IEC/767/2022-2023.

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