journal of
contemporary
pharmacy practice

evidence-based medicine review

Published online: December, 2017

Adjunctive Azithromycin Prophylaxis for Cesarean Delivery

Genene Salman, PharmD, BCPS, BCCCP, CNSC; Henry Hua, PhD;
Noelle de Leon, PharmD, BCPS, BCCCP; LaDonna Oelschlaeger, PharmD, BCPS

• Patient population: 2,013 women were pregnant with one child for ≥ 24 weeks and underwent unplanned cesarean section.

• Intervention: 1,019 women received azithromycin 500 mg intravenously plus standard antibiotic prophylaxis (cefazolin) or the alternative antibiotic prophylaxis (clindamycin ± gentamicin) in the case of penicillin allergy.

• Comparison: 994 women received the standard or alternative antibiotic prophylaxis and a saline placebo.

• Outcome: The primary outcome was a composite of maternal postoperative infections with a follow-up period of 6 weeks; secondary outcomes included neonatal death and serious neonatal complications until 3 months of age and maternal adverse events occurring within 6 weeks.

Trial Validity	**Risk of Bias**		
Start of Trial	**High**	**Possible / Unclear**	**Low**
Randomization / Concealment			
• Patients were randomized in a 1:1 manner via a computer-generated block-designed system, which stratified patients by site. The computer-generated block-designed concealment minimized the introduction of bias.			**X**
Baseline Characteristics			
• Baseline characteristics including age, body-mass index, diagnosis of gestational diabetes mellitus and chronic hypertension, and use of alcohol and illegal substances were comparable between azithromycin and placebo groups. • The azithromycin and placebo groups had similar characteristics relating to the cesarean procedures, including primary indication for cesarean delivery, receipt of standard antibiotic prophylaxis, and timing of the study-drug administration. • The placebo group consisted of greater percentage of patients who smoked during pregnancy than the azithromycin group (12.3% vs. 9.5%; p=0.047). Smoking during pregnancy may be linked to a wide range of complications, potentially biasing the placebo group for worse outcomes than the azithromycin group. In addition, the degree of smoking was not mentioned. • The study represented a diverse population spanning 14 hospitals across the United States. There were a similar number of non-Hispanic black (34%) and white (35%) women, in comparison to Hispanic women (20%) and those categorized as others (10%). On average, the women were 28 years old and had a body-mass index of approximately 35 kg/m^2.		**X**	

Trial Validity	Risk of Bias		
During Trial	**High**	**Possible / Unclear**	**Low**
Blinding			
• The patients, clinical research staff, outcome assessors, data collectors, and analysts were unaware of the treatment assignments throughout the study. However, the investigational pharmacists involved in the preparation of azithromycin were able to view the identity of the patients' treatment assignments via a secure website.			X
Equal Treatment			
• Azithromycin is available by prescription. The open-label use of azithromycin was not explicitly stated. • Patients receiving antimicrobial therapy for reasons other than group B streptococcus were excluded, reducing the likelihood of unequal treatment between the groups. The percentage of patients who tested positive for group B streptococcus was found to be similar between the groups. However, since the exact percentage of patients who received antibiotics for group B streptococcus and the identity of medications were not disclosed, bias may have been introduced. The impact of this bias is unknown. • According to the study protocol, supplemental doses of cefazolin to patients who were morbidly obese or who had significant hemorrhage may have been given at the discretion of the clinician. Details of any dose variations may have been helpful to show homogeneity of dosing between the groups, but this information was not provided. Thus, differences in clinician dosing may have resulted in unequal treatment, and the direction of bias is unclear. • Additionally, the alternative antibiotics (clindamycin alone or in combination with gentamicin) were given to patients with a penicillin allergy. Gentamicin is an antibiotic with a broader spectrum of coverage in comparison to cefazolin and may have enhanced the treatment. Since it was not clear how many patients received this alternative treatment and if it was evenly distributed between the two groups, there may be the possibility that the study groups were not treated equally. However, the direction of this bias is uncertain.		X	

Trial Validity	Risk of Bias		
End of Trial	**High**	**Possible / Unclear**	**Low**
Completeness of Outcome Date			
• The total percentage of mothers who did not follow up at 6 weeks was 2.6% (52 out of 2,013), while the total percentage of infants who were not evaluated at the 3-month follow-up was 5.4% (109 out of 2,013). The percentage of mothers and infants that did not complete the trial was similar between the two groups. • Of the 52 mothers who did not complete the trial at 6 weeks, 25 (2.6%) were from the azithromycin group, and 27 (2.7%) were from the placebo group. Of the 109 infants who did not reach the 3-month child follow-up, 54 (5.3%) were from the azithromycin group, and 55 (5.5%) were from the placebo group. • Comparing the total percentage of mothers who were lost to follow-up within 6 weeks (2.6%) to the absolute risk reduction of the primary composite outcome (5.9%), the primary composite outcome is not likely to be affected by the incomplete data. However, since the absolute risk increase in maternal gastrointestinal (GI) symptoms (1.3%) was lower than the total percentage of mothers lost to follow-up (2.6%), the results may be skewed with an unknown direction. • The total percentage of infants lost to follow-up (5.4%) was greater than the absolute risk increase in neonatal respiratory distress (0.8%) at 3 months, resulting in a possibility that the results may be distorted due to the missing data.		**X**	
Method of Outcome Analysis			
• The intention-to-treat analysis was utilized to determine the primary and secondary outcomes. This method of analysis prevents the bias that may arise when patients do not complete the study.			**X**

Trial Results							
Efficacy Outcome	[Azithromycin + Standard Antibiotic Prophylaxis] N=1019	[Standard Antibiotic Prophylaxis] N=994	Relative Risk (RR) and 95% Confidence Interval	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	P-value	Number Needed to Treat (NNT)
Primary Composite Outcome[1]	62 (6.1%)	119 (12.0%)	RR 0.51 (0.38-0.68)	49%	5.9%	<0.001	NNT= 17

[1]The primary composite outcome consisted of endometritis, wound infection, which included necrotizing fasciitis and deep wound infection, and other infections such as abdominal or pelvic abscess, septic pelvic thrombophlebitis, maternal sepsis, pyelonephritis, pneumonia, and meningitis. The azithromycin group had a significantly lower rate of endometritis as compared to placebo (3.8% vs. 6.1%; p=0.02) as well as wound infection (2.4% vs. 6.6%; p<0.001). The primary composite outcome was based on the number of patients who were found to have one or more infections. Accordingly, one patient who had multiple infections would still be counted as one outcome occurrence.

Adverse Events	Azithromycin Group N=1019	Placebo Group N=994	Absolute Risk Increase (ARI)	p-value
Neonatal complication: respiratory distress syndrome[2]	42 (4.1%)	33 (3.3%)	0.8%	0.34
Maternal GI symptoms[3] (any vomiting, diarrhea, or ileus)	79 (7.8%)	64 (6.4%)	1.3%	0.25

[2]Respiratory distress syndrome was a component of the composite neonatal complications and was not significantly different between the two groups. [3]The occurrence of maternal GI symptoms was a component of other/individual maternal adverse events composite outcome.

All maternal serious adverse events were a secondary composite outcome, which included maternal death, severe maternal allergic reaction, any adverse event with discontinued study medication, pulmonary embolism, intensive care unit admission, and cardiac events. The secondary composite outcome of all maternal serious adverse events was significantly lower in the azithromycin group (1.5%) versus placebo (2.9%) (p=0.03).

Trial Applicability

Patient Applicability

• The results of this study would be applicable to women who are pregnant with one child for 24 weeks or greater and are undergoing an unplanned cesarean delivery. This study would not apply to women pregnant with more than one child or with a scheduled cesarean section. Further, patients with co-morbid conditions such as severe liver dysfunction, renal dysfunction, and cardiac abnormalities did not participate in this trial.

• Extended-spectrum prophylaxis with azithromycin would broaden coverage to ureaplasma organisms compared to standard antibiotic prophylaxis regimens. Since culture results of ureaplasma from the infected patients were not reported, it is unclear if all patients matching the study's eligibility criteria should be assumed to carry ureaplasma as part of their lower genital tract flora or if clinicians should further streamline therapy based on history and risk factors.

Intervention Applicability

• Azithromycin is a Category B extended-spectrum antibiotic used to treat many infections and is available in oral and intravenous routes by prescription at an affordable cost.

• The standard antibiotic prophylaxis regimens are commonly used preoperatively in practice.

Patient-Important Outcomes Measured

• The primary and secondary outcomes were clinical endpoints that were relevant and essential for understanding the clinical implications of patients undergoing non-elective cesarean section. Tita et al. reported results of the overall composite outcomes as well as the corresponding components. For a detailed description of the composite outcomes and the criteria clinicians used to make their diagnosis, it is recommended to refer to the study and the supplementary appendix.

• The determination of the primary composite outcome was based on the number of infected post-partum patients, instead of the total of number of infections. (Some patients may have had multiple infections.) It is unclear if counting the total number of infections would have any bearing on the results. Similarly, secondary composite outcomes were based on the number of patients experiencing adverse event(s) or complication(s). It is unknown if a different approach to reporting the secondary composite outcome would affect the results.

• Azithromycin has been associated with cardiovascular adverse effects, including QTc prolongation and ventricular arrhythmias. The results did not show an increase in cardiac events, and patients with a history of arrhythmias or cardiomyopathy were excluded from the study.

Balance of Benefits vs. Harms

• Azithromycin is a widely used antibiotic for multiple infections and is generally well tolerated. This study demonstrated that adjunctive azithromycin for unscheduled cesarean delivery resulted in an absolute reduction in risk of overall postoperative infection rate (absolute risk reduction; ARR 5.9%), which is clinically as well as statistically significant (p <0.001).

• Azithromycin appears to have a good safety profile in both the mothers as well as the infants. The secondary composite outcome which included neonatal death and complications at 3 months was similar between the study groups azithromycin group (14.3%) versus placebo (13.6%) with an absolute risk difference of 0.7% (p=0.63). Further, the women receiving adjunctive azithromycin had fewer serious adverse events (1.5%) at 6 weeks compared to placebo (2.9%) with an absolute risk difference of 1.4% (p =0.03). However, since a large number of the mothers and infants did not follow up as directed, these secondary outcomes may be skewed.

• If 1000 patients undergoing non-elective cesarean delivery were treated with adjunctive azithromycin compared to placebo, there would be 17 fewer postoperative infections.

• The overall favorable outcome should be weighted with the cost-effectiveness of expanded use of azithromycin and the possibility of increasing antibiotic exposure.

Conclusion for Healthcare Professionals
In this study, patients who received adjunctive intravenous azithromycin with the standard antibiotic prophylaxis for nonelective cesarean delivery had a relative risk reduction of 49% in postoperative infection rate ($p<0.001$) compared to those who received standard antibiotic prophylaxis alone. Azithromycin appeared to be well tolerated in the exposed mothers and infants. However, the two groups may not have been balanced, as standard antibiotic prophylaxis treatments may have differed between the groups, and smoking during pregnancy was higher in the placebo group than the azithromycin group. Also, a greater percentage of patients were lost to follow-up in comparison to the absolute risk differences of the secondary outcomes discussed herein, introducing a potential bias with unknown impact. Furthermore, since ureaplasma cultures were not reported, it is not definitive that ureaplasma was the causative organism for the development of the infections. Taking into consideration the above factors, azithromycin prophylaxis may be beneficial for patients meeting the eligibility criteria and with high suspicion of acquiring postoperative infections.

Conclusion for Patients
Azithromycin is a commonly used antibiotic for a variety of infections and is relatively inexpensive. The study showed that women who underwent an unplanned cesarean section had a lower chance of contracting infections after surgery when given azithromycin in addition to standard antibiotics than with standard antibiotics alone. The mothers and their infants who were exposed to azithromycin appeared to have tolerated it well. A limitation to the study was that the placebo group had more smokers than the azithromycin group, possibly biasing the results. Further, it is not clear if the bacteria that azithromycin is thought to target caused the infections. Overall, the addition of azithromycin for unscheduled cesarean section may be beneficial for some patients at high risk for infections after surgery.

About the Authors

Genene Salman, PharmD, BCPS, BCCCP, CNSC received her PharmD from USC. She worked in a variety of inpatient pharmacy settings as a clinical pharmacist before joining Marshall B. Ketchum University College of Pharmacy in Fullerton, California, as an Assistant Professor. She is also pursuing specialized certifications in Biostatistics and Clinical Trials Design and Management at UC San Diego.

Henry Hua received his PhD in cognitive psychology from the University of Memphis. He currently teaches communications, social sciences, and statistics at Marshall B. Ketchum University in Fullerton, California.

LaDonna Oelschlaeger is an Associate Professor at Marshall B. Ketchum University College of Pharmacy. She received her PharmD from Purdue University and completed a Pharmacy Practice Residency at the Veterans Administration. Dr. Oelschlaeger practices in an acute care setting and is board certified in pharmacotherapy.

Noelle de Leon, PharmD, BCPS, BCCCP is a Clinical Pharmacist specializing in Critical Care at UC San Francisco Medical Center and an Assistant Clinical Professor at the UC San Francisco School of Pharmacy in San Francisco, California.

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