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Timing of Adjunctive Azithromycin for Unscheduled Cesarean Delivery and Postdelivery Infection

Ayodeji Sanusi, MD MPH[1,2],

Yuanfan Ye, PhD[2,3],

Kim Boggess, MD[4],

George Saade, MD[5],

Sherri Longo, MD[6],

Erin Clark, MD[7],

Sean Esplin, MD[7],

Kirsten Cleary, MD[8],

Ron Wapner, MD[8],

Michelle Owens, MD[9],

Sean Blackwell, MD[10],

Jeff M. Szychowski, PhD[1,2,3],

Alan T.N. Tita, MD PhD[1,2],

Akila Subramaniam, MD MPH[1,2]

[1]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Alabama

[2]Center for Women's Reproductive Health, University of Alabama at Birmingham, Alabama

[3]Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Alabama

[4]Departments of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, Chapel Hill, and Mission Hospital, Asheville, North Carolina

[5]Departments of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, Texas

[6]Departments of Obstetrics and Gynecology, Ochsner Health System, New Orleans, Louisiana

[7]Departments of Obstetrics and Gynecology, University of Utah and Intermountain Health Care, Salt Lake City, Utah

[8]Departments of Obstetrics and Gynecology, Columbia University, New York

[9]Departments of Obstetrics and Gynecology, University of Mississippi, Jackson, Mississippi

Address for correspondence: Ayodeji Sanusi, MD MPH, Division of Maternal and Fetal Medicine, Department of Obstetrics and Gynecology, The University of Alabama at Birmingham, Women Infants and Children, Birmingham, AL, aasanusi@uabmc.edu.

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[10]Departments of Obstetrics and Gynecology, University of Texas Health Sciences Center, Houston, Texas

Abstract

Objective: To estimate the association between timing of administration of adjunctive azithromycin for prophylaxis at unscheduled cesarean delivery and maternal infection and neonatal morbidity.

Methods: We conducted a secondary analysis of a randomized trial of adjunctive azithromycin prophylaxis in patients with singleton gestation undergoing unscheduled cesarean delivery. The primary exposure was timing of initiation of study drug (after skin incision, or 0-30 mins, >30-60 mins and >60 mins prior to skin incision). The primary outcome was a composite of endometritis, wound infection and other maternal infections occurring up to 6 weeks after cesarean delivery. Secondary outcomes included composite neonatal morbidity, neonatal ICU admission >72 hours, and neonatal sepsis. The association of azithromycin with outcomes was compared within each antibiotic timing group and presented as risk ratios (RRs) with 95% confidence intervals (CIs). A Breslow-Day homogeneity test was applied to assess differences in association by antibiotic timing.

Results: Of 2013 participants, antibiotics were initiated after skin incision (median 3 minutes, range 0-229 minutes) in 269 (13.4%), 0-30 minutes preceding skin incision in 1378 (68.5%), >30-60 minutes prior to skin incision in 270 (13.4%) and >60 minutes (median 85 minutes, range 61-218 minutes) prior in 96 (4.8%). The RRs (95% CIs) of infectious composite outcome for azithromycin compared to placebo were significantly lower for groups initiating azithromycin after skin incision or within one hour prior to cesarean incision (after skin incision RR 0.31 [0.13-0.76]; 0-30 mins, 0.62 [0.44-0.89]; >30-60 mins, 0.31 [0.13-0.66]). Risks were not significantly different in patients receiving azithromycin >60 mins before skin incision (0.59 [0.10-3.36]). Results were similar when endometritis and wound infections were analyzed separately. Neonatal outcomes were not significantly different for azithromycin compared to placebo across all timing groups.

Conclusions: Adjunctive azithromycin administration up to 60 minutes before or a median of 3 minutes after skin incision was associated with reduced risks of maternal composite postoperative infection in unscheduled cesarean deliveries.

Clinical Trial Registration: ClinicalTrials.gov, NCT01235546.

Precis:

In patients undergoing unscheduled cesarean delivery, adjunctive azithromycin administration up to 60 minutes before, or at median of 3 minutes after skin incision was associated with reduced risks of post-operative infection.

Introduction

Cesarean delivery is the single most important risk factor for postpartum uterine infection and is associated with a 5-10 fold higher infectious morbidity compared to vaginal delivery.[1–4] These infection risks are higher among unscheduled cesareans.[5–9] To

mitigate the risk of infection, pre-operative antibiotic prophylaxis with a first generation cephalosporin (cefazolin) prior to skin incision is recommended.[10] However, even with routine prophylaxis, up to 12% of unscheduled cesarean deliveries receiving standard pre-operative antibiotic prophylaxis develop postpartum infections.[11,12] This is reduced by half with the addition of adjunctive azithromycin for surgical prophylaxis.[13] However, there are limited data on the association of timing of azithromycin administration and post cesarean infection risk.

Time of antibiotic administration relative to skin incision is a major determinant of peak tissue antibiotic concentration.[10,14–18] Azithromycin attains peak maternal plasma concentration (exceeding the minimal inhibitory concentration [MIC] for Ureaplasma) within one hour and then rapidly declines over 1-2 hours to reach a steady state.[16] Thus, timing of azithromycin administration relative to skin incision is important to exceed the MIC of susceptible microorganisms implicated in post-cesarean infections.

Therefore, our primary objective was to evaluate the association between timing of adjunctive azithromycin administration for prophylaxis at unscheduled cesarean delivery after labor and maternal and neonatal infectious morbidity.

Methods

We performed a secondary analysis of a randomized controlled trial of adjunctive azithromycin prophylaxis for cesarean delivery (Cesarean Section Optimal Antibiotic Prophylaxis[CSOAP] trial NCT01235546) conducted at 14 centers in the United States. The institutional review boards at each center approved the parent trial and the University of Alabama at Birmingham's institutional review board deemed this secondary analysis of deidentified data exempt (as information was recorded in a manner that the identity of study participants could not be readily ascertained). The parent trial was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and Pfizer donated the study medication but did not participate in the design, conduct or reporting of either the parent trial or this secondary analysis. The inclusion and exclusion criteria and results of this trial have been previously described. Briefly, the trial included patients with singletons gestations at or greater than 24 weeks of gestation undergoing unscheduled cesarean delivery during labor or with ruptured membranes for > 4 hours and no contraindication to azithromycin.[13]

The primary exposure for this secondary analysis was timing of study drug administration after skin incision (administered as soon as possible), or 0 to 30mins, >30 to 60mins, or > 60mins prior to skin incision. Patients in the primary trial were randomly assigned to 500mg of azithromycin in 250ml of saline infusion or an identical appearing saline placebo infused over one hour. The time of administration was defined as the time the infusion was connected to the patient. During the course of the trial, antibiotic prophylaxis, mostly with a first-generation cephalosporin (cefazolin), was administered over a five-minute period as an intravenous push, followed by the study drug (azithromycin or placebo). Details of the timing of administration of study drug were prospectively ascertained during the course of the primary trial. Of note, only a single dose of adjunctive azithromycin was administered.

The primary outcome of this secondary analysis was a maternal post-operative infection composite of endometritis, wound infection or other maternal infections (abdominopelvic abscess, maternal sepsis, pelvic septic thrombophlebitis, pyelonephritis, pneumonia or meningitis) occurring within six weeks of cesarean delivery as defined in the primary study.[13] Maternal secondary outcomes were individual components of the primary composite outcome – endometritis and wound infection. The neonatal composite outcome included neonatal death, neonatal sepsis, other serious neonatal complications: necrotizing enterocolitis, respiratory distress syndrome, periventricular leukomalacia, grade 3 or higher intraventricular hemorrhage and neonatal ICU admission greater than 72 hours. The primary outcome and its components were ascertained through central adjudication by investigators unaware of treatment assignments. Other maternal and infant outcomes were ascertained by trained research staff through review of the electronic medical records and direct questioning in person or by telephone. All outcomes are defined in detail in the primary report.[13]
Race and ethnicity were self-reported by study participants into prespecified categories, including 'none of the above' which was also a prespecified formal category in the database. Information on race and ethnicity were collected as various studies have demonstrated racial and ethnic disparities in cesarean morbidity[19,20]; however these were ultimately not included as covariates in our analyses.

Differences in baseline variables by azithromycin versus placebo assignment were examined within each antibiotic timing group. Study outcomes, risk ratios (95% CI) for azithromycin versus placebo, were computed within each antibiotic timing group using placebo as the reference. A Breslow-Day test for homogeneity was applied to assess differences in associations among groups. In additional analyses, log binomial multivariable models were adjusted for characteristics identified as statistically significantly different between participants receiving azithromycin and placebo in each antibiotic timing group. All analyses were done with the SAS software version 9.4 and significance level was set at a p-value of <0.05 for all analyses.

Results

Of 2013 participants from the parent trial, 269 (13.4%) received prophylactic antibiotics after skin incision (median 3 minutes, range 0-229 minutes; 250 [92.9%] of whom received antibiotics < 60 minutes after incision), 1378 (68.5%) in the 30 minutes preceding the skin incision, 270 (13.4%) in >30 to 60 minutes prior to skin incision, and 96 (4.8%) received antibiotics >60 minutes (median 85 minutes, range 61-218minutes) prior to skin incision (Table 1). Only membrane status at delivery was significantly different by azithromycin (or placebo) reception status in participants receiving azithromycin after skin incision.

A total of 181 (9.0%) patients met the composite primary outcome of endometritis, wound infection or other maternal infection within six weeks of delivery, the majority (65.7%) of whom received antibiotics in the 30 minutes preceding the skin incision (Table 2). Receiving azithromycin (compared to placebo) after skin incision or 0-30 mins, >30-60 mins prior to skin incision was associated with a significant reduction in the risk of the primary outcome. Azithromycin administered more than 60 minutes prior to skin incision was not significantly associated (RR 0.59[0.10-3.36]) with a reduction in the primary outcome (Table 2). The

pattern of significant risk reduction was consistent for the outcome of wound infection among patients receiving antibiotics 0-30mins and >30-60mins prior to skin incision. Further, azithromycin administration was significantly associated with a reduced risk of endometritis when administered after cesarean incision or >30-60 minutes prior to skin incision. Results were unchanged in models adjusted for membrane status at randomization.

Regardless of time of administration of azithromycin, there were no significant differences in the neonatal composite outcome, suspected or confirmed neonatal sepsis or the risk of neonatal intensive care unit admission (Table 3). The Breslow-Day test for homogeneity did not suggest any significant differences in maternal and neonatal outcomes between the antibiotic timing groups ($p>0.05$).

Discussion

In this secondary analysis, azithromycin administration was associated with a reduced risk of composite maternal post-cesarean infection when administered within an hour preceding skin incision, and when administered after (median 3 minutes, range 0 to 229 minutes) skin incision. Thus, administering azithromycin up to 60 minutes pre-incision or even after skin incision is beneficial in reducing postoperative maternal infections at unplanned cesarean sections. Timing of azithromycin administration however was not significantly associated with neonatal outcomes.

Most postpartum infections are polymicrobial (gram positive cocci, gram negative rods, anaerobes, Mycoplasma and Ureaplasma). Cefazolin, a commonly used first generation cephalosporin for cesarean delivery prophylaxis is active against many gram positive and some gram-negative bacteria organisms. In fact, administration of 2 grams of intravenous cefazolin within one hour prior to cesarean incision achieves MIC for gram negative rods in most patients with therapeutic concentrations in umbilical cord at delivery and persisting in newborns up to five hours after delivery.[13,21–23] A twofold higher risk of surgical site infection (RR 2.10 [1.20-3.80]) when cefazolin only is administered more than one hour before skin incision, compared to administration within an hour prior to cesarean incision is supported by these pharmacokinetic parameters.[24] Mycoplasma, Ureaplasma and anaerobes are not effectively treated by cephalosporins but can be treated with macrolide antibiotics such as azithromycin. Evaluating placental tissue collected during the parent CSOAP trial, azithromycin was even demonstrated to have a range of antimicrobial activity beyond Mycoplasmas and Ureplasmas.[25] In pregnant patients receiving single dose 500mg of azithromycin within one hour prior to skin incision, peak maternal serum concentration are attained within one hour and azithromycin is detectable in fetal compartments within 30 minutes and in sustained concentrations in breast milk up to 48 hours after administration. Azithromycin has a considerably longer half-life (6.7hours [95% CI 6.4-7.6]) compared to standard cephalosporins, thus it is plausible that timing beyond the recommended one hour prior to incision could be considered.

Numerous studies have examined the timing of administration of standard cesarean section prophylaxis. Most of these studies conclude that antibiotic administration prior to cord clamping or skin incision is associated with a lower risk of post-cesarean infectious

morbidity.[12,26–31] However, a more recent study among 55,901 patients in 75 Swiss hospitals between 2008-2019, examined the risk of surgical site infection (SSI) after cesarean sections where the standard antibiotic (cefuroxime, cefazolin, amoxicillin and clavulanate, ceftriaxone) was administered after umbilical cord clamping compared to prior to surgical incision and found no difference (OR 1.14 [0.96-1.36]) in the odds of a SSI between both groups.[32] Adjunctive azithromycin given at unscheduled cesareans has been shown to lower the risk of post cesarean section infectious morbidity by almost half,[13] and azithromycin prophylaxis at cesarean delivery is administered over one hour as recommended by the FDA. Therefore, the protective association of adjunctive azithromycin in patients receiving azithromycin within 60 minutes prior to, or after skin incision is not unexpected.

Of note, we failed to find an association between timing of administration of azithromycin and short-term neonatal outcomes, including neonatal suspected or confirmed infections. This could be plausibly due to the MIC of microorganisms implicated in neonatal infections being higher than azithromycin's concentration in the fetal compartment, following single dose administration prior to or as soon as possible after skin incision. However, our findings are consistent with the primary trial which show no safety signals or adverse outcomes in neonates exposed to adjunctive azithromycin.[13]

The strengths of this study include the relatively large number of patients recruited into the trial with rigorous exposure and outcome ascertainment and the standardized definitions of surgical site infections. Also, study outcomes including those ascertained from interviews at the postpartum and three-month telephone visits were verified using medical records reducing the risk of recall bias. Limitations include the small numbers of outcomes especially among patients receiving azithromycin more than 60 minutes prior to skin incision which limits the strength of inferences that can be drawn from this group. Although we conducted multiple comparisons with the risk of false positive findings, there was a specified primary comparison to evaluate differences in association on the primary composite by timing of administration, and the findings were consistent with those of the primary paper. We do acknowledge power to detect significant interactions is likely limited. We could not assess the association of redosing azithromycin with post cesarean infection in certain patients (e.g postpartum hemorrhage) as this was outside the scope of the original trial protocol. However, only three patients experienced postpartum hemorrhage and would not likely change our results.

In summary, this study's findings provide evidence for the beneficial association of adjunctive azithromycin when administered in the hour preceding skin incision or even after skin incision.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Sherri Longo reported that money was paid to her institution: University of Alabama received the primary NIH grant and Ochsner (her institution) participated in the study with her as the PI at Ochsner (received financial support from UAB). Michelle Owens reported receiving payment from AMAG pharmaceuticals, Progenity, and Quidel. Alan T.N. Tita reported that money was paid to his institution (University of Alabama at Birmingham) from Pfizer and the CDC. Sean Esplin served on the scientific advisory board of Clinical Innovations and hold stock for Sera Prognostics. Sean Blackwell reported financial support from the NIH/NICHD, Hologic, AMAG and Clinical Computer Systems Inc. The other authors did not report any potential conflicts of interest.

Each author has confirmed compliance with the journal's requirements for authorship.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *Not available.*

What other documents will be available? *Not available.*

When will data be available (start and end dates)? *Not applicable.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable.*

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Table 1:

Baseline characteristics of patients receiving adjunctive azithromycin or placebo at unscheduled cesarean delivery in the Cesarean Section Optimal Antibiotic Prophylaxis trial

Characteristic	**After skin incision (Median 3 mins, range 0-229mins) N=269**		**0-30mins pre-incision N=1378**		**>30-60mins pre-incision N=270**		**>60mins pre-incision (Median 85 mins, range 61-218 mins) N=96**	
	Azithromycin n=135	**Placebo n=134**	**Azithromycin n=693**	**Placebo n-685**	**Azithromycin n=140**	**Placebo n=130**	**Azithromycin n=51**	**Placebo n=45**
Maternal Age (years)	28.9 ± 6.5	27.9 ± 6.8	28.1 ± 6.1	28.5 ± 6.5	27.8 ± 5.8	28.2 ± 6.3	29.2 ± 6.4	28.9 ± 6.2
Race and ethnicity								
Hispanic	19 (14.1)	11 (8.2)	128 (18.5)	138 (20.1)	39 (27.9)	41 (31.5)	17 (33.3)	18 (40.0)
Non-Hispanic Black	47 (34.8)	53 (39.6)	244 (35.2)	237 (34.6)	48 (34.3)	41 (31.5)	12 (23.5)	10 (22.2)
Non-Hispanic White	48 (35.6)	47 (35.1)	246 (35.5)	242 (35.3)	43 (30.7)	41 (31.5)	19 (37.3)	12 (26.7)
None of the above	21 (15.6)	23 (17.2)	75 (10.8)	68 (9.9)	10 (7.7)	7 (5.4)	3 (5.9)	5 (11.1)
Medicaid	82 (61.2)	84 (63.2)	424 (61.2)	412 (60.1)	84 (60.0)	76 (59.8)	32 (64.0)	28 (63.6)
Nulliparous	74 (54.8)	83 (61.9)	420 (60.6)	405 (59.1)	88 (62.9)	83 (63.8)	21 (41.2)	21 (46.7)
Comorbidities	27 (20.0)	19 (14.2)	116 (16.7)	127 (18.5)	22 (15.7)	22 (16.9)	8 (15.7)	7 (15.6)
Substance use	13 (9.6)	16 (11.9)	90 (13.0)	109 (15.9)	28 (20.0)	29 (22.3)	12 (23.5)	10 (22.2)
Preterm birth (<37 weeks)	23 (17.0)	18 (13.4)	69 (10.0)	83 (12.1)	19 (13.6)	15 (11.5)	6 (11.8)	4 (8.9)
Group B streptococcus status	38 (28.2)	38 (28.4)	170 (24.5)	189 (27.6)	29 (20.7)	28 (21.5)	12 (23.5)	11 (24.4)
Spontaneous rupture of membranes	56 (41.8) *	37 (27.8) *	247 (35.8)	229 (33.5)	49 (35.0)	50 (38.5)	21 (41.2)	11 (24.4)
Body mass index (kg/m^2)	34.7 ± 7.4	34.2 ±7.8	35.2 ± 7.7	35.8 ± 7.9	36.3 ± 8.2	35.4 ± 7.7	36.1 ± 7.8	35.6 ± 7.2
Duration of ruptured membranes (hours)	16.8 ± 55.9	9.4 ± 7.3	12.7 ± 41.2	10.6 ±22.5	10.7 ± 8.1	12.0 ± 10.7	16.3 ± 56.4	9.9 ± 7.5
Standard prophylactic antibiotic †	134 (99.3)	129 (96.3)	680 (98.1)	676 (98.7)	137 (97.9)	128 (98.5)	49 (96.1)	43 (95.6)

*Significantly different at p<0.05 in azithromycin (vs placebo) status

†Standard prophylactic antibiotic was routinely cefazolin per protocol except in patients with penicillin or cephalosporin allergy who received the local alternative- clindamycin or clindamycin plus gentamicin.

‡Comorbidities include pregestational diabetes, chronic hypertension, other cardiac disease or autoimmune disease

// Column total not 100% for health insurance type (Medicaid) and Spontaneous rupture of membranes) due to 1-3 participants missing data on these variables

Table 2:

Number, proportion (with 95% confidence intervals [CI]), and crude risk ratios (with 95% CIs) showing the association of adjunctive azithromycin versus placebo with the risk of infectious maternal morbidity among patients undergoing unscheduled cesarean deliveries by time of administration of study drug

Outcomes	**After skin incision (Median 3 mins, range 0-229mins) N=269**		**0-30mins pre-incision N=1378**		**>30-60mins pre-incision N=270**		**>60mins pre-incision (Median 85mins, range 61-218 mins) N= 96**		**Interaction p-value**
	Azithromycin n=135	**Placebo (ref) * n=134**	**Azithromycin n=693**	**Placebo (ref) * n=685**	**Azithromycin n=140**	**Placebo (ref) * n=130**	**Azithromycin n=51**	**Placebo (ref) * n=45**	
Primary composite outcome N=181	6 (4.4) [1.8-10.3]	19 (14.2) [8.7-22.2]	46 (6.6) [4.8-9.1]	73 (10.7) [8.3-13.6]	8 (5.7) [2.7-11.8]	24 (18.5) [12.6-27.2]	2 (3.9) [0.9-15.2]	3 (6.7) [0.2-20.0]	0.18
	0.31 (0.13-0.76)		0.62 (0.44-0.89)		0.31 (0.13-0.66)		0.59 (0.10-3.36)		
Endometritis N=100	2 (1.5) [0.3-6.1]	12 (9.0) [4.8-16.1]	32 (4.6) [3.1-6.8]	34 (5.0) [3.4-7.2]	5 (3.6) [1.4-9.0]	13 (10.0) [5.5-17.5]	0 (0.0) [0.0-9.0]	2 (4.4) [1.0-17.0]	0.22
	0.16 (0.04-0.73)		0.93 (0.58-1.49)		0.36 (0.13-0.97)		†		
Wound infection N=90	4 (3.0) [1.0-8.3]	10 (7.5) [3.8-14.2]	15 (2.2) [1.2-3.8]	42 (6.1) [4.4-8.2]	3 (2.1) [0.6-7.0]	12 (9.2) [5.0-16.5]	2 (3.9) [0.9-15.2]	2 (4.4) [1.0-17.0]	0.68
	0.40 (0.13-1.23)		0.35 (0.20-0.63)		0.23 (0.07-0.80)		0.88 (0.13-6.01)		

*(ref)- Reference group

†Regression model did not converge due to small case numbers

‡Results for other infections were excluded from table due to non-convergence of models from small case numbers

§Numbers in brackets are 95% confidence intervals for the proportions

Table 3:

Number, proportion (with 95% confidence intervals [CI]), and crude risk ratios (with 95% CIs) showing the association of adjunctive azithromycin versus placebo with the risk of secondary neonatal outcomes undergoing unscheduled cesarean deliveries by time of administration of study drug

Outcomes	**After skin incision (Median 3mins, range 0-229mins) N=269**		**0-30mins pre-incision N= 1378**		**>30-60mins pre-incision N=270**		**>60mins pre-incision (Median 85mins, range 61-218mins) N=96**		**Interaction p-value**
	Azithromycin n=135	**Placebo (ref) * n=134**	**Azithromycin n=693**	**Placebo (ref) * n=685**	**Azithromycin n=140**	**Placebo (ref) * n=130**	**Azithromycin n=51**	**Placebo (ref) * n=45**	
Composite neonatal outcome N=281	26 (19.3) [12.8-27.9]	27 (20.1) [13.5-28.9]	95 (13.7) [11.0-16.9]	86 (12.6) [10.0-15.7]	19 (13.6) [8.3-21.3]	14 (10.8) [6.1-18.4]	6 (11.8) [5.0-25.4]	8 (17.8) [8.5-33.6]	0.75
	0.96 (0.59-1.55)		1.10 (0.83-1.43)		1.26 (0.66-2.41)		0.66 (0.25-1.76)		
Suspected or confirmed neonatal sepsis N=246	21 (15.6) [9.8-23.8]	24 (17.9) [11.7-26.5]	76 (11.0) [8.6-13.9]	79 (11.5) [9.1-14.6]	18 (12.9) [7.8-20.5]	14 (10.8) [6.1-18.4]	6 (11.8) [5.0-25.4]	8 (17.8) [8.5-33.6]	0.82
	0.87 (0.51-1.48)		0.95 (0.71-1.28)		1.19 (0.62-2.30)		0.66 (0.25-1.76)		
NICU admission (>72 hr) N=262	26 (19.3) [12.8-27.9]	26 (19.4) [12.9-28.1]	80 (11.5) [9.1-14.5]	96(14.0) [11.3-17.3]	17 (12.1) [7.2-19.7]	10 (7.7) [3.9-14.6]	4 (7.8) [2.7-20.5]	3 (6.7) [2.0-20.0]	0.41
	0.99 (0.61-1.62)		0.82 (0.62-1.09)		1.58 (0.75-3.32)		1.18 (0.28-4.98)		

*(ref)- Reference group

†Numbers in brackets are 95% confidence intervals for the proportions

‡Composite neonatal outcome included neonatal death, neonatal sepsis, other serious neonatal complications: necrotizing enterocolitis, respiratory distress syndrome, periventricular leukomalacia, grade 3 or higher intraventricular hemorrhage and neonatal ICU admission greater than 72 hours.