

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

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### 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.  
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### 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<sup>2</sup>) were associated with increased risk (5). Thigpen et al studied

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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  $\geq 37$  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 theoretically 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<sup>2</sup> 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 <sup>2</sup> )	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
<b>Maternal fever</b>			
2 <sup>nd</sup> day	9(4.6)	3(3.3)	.756
until 40 <sup>th</sup> day	1(0.5)	0(0.0)	1.0
Total	10(5.1)	3(3.3)	0.761
<b>Surgical site opening</b>	0(0.0)	1(1.1)	0.317
<b>Metritis</b>	0(0.0)	0(0.0)	-
<b>Need for IV line</b>			
1 <sup>st</sup> day	5(2.6)	1(1.1)	0.668
3 <sup>rd</sup> day	4(2.0)	1(1.1)	1.0
7 <sup>th</sup> day	3(1.5)	0(0.0)	0.554
Total	5(2.6)	1(1.1)	0.668
<b>Neonatal sepsis</b>			
1 <sup>st</sup> day	4(2.0)	1(1.1)	1.0
3 <sup>rd</sup> day	3(1.5)	1(1.1)	1.0
7 <sup>th</sup> day	3(1.5)	0(0.0)	0.554
Total	4(2.0)	1(1.1)	1.0
<b>Need for NICU</b>			
1 <sup>st</sup> day	5(2.6)	1(1.1)	0.668
3 <sup>rd</sup> day	4(2.0)	1(1.1)	1.0
7 <sup>th</sup> 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
<b>Age (year)</b>			
<25	66(33.7)	40(44.0)	0.208
25-29	60(30.6)	26(28.6)	
>29	70(35.7)	25(27.5)	
<b>Parity</b>			
1	92(46.9)	42(46.2)	0.092
2	55(28.1)	35(38.5)	
3-6	49(25)	14(15.4)	
<b>Cesarean type</b>			
elective	179(91.3)	74(81.3)	0.015
non elective	17(8.7)	17(18.7)	
<b>BMI* (kg/m<sup>2</sup>)</b>			
≤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

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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  $\leq 1500$  grams, maternal administration of parenteral 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.

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