Iranian Journal of Clinical Infectious Diseases
2009;4(2):71-76

ORIGINAL ARTICLE

Timing of prophylactic antibiotic administration in term cesarean section: A randomized clinical trial

Fariba Almassi Nokiani[1], Hossein Akbari[2*], Mansour Rezaei[3]

[1] *Department of Gynecology and Obstetrics, Iran University of Medical Sciences, Tehran, Iran*

[2] *Fertility and Infertility Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran*

[3] *Department of Plastic and Reconstructive Surgery, Iran University of Medical Sciences, Tehran, Iran*

ABSTRACT

Background: Antibiotic prophylaxis would benefit all cesarean section patients and may decrease morbidity and length of hospital stay. The present study was conducted to determine whether the administration of cefazolin prior to skin incision was superior to administration at the time of umbilical cord clamping for prevention of post-cesarean maternal-neonatal infections morbidity.

Patients and methods: This was a randomized, double-blinded clinical trial. During the study period, 287 cesarean sections for singleton term pregnancies with intact membranes or passed less than 18 hours from rupture of membrane were entered. A total of 196 patients received 2gr cefazolin before incision and 91 patients received 2gr cefazolin after cord clamping. The occurrence of surgical site opening, total infectious morbidity and neonatal complications were compared between these groups.

Results: Two groups were demographically identical. Rate of IV line need (RR=1.87, 95%CI:0.21-17.02), neonatal sepsis (RR=1.39, 95%CI:0.14-13.64) and NICU admission (RR=0.19, 95%CI: 0.21-17.02) were not significantly differed between groups.

Conclusion: We suggest the standard cefazolin prophylaxis (after cord clamping) for elective cesarean section and cefazolin before incision for non elective cesarean section. Therefore, administration of prophylactic cefazolin prior to incision will not increase the rate of neonatal sepsis.

Keywords: *Prophylactic antibiotic, Cesarean section, Maternal infection, Neonatal infection, Cefazolin.*
(Iranian Journal of Clinical Infectious Diseases 2009;4(2):71-76).

INTRODUCTION

Reduction of post-cesarean surgical site infection (SSI) is of utmost importance in infection control activities. Currently, prophylactic antibiotics are proved to be effective in lowering postoperative infection. Antibiotic prophylaxis would benefit all cesarean section patients and may decrease morbidity and length of hospital stay (1-3). In a survey in UK, the rate of post-cesarean SSI was 11.2%, of which 71% were detected during post discharge surveillance. Body mass index (BMI) and choice of skin closure were associated with SSI in that population (4). In another survey in Norway, the total rate of post-cesarean SSI was 8.9% while it was 1.8% at hospital discharge. Similarly to UK study, operating time (>38 minutes) and BMI (>30 kg/m^2) were associated with increased risk (5). Thigpen et al studied

Received: 15 July 2008 *Accepted*: 14 June 2009
Reprint or Correspondence: Hossein Akbari, MD.
Fatemeh Hospital, 21th street, Yousef abad, Tehran, Iran.
E-mail: hakbari1339@yahoo.com

cefazolin administration either before skin incision or right after cord clamping and demonstrated similar maternal infectious morbidity in both groups (6). Wax assigned 90 consecutive laboring women undergoing cesarean delivery at ≥37 weeks gestation to two groups of 1gr cefazolin administered preoperatively or after cord clamping and concluded that preoperative cefazolin was as effective as the dose administered after cord clamping, however, slightly increased risk of sepsis in newborns was shown (7). In Sullivan study, administration of prophylactic cefazolin prior to skin incision resulted in a decreased endomyometritis and total post-cesarean infectious morbidity, compared with those received antibiotic at the time of cord clamping. They did not report increased neonatal septic complications (8). Finally, another survey demonstrated that infants whose mothers received intrapartum antibiotic prophylaxis stayed 6 hours longer in hospitals (9).

Now concerns over unnecessary fetal exposure to antibiotics is responsible for the usual practice of delaying antibiotic prophylaxis for cesarean until after the umbilical cord is clamped (2). The fetal concern involves masking of infection or pressure toward infection with resistant organisms. Thus in regard to the timing of antibiotic prophylaxis at cesarean, the interest of the mother and the fetus are theoritically divergent and this randomized trial has evaluated whether this apparent divergence is in fact real.

PATIENTS and METHODS

During this randomized double-blinded clinical trial in Kermanshah, 287 women with singleton pregnancy scheduled to have cesarean delivery from February 2007 to March 2008 received 2 grams cefazolin either 30-60 minute before incision or at the time of cord clamping while all subjects received another 2 grams cefazolin 6 hours after operation. We selected deliveries performed between 8AM and 2PM of each working day since most of these cases were electively undergone cesarean section (before onset of labor), however, some cases of emergency cesarean sections were also exist.

Demographic features including age, parity, BMI (body mass index) and cause of cesarean section did not significantly differ between groups. All mothers had BMI of 19-28kg/m^2 and gestation age of at least 37 weeks. For all of the subjects, it was the first cesarean section and all were normal healthy women without any confirmed systemic disease like diabetes mellitus, hypertension, immune compromised diseases, coagulation disorders, and heart or renal failure. All were afebrile and amniotic membrane was intact or ruptured not more than 18 hours. They all received general anesthesia for cesarean section. Routinely, we discharged all subjects at the third day following the cesarean section unless any morbidity occurred.

A single resident of obstetrics and gynecology recorded the initial data at days 1, 3, 7 and 30 following the cesarean section. Surgical site opening was defined as wound dehiscence and endometritis as fever, open cervix in vaginal examination and vaginal bleeding. A trained nurse gathered data for newborns at days 1, 3 and 7. The need for IV line and sepsis work up was achieved by a well-oriented pediatrician with special attention to feeding, newborn reflexes, diarrhea, vomiting, cyanosis and respiratory distress. Two different researchers performed cesarean sections and follow up of the subjects and newborns (double blind). The research protocol was approved by the Medical Ethics Committee of Kermanshah University of Medical Sciences. All patients were requested to complete an informed consent.

Data were analyzed using SPSS software (version 11.5, SPSS Inc., USA). Chi square and Fisher's exact test were applied to compare categorical variables while Leven's test was used for equality of variances and independent sample t test for equality of continues variables.

RESULTS

Tables 1 and 2 represent demographic characteristics of both groups. As noted, there was no significant difference between groups.

Table 1. Demographic characteristics of subjects underwent cesarean section and received cefazolin prior to incision or after clamping

Variables	Before incision (n=196)	After clamping (n=91)	P
Age (year)	27.3 ± 6.03	26.3 ± 6.07	0.191
Parity	1.91 ± 1.12	1.80 ± 1.0	0.419
BMI (kg/m^2)	20.16 ± 2.65	19.87 ± 2.18	0.321
Newborn hospitalization (day)	2.99 ± 0.07	2.99 ± 0.11	0.578
Mother hospitalization (day)	3.08 ± 0.74	3.02 ± 0.45	0.515

Table 3 summarizes the maternal and neonatal outcomes in both groups including fever, surgical site opening and endometritis in mother and need for IV line and NICU and sepsis in newborn. The differences in all subdirectories did not reach a statistically significant level. Meanwhile, the administered dose of cefazolin was not associated with neonatal sepsis.

Table 3. Maternal and neonatal outcomes in subjects underwent cesarean section and received cefazolin prior to incision or after clamping

Variables	Before incision (n=196)	After clamping (n=91)	P
Maternal fever			
2nd day	9(4.6)	3(3.3)	.756
until 40th day	1(0.5)	0(0.0)	1.0
Total	10(5.1)	3(3.3)	0.761
Surgical site opening	0(0.0)	1(1.1)	0.317
Metritis	0(0.0)	(0.0)	-
Need for IV line			
1st day	5(2.6)	1(1.1)	0.668
3rd day	4(2.0)	1(1.1)	1.0
7th day	3(1.5)	0(0.0)	0.554
Total	5(2.6)	1(1.1)	0.668
Neonatal sepsis			
1st day	4(2.0)	1(1.1)	1.0
3rd day	3(1.5)	1(1.1)	1.0
7th day	3(1.5)	0(0.0)	0.554
Total	4(2.0)	1(1.1)	1.0
Need for NICU			
1st day	5(2.6)	1(1.1)	0.668
3rd day	4(2.0)	1(1.1)	1.0
7th day	3(1.5)	0(0.0)	0.554
Total	5(2.6)	1(1.1)	0.668

Table 2. Distribution of demographic characteristics of subjects underwent cesarean section and received cefazolin prior to incision or after clamping

Variables	Before incision (n=196)	After clamping (n=91)	P
Age (year)			
<25	66(33.7)	40(44.0)	
25-29	60(30.6)	26(28.6)	0.208
>29	70(35.7)	25(27.5)	
Parity			
1	92(46.9)	42(46.2)	
2	55(28.1)	35(38.5)	0.092
3-6	49(25)	14(15.4)	
Cesarean type			
elective	179(91.3)	74(81.3)	0.015
non elective	17(8.7)	17(18.7)	
BMI* (kg/m^2)			
≤25	177(90.3)	86(94.5)	0.262
>25	19(9.7)	5(5.5)	

* Body mass index

DISCUSSION

Although prophylactic antibiotics have been shown to reduce the incidence of postoperative infections morbidity after cesarean delivery (1-5), the most effective regimens and timing of administration have not been established. Some has suggested antibiotic prophylaxis only for emergency cesarean section (10,11) and others demonstrated that prophylactic antibiotics are effective and cost saving for all cesareans (elective and non elective) (3, 12-16). Some investigators recommended cefazolin (2), while cephalotin (17), cefazolin plus metronidazole (18,19), ampicillin (14), and metronidazole plus gentamicin (20) have also been proposed by others. Controversies are also exist regarding the timing of antibiotic administration since some suggested prior incision (8,18), but others proposed after cord clamping (2,21). Single dose administration or triple dose is another issue of discrepancy (2,18,22,23).

In the present study maternal and neonatal infectious morbidity did not differ significantly among subjects underwent cesarean section and received cefazolin prior to incision or after clamping. In a meta-analysis considering antibiotic prophylaxis for cesarean section (81 trials were

included), a significant decrease in incidence of endometritis (66-75%) and similar reduction in wound infections were observed, hence, authors recommended prophylactic antibiotics to women undergoing elective or non elective cesarean section. Indeed, they reported a relative risk of 0.38 for endometritis among elective and 0.39 among non elective cesarean section subjects (3).

Use of prophylactic antibiotics in women undergoing cesarean section reduced the incidence of episodes of fever, endometritis, wound infection, urinary tract and other serious infections after cesarean section. In one survey, 441 women undergoing cesarean section were randomly assigned either to a single dose of 1gr intravenous cefazolin or placebo after clamping of umbilical cord. In elective cesarean sections no statistically significant differences were found in post operative febrile morbidity and infection-related complications, therefore, they concluded that routine use of a single dose of cefazolin is safe and effective in emergency but not elective cesarean section (11). In our study, the rate of infectious morbidity in two groups was similar and low, it is in part could be explained by the fact that most of our patients were elective cases. The rate of post partum infection is about 5% in most of the previous reports, however, in a study in Norway the rate of surgical site infection after cesarean was 8.9% until 30 days post operation (5).

There are controversies in the timing of antibiotic administration in cesarean section, since theoretically it could increase the neonatal complications. In our setting, hospital stay, need for IV line and sepsis were not significantly differed between subjects underwent cesarean section and received cefazolin prior to incision or after clamping. Moore et al. explored potential associations between intrapartum antimicrobial prophylaxis use and changes in the causes of early onset sepsis and concluded that antibiotic prophylaxis declined the incidence of early onset infection due to group B streptococci (24). Furthermore, Daley suggested that the increasing use of intrapartum antibiotics produced a steady decline in early onset group B streptococcal disease in Australia and there was also a trend to decreasing early onset E.coli sepsis in all babies (25). Edwards et al compared the relative effects of intrapartum antibiotic prophylaxis regimens on patterns of early onset neonatal sepsis, for which mothers have received ampicillin before delivery for prophylaxis. They had concluded that antibiotic prophylaxis before delivery improved the pattern of sepsis (26). In another survey in 374 infants with birth weight ≤1500 grams, maternal administration of parentral antibiotics in the pre-delivery period was associated with a decreased risk of developing cystic periventricular leukomalacia and maternal antibiotics did not change the risk of mortality, sepsis and severe intraventricular hemorrhage (27). Bromberger et al demonstrated that exposure to antibiotics during labor did not change the clinical spectrum of disease or the onset of clinical signs of infection within 24 hours of birth for term infants with GBS infection and concluded that 48 hours stay is not required to monitor asymptomatic term infants exposed to intrapartum antibiotics for onset of GBS infection (28). In another study, carriers of GBS disease were detected by screening all women at 28 weeks and treated with intravenous ampicillin in labor, 1gr every 6 hours until delivery. The intervention has coincided with a significant decrease in the incidence of blood culture positive, early onset group B streptococcal disease (EOGBSD) to 0.2 and urine streptococcal antigen positive disease to 0.6 per 1000 live births. With no intervention the rates for EOGBSD remain largely unchanged at about 2 per 1000 lives (29).

Previously, the standard approach was to evaluate and treat empirically all neonates whose mothers received antibiotics during labor, regardless of whether the infant had any signs or symptoms suggestive of infection. With the advent of recommendations for intrapartum antibiotic therapy to prevent early onset neonatal GBS

infection, this strategy is no longer practicable, because too many infants would thus be evaluated and treated needlessly. The administration of intravenous antibiotics to laboring mothers appears to reduce the incidence of group B streptococcal infections in neonates (30).

In conclusion, we suggest the standard cefazolin prophylaxis (after cord clamping) for elective cesarean section. Moreover, we suggest cefazolin before incision for non elective cesarean section.

REFERENCES

1. Killian CA, Graffunder EM, Vinciguerra TJ, Venezia RA. Risk factors for surgical site infections following cesarean section. Infect Control Hosp Epidemiol 2001;22(10):613-7.

2. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap III LC, Wensrom KD, editors. Williams Obstetrics. 21st edition. New York, WB Saunders. 2005; p:587-606.

3. Smaill F Hofmeyr GJ. Antibiotic prophylaxis for cesarean section,. Cochrane Database Syst Rev 2002;3: CD000933.

4. Johnson A, Young D, Reilly J. Cesarean section surgical site infection surveillance. J Hosp Infect 2006;64(1): 30-5.

5. OpØien HK, ValbØ A,Grinde Andersen A, Walberg M. Post cesarean surgical site infections according to CDC standards: Rates and risk factors: A prospective cohort study. Acta Obstet Gynecol Scand 2007;86(9): 1097-102.

6. Thigpen BD, Hood WA, Chauhan S, Bufkin L, Bofill J, Magann E, et al. Timing of prophylactic antibiotic administration in the uninfected laboring gravida: A randomized clinical trial. Am J Obstet Gynecol 2005;192(6):1864-68.

7. Wax JR, Hersey K, Philput C, Wright MS, Nichols KV, Eggleston MK, et al. Single dose cefazolin prophylaxis for post cesarean infections: before vs. after cord clamping. J Matern Fetal Med 1997;6(1):61-5.

8. Sullivan SA, Smith T, Chang E, Hulsey T, Van dorsten JP, Soper D. Administration of cefazolin prior to skin incision is superior to cefazolin at cord clamping in preventing post cesarean infections morbidity: a randomized, controlled trial. Obstet Gynecol Survey 2007;62(10):640.

9. Balter S, Zell ER, O'Brien KL, Roome A, Noga H, Thayu M, et al. Impact of intrapartum antibiotics on the care and evaluation of the neonate. Pediatr Infec Dis J 2003;22(10): 853-57.

10. Rizk DE, Nsanze H, Mabrouk MH, Mustafa N, Thomas L, Kumar M. Systemic antibiotic prophylaxis in elective cesarean delivery. Int J Gynaecol Obstet 1998;61(3):245-51.

11. Rouzi AA, Khalifa F, Ba'aqeel H, Al Hamdan HS, Bondagji N. The routine use of cefazolin in cesarean section. Int J Gynaecol Obstet 2000;69(2): 107-12.

12. Phelan JP, Pruyn SC. Prophylactic antibiotics in cesarean section: A double blind study of cefazolin. Am J Obstet Gynecol 1979;133(5):474-8.

13. Wong R, Gee CL, Ledger WJ. Prophylactic use of cefazolin in monitored obstetric patients undergoing cesarean section. Obstet Gynecol 1978;51(4):407-11.

14. Rauniar GP, Das BP, Banerje B, Bhattacharya SK. Current status of prophylactic use of antimicrobial agents for cesarean section in a tertiary care teaching hospital in eastern Nepal. Nepal Mad Coll J 2006;8(1): 14-8.

15. Mah MW, Pyper AM, Oni GA, Memish ZA. Impact of antibiotic prophylaxis on wound infection after cesarean section in a situation of expected higher risk. Am J Infect Control 2001;29(2): 85-8.

16. Shah S, Mazher Y, John IS. Single or triple dose piperacillin prophylaxis in elective cesarean section. Int J Gynaecol Obstet 1998;62(1): 23-9.

17. Rudge MV, Atallah AN, Peracoli JC, Tristao AR, Mendonca NM. Randomized controlled trial on prevention of post cesarean infection using penicillin and cephalotin in Brazil. Acta Obstet Gynecol Scand 2006;85(8):945-8.

18. Meyer NL, Hosier KV, Scott K, Lipscomb GH. Cefazolin versus cefazolin plus metronidazole for antibiotic prophylaxis at cesarean section. South Med J 2003;96(10):992-5.

19. Chelmow D, Hennesy M, Evantash EG. Prophylactic antibiotics for non laboring patients with intact membranes undergoing cesarean delivery: An economic analysis. Am J Obstet Gynecol 2004;191(5): 1661-5.

20. Kayihura V, Osman NB, Bugalho A, Bergstrom S. Choice of antibiotics for infection prophylaxis in emergency cesarean sections in low-income countries: A cost–benefit study in Mozambique. Acta Obstet Gynecol Scand 2003;82(7):636-41.

21. Andrews WW, Hauth JC, Cliver SP, Savage K, Goldenberg RL. Randomized clinical trial of extended spectrum antibiotic prophylaxis with coverage for

Ureaplasma urealyticum to reduce post cesarean delivery endometritis. Obstet Gynecol 2003;101(6):1183-9.

22. Huskins WC, Ba Thike K, Festin MR, Limpongsanurak S, Lumbiganon P, Peedicayil A, et al. Prophylaxis in cesarean section. Int J Gynaecol Obstet 2001;73(2): 141-5.

23. Noyes N, Berkeley AS, Freedman K, Ledger W. Incidence of postpartum endomyometritis following single-dose antibiotic prophylaxis with either ampicillin /sulbactam, cefazolin, or cefotetan in high risk cesarean section patients. Infect Dis Obstet Gynecol 1998;6(5): 220-3.

24. Moore MR, Schrag SJ, Schuchat A. Effects of intrapartum antimicrobial prophylaxis for prevention of group B streptococcal disease on the incidence and ecology of early – onset neonatal sepsis. Lancet Infect Dis 2003;3(4): 201-3.

25. Daley AJ, Isaacs D. Ten years study on the effect of intrapartum antibiotic prophylaxis on early onset group B streptococcal and Escherihia coli neonatal sepsis in Australasia. Pediatr Infect Dis J 2004;23(7):630-4.

26. Edwards RK, Jamie WE, Sterner D, Gentry S, Counts K, Duff P. Intrapartum antibiotic prophylaxis and early onset neonatal sepsis patterns. Infect Dis Obstet Gynecol 2003;11(4): 221-6.

27. Paul DA, Coleman MM, Leef KH, Tuttle D, Stefano JL. Maternal antibiotics and decreased periventricular leukomalacia in very low birth weight infants. Arch Pediatr Adolesc Med 2003;157:145-46.

28. Bromberger P, Lawrence JM, Braun D, Saunders B, Contreras R, Petitti DB. The influence of intrapartum antibiotics on the clinical spectrum of early onset group B streptococcal infection in term infants. Pediatrics 2000;106(2 pt 1):244-50.

29. Jeffery HE, Lahra MM. Eight years outcome of universal screening and intra partum antibiotics for maternal group B streptococcal carriers. Pediatrics 1998;101(1):67-73.

30. Allen SR. Management of asymptomatic term neonates whose mothers received intra partum antibiotics part 1: Rationale for intra partum antibiotic therapy. Clin Pediatr 1997;36(10):563-68.