Research Article

Single vs Multiple Dose of Cefazolin Prophylaxis in Elective Cesarean Section

Perbandingan Cefazolin Dosis Tunggal dengan Dosis Multipel pada Seksio Sesarea Berencana

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Abstract

Introduction: Caesarean section (CS) is one of port d' entrée from infection in women and it is related to maternal morbidity during puerpureal period. Until now, there is still lack of consensus regarding prophylactic antibiotic protocol before CS procedure. This study aims to determine the comparative efficacy between single dose and multiple doses of cefazolin prior incision toward the incidence of maternal infection.

Methods: This was a single-blind, randomized, clinical trial study with two methods of intervention including 2-gram single dose cefazolin at 30 minutes' prior incision and 2-gram single dose cefazolin at 30 minutes' prior incision continued 1-gram cefazolin after 8 hours of procedure. We recruited women undergone elective CS at Fatmawati and Anna Hospital, Jakarta from January to March 2016. The primary outcomes were surgical site infection, urinary tract infection, and endometritis based on clinical findings during 30 days of follow-up period.

Results: A total of 46 subjects were recruited which 23 of them were in single dose cefazolin group and the other 23 subjects were in multiple dose of cefazolin group. There were 9 subjects having infection (19.6%). There was no statistical difference in the incidence of infection between two groups (p=1.00; relative risk 0.80, 95% CI 0.25-2.61).

Conclusion: Single dose of cefazolin shows similar rates of infection incidence to multiple dose. Therefore, single dose of cefazolin can be a protocol in CS based on its efficacy and efficiency.

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Keywords: cefazolin, maternal infection, multipe dose, single dose

Abstrak

***Tujuan**: Operasi seksio sesarea (SC) merupakan salah satu pintu masuk infeksi yang berkaitan dengan morbiditas maternal pasca-persalinan. Hingga saat ini, belum ada protokol tetap mengenai dosis antibiotik profilaksis sebelum prosedur SC. Penelitian ini bertujuan mengetahui adakah perbedaan kejadian infeksi pascapersalinan dengan penggunaan cefazolin profilaksis dosis tunggal dan multipel.*

***Metode**: Penelitian ini merupakan penelitian uji klinis acak tersamar tunggal dengan dua kelompok perlakuan yaitu cefazolin dosis tunggal 2 gram pada 30 menit sebelum insisi dan cefazolin dosis multipel (cefazolin dosis tunggal 2 gram pada 30 menit sebelum insisi dan 1 gram pada delapan jam setelah dosis awal). Penelitian dilakukan pada wanita yang menjalani operasi SC berencana di RS Fatmawati dan RS Anna, Jakarta pada Januari - Maret 2016. Luaran utama yang dinilai adalah infeksi selama 30 hari setelah prosedur meliputi infeksi luka operasi, infeksi saluran kemih dan endometritis berdasarkan temuan klinis.*

***Hasil**: Didapatkan 46 subjek dengan 23 subjek pada kelompok cefazolin dosis tunggal dan 23 subjek pada cefazolin dosis multipel. Didapatkan 9 dari seluruh subjek mengalami infeksi (19,6%). Tidak ditemukan perbedaan kejadian infeksi pada kedua kelompok perlakuan (p=1,00; risiko relatif 0,8 95% IK 0,25- 2,61).*

***Kesimpulan**: Dosis tunggal cefazolin memperlihatkan angka kejadian infeksi yang serupa dengan dosis ganda. Oleh karena itu, pemberian dosis tunggal dapat dijadikan petunjuk dalam prosedur SC terkait efikasi dan efisiensinya.*

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***Kata kunci**: cefazolin, dosis multipel, dosis tunggal, infeksi pasca-operasi*

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INTRODUCTION

In Indonesia, there is unavailable data of cesarean section (CS) rate. Meanwhile, there were around 1,341 CS procedure per year in Dr. Cipto Mangunkusumo hospital as the center of referral hospital in Indonesia. It meant that CS procedure covered 38% of all delivery cases. In 1999-2000, 13.9% CS was performed without medical indication.[1] Cesarean section often leads to complications, including surgical site infection (SSI), endometritis, and urinary tract infection.[2] These complications can increase the length of stay in hospital which impacts to the health expense. According to data in United States, complications after CS procedure resulted 10 days of extra care in hospital and it spent about USD 2,000 per case.[3] Meanwhile, the risk of complications after CS was different from 0.3% to almost 25.3% in Turkey.[4] Committee of Prevention and Infection Control at

Dr. Cipto Mangunkusumo Hospital stated that in Department of Obstetrics and Gynecology starting from January to December 2011, the incidence of infection was varied between 0.8% and 37.5%.

Currently, standardization of procedures for antibiotic prophylaxis, the type and mode of administration to patients undergoing CS are still unclear and they are varied among operators; however, this procedure is commonly used. Mini pilot study in Dr. Cipto Mangunkusumo hospital showed that there were different antibiotics for CS procedure consisting of Clavomax 1 g intravenous route at 60 minutes prior to incision, Cefazolin 2 g intravenous route at 30-60 minutes prior to incision, and Ceftriaxone 2 g intravenous route at 30 minutes before incision or after CS surgery.[5] Another study in the United States stated that 95.5% operators used a class of antibiotics in the first generation of cephalosporine; whereas, 84.4% of them used cefazolin as prophylactic in CS.[6]

Of the various types on infection prevention in CS, one of the major cost component is the use of antibiotics. Antibiotics are given 30 minutes before incision to reach the highest concentration on the tissue to prevent wound infection effectively. Sometimes, the complications are worsened by general condition and low nutritional status.[7] Antibiotics are usually given before performing surgery; nevertheless, several narrow spectrum antibiotics sometimes were injected after cord clamping for the baby's interest. On the other studies, broad spectrum antibiotics had proof to be able to lower the number of maternal morbidity without affecting the baby.[2] Looking to the differences in infection prevention procedures in CS procedure, we consider that we have to conduct the study about the administration of antibiotic prophylaxis in CS procedure. Therefore, this study aims to determine the comparative efficacy between single dose and multiple doses of cefazolin prior incision toward the incidence of maternal infection.

METHODS

This study was a single blinded randomized clinical trial study between single dose of cefazolin prophylaxis as control group and multiple doses of cefazolin as intervention group in patients undergoing elective CS surgery. The study was conducted at Fatmawati and Anna Hospital from January to March 2016.

Subjects in this study were pregnant women who delivered by elective CS at Fatmawati and Anna Hospital from January to March 2016 fulfilling the inclusion criteria. The inclusion criteria were pregnant women that planned to perform the elective CS and they were willing to participate in this study. Meanwhile, the exclusion criteria were women with history of allergy to cephalosporin generation, signs and symptoms of infection prior to surgery, immunonsuppressive disease, and having an auto-immune disease.

We recruited samples by consecutive sampling. We took all pregnant women who gave birth by elective CS in the Fatmawati and Anna Hospital according to inclusion and exclusion criteria.

We examined patiens' history and performed physical examination. Healthy patients would go into routine blood test to rule out the infection. Patients who matched the criteria for inclusion obtained explanation and information about this study. Those who agreed to be subject were asked to sign the informed consent. We told subjects to complete the characteristics' demography for this study. Subjects were asked about their full name, complete address, and phone number. Subjects got the serial number and to enroll in this study, they opened the envelope containing of randomization of intervention. Trained personnel determined the treatment given to the subject. Subjects were divided into 2 groups namely group 1 which got 2-gram cefazolin antibiotic once at 30 minutes before incision and group 2 obtaining 2-gram cefazolin at 30 minutes before incision and continued by 1-gram cefazolin at 8 hours after CS procedure.

Patients then underwent CS surgery. During the surgery, we monitored the duration of surgery and the amount of blood lost. Subjects who experienced surgery beyond 3 hours and the amount of blood >1500 cc were excluded and considered as drop out. We did not count the drop out subjects into analysis which meant that we did not do the intention to threat analysis. The subject of study was prohibited taking antibiotics or traditional medicine after surgery.

Observation was held on days-1, 2, 3, 7, 14, and 30. We observed them through examination of vital signs including blood pressure, heart rate, respiratory rate, temperature and also other clinical complaints. Signs of infection in SSI and urinalysis were also assessed at 24-hour post-

surgery. Urinalysis was performed to check the bacteria in the urine. Any patiens with positive bacteria in urine considered as infected. Patients who were lost to follow-up counted as drop out.

Data were analyzed statistically. Researchers analyzed normality of numerical data using Shapiro-Wilk test due to small sample size. The data then were presented in mean (standard deviation) for normal distribution or median (minimum-maximum) for abnormal distribution. Data on the number of infection frequency between 2 groups were analyzed using Fisher-exact test. The relative risk (RR) were calculated with 95% confidence interval at each output. We did not do the intention to threat analysis. We used SPSS version 22 for Windows.

RESULTS

Total subjects obtained in this study were 58 women; which 46 of them were followed until the end of study. They consisted of 23 women in each study group (single dose and multiple doses of cefazolin administration). There were 12 women dropped out (5 women from single dose group and 7 women from multiple dose group). The mean age of the women was 31.5 (SD 5.7) years old and the median of parity was 1 (min-max 0-4) time (s).

The characteristics of women based on laboratory parameters were assessed through blood test and urinalysis. Based on the results of blood test, the mean of hemoglobin value was 11.4 (SD 1.4) g/dl; median of leukocyte was 10,696/μl with the value from 4,500 to 25,300/μl. All patients' urinalysis showed negative result of nitrite and bacteria; however, the majority of results described +1 of epithelial cells.

Of the total 46 women, we found 9 women (19.6%) having an infection during follow-up period. Infection occurred in the form of asymptomatic bacteriuria. Four incidences of infection were happened in subject obtaining a single dose of cefazolin (8.7%, p=1.00), and five infections were occurred in subjects in multiple doses of cefazolin (10.9%, p=1.00). We did not found subject with wound infection and endometritis.

Table 1. Age and Parity Characteristics of Women in This Study

Characteristics	Total	Single dose of Cefazolin (N= 23)	Multiple dose of Cefazolin (N= 23)
Age (years old)			
Mean (SD)	31.5 (5.7)	32.5 (5.7)	30.5 (5.7)
Parity			
Median (min-max)	1 (0-4)	1 (0-4)	1 (0-2)
Mode	1	1	1

** Normally distributed numerical data were presented as mean (standard deviation); Abnormally distributed data were presented in median (minimum-maximum)*

Table 2. Characteristics of Women based on Laboratorium Examination before Cesarean Section (CS) Surgery

Variables	Single dose of cefazolin (N=23)	Multiple dose of cefazolin (N=23)
Blood analysis		
Hemoglobin (g/dl) (mean (SD))	11.1 (1.2)	11.7 (1.6)
Leukocyte (/μl) (median (min-max))	10,980	88,400
	(5,980-25,300)	(4,500-17,720)

Variables	Single dose of cefazolin (N=23)	Multiple dose of cefazolin (N=23)
Urinalysis		
Color		
Pale yellow	22	22
Yellow	1	1
Clarity		
Clear	11	12
Slightly turbid	10	10
Turbid	2	1
pH (median (min-max))	6.5 (5-7)	6.5 (6-7)
Nitrite		
Positive	0	0
Negative	23	23
Leukocyte esterase		
Positive	18	18
Negative	5	5
Epithelial cells		
Positive 2	1	1
Positive 1	18	22
Negative	4	0
Bacteria		
Positive	0	0
Negative	23	23

** Normally distributed numerical data were presented as mean (standard deviation); Abnormally distributed data were presented in median (minimum-maximum); Categorical data were presented as frequency.*

Table 3. Infection Incidence After Cesarean Section (CS) Surgery

Variables	Single dose of cefazolin N=23 (%)	Multiple dose of cefazolin N=23 (%)	p	RR (95% CI)
Post surgery infection	4 (8.7%)	5 (10.9%)	1.00*	0.80 (0.25-2.61)
Surgical wound infection	0 (0%)	0 (0%)	-	-
Urinary tract infection	4 (8.7%)	5 (10.9%)	1.00*	0.80 (0.25-2.61)
Endometritis	0 (0%)	0 (0%)	-	-
Fever morbidity	0 (0%)	0 (0%)	-	-

*RR= relative risk of single dose group to multiple dose group; *Fisher-exact Test*

DISCUSSION

This study was a single blinded randomized clinical trial that compared the effectiveness of single vs multiple doses of cefazolin in preventing maternal infection after elective surgery of CS. The main finding of this study was similar incidence of infection between two groups. Therefore, we propose the use of a single dose of cefazolin as prophylactic antibiotic in elective CS to be applied in our practice.

In this study, the primary outcome was the incidence of post-operative infection including SSI, urinary tract infection, and endometritis. These three infections are the highest risk of infection up to 5-20 folds compared with women with vaginal delivery.[8] These three infections also contribute to the morbidity causing high cost of hospital treatment to post labour women.[9]

There were limitations to this study. The small sample size including 46 women lowered power of this study. In the determination of urinary tract infection, we confirmed the diagnosis only through urinalysis without culture examination due to limited resources; thus, it might be impacted to the false positive results.

Subjects of this study focused on women with elective CS which actually had a relatively low risk of infection. In the last decade, there was a trend of increasing demand for elective CS related to patients' request so that we considered that this study became essential to determine the effectiveness of prophylactic antibiotic.[10,11]

The result found that the incidence of infection happened in 9 of 46 women (19.6%) where all infections were asymptomatic bacteriuria. The incidence of infection was slightly higher than previous report which stated that the incidence of postoperative infection in the study by Witt, et al. comparing cefazolin before incision, after cord clamping, and placebo. Administrating cefazolin before the incision pointed out 4.9% of post-operative infection incidence.[12] Kalaranjini, et al. also conducted a similar study and found that no subjects with endometritis found by administration of cefazolin as a prophylactic antibiotic. The incidence of fever and urinary tract infection was also low below 2.5%.[13] The incidence was higher in this study due to differences in the operational definition and determination of the urinary tract infection status compared with previous studies. On the other hand, we did not reveal the cases of endometritis and SSI. This study was consistent with previous study confirming the importance of antibiotic prophylaxis; however, subjects with placebo had postoperative incidence of infection up to 12.1%.[13] In another study, Tita, et al. concluded that the administration of prophylactic antibiotic decreased the incidence of infection by 50%.[11] Smaill, et al. also mentioned that prophylaxis in elective CS or non-elective CS could decrease the risk of infection by 70%.[14]

In this study, we performed single dose of cefazolin before incision. This is in line with the conclusion of systematic review that also supported the provision of cefazolin as a prophylactic antibiotic regimen of choice before incision.[10] Through the development of study related to prophylactic antibiotic regiment and the right time of administration in CS during last decade, systematic review by Mackeen, et al. stated that of 10 recent studies concluded that prophylactic antibiotic before incision was superior compared with administration after cord clamping. (RR 0.57 (95% CI 0.45-0.72)).[15]

Differences in dosage of prophylactic antibiotic also had been studied previously. The study compared the effectiveness of prophylactic antibiotic of multiple doses and a single dose. The antibiotic was ampicillin/amoxicillin and metronidazole. The study indicated that there were no difference of maternal infection risks in these two treatments. Thus, it was important to reduce the burden of labor cost in women undergoing CS surgery. Moreover, there has not been consensus in general and consistently applied so that the finding of this study could form the basis of daily clinical practice guideline.[16] Trials in emergency CS without the risk of infection by using regiment of gentamicin and metronidazole concluded that a single dose was sufficient to reduce the risk of SSI and there was not different result between multiple dose and a single dose.[17]

We obtained study results' difference in the incidence of infection was between 4/23 and 5/23 so that it was interpreted as similar clinical efficacy. Apart from that, Fischer exact test revealed $p>0.05$, which meant no statistically significant.[18]

Based on the result of this study, it showed that there were not significant differences in giving cefazolin either single or multiple doses to the incidence of infection. This might imply that the effectiveness of a single dose of cefazolin was as effective as the provision of multiple doses of cefazolin to prevent postoperative maternal infection after elective CS.

One variable that had not been investigated in this study was the morbidity in neonates. However, administration of cefazolin as prophylaxis indicated low incidence of neonatal infection (≤13%) in women who underwent CS surgery with a low risk of infection. However, systematic review on the administration of prophylactic antibiotic stated that we locked number of studies focussing on side effects and incidence of infection in neonates so that we could not conclude the effectiveness of prophylactic antibiotic to the neonatal outcome.[14]

CONCLUSION

Cefazolin effectively prevents maternal infection in postoperative elective CS and there is no difference in the effectiveness between a single dose and multiple doses of cefazolin in preventing maternal infection.

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REFERENCES

1. Wounds WW. An overview of surgical site infections: Aetiology, incidence and risk factors. EMWA. 2005; 5.
2. Mitt P, Lang K, Peri A, Maimets M. Surgical-site infections following cesarean section in an Estonian university hospital: Postdischarge surveillance and analysis of risk factors. Infect Control Hosp Epidemiol. 2005; 26(5): 449-54.
3. Ronald F, Jack S, Juan P, Edi V, Shali M, Sun K, et al. Current debate on the use of antibiotic prophylaxis for cesarean section. BJOG. 2011; 2: 193-201.
4. WHO. WHO statement of cesarean section rate. 2015. [Internet] Available from:http://apps.who.int/iris/bit-stream/10665/161442/1/WHO_RHR_15.02_eng.pdf
5. Huskins WC, Ba-Thike K, Festin MR, Limpongsanurak S, Lumbiganon P, Peedicayil A, et al. An international survey of practice variation in the use of antibiotic prophylaxis in cesarean section. Int J Gynecol Obstet. 2001; 73(2): 141-5.
6. Amy E, Jennifer D, Suzanne P, Luisa A, William A, Alan T. Antibiotic prophylaxis for cesarean delivery: survey of maternal-fetal medicine physicians in the U.S. J Maternal-Fetal Neonatal Med. 2012; 25(8): 1264-6.
7. Ezra M. Karakteristik Ibu yang mengalami persalinan dengan seksio sesarea yang dirawat inap di Rumah Sakit Umum Daerah Sidikalang Tahun 2007. USU Repository 2008.
8. Gibbs RS. Clinical risk factors for puerperal infection. Obstet Gynecol. 1980; 55(3): 178S-83S.
9. Perencevich EN, Sands KE, Cosgrove SE, Guadagnoli E, Meara E, Platt R. Health and economic impact of surgical site infections diagnosed after hospital discharge. Emerging infectious diseases. 2003; 9(2): 196.
10. Witt A, Döner M, Petricevic L, Berger A, Germann P, Heinze G, et al. Antibiotic prophylaxis before surgery vs after cord clamping in elective cesarean delivery: a double-blind, prospective, randomized, placebo-controlled trial. Arch Sur. 2011; 146(12): 1404-9.
11. MacDorman MF, Menacker F, Declercq E. Cesarean birth in the United States: Epidemiology, trends, and outcomes. Clin Perinatol. 2008; 35(2): 293-307.
12. Witt A, Döner M, Petricevic L, Berger A, Germann P, Heinze G, et al. Antibiotic prophylaxis before surgery vs after cord clamping in elective cesarean delivery: A double-blind, prospective, randomized, placebo-controlled trial. Arch Sur. 2011; 146(12): 1404-9.
13. Kalaranjini S, Veena P, Rani R. Comparison of administration of single dose ceftriaxone for elective caesarean section before skin incision and after cord clamping in preventing post-operative infectious morbidity. Arch Gynecol Obstet. 2013; 288(6): 1263-8.
14. Smaill F, Hofmeyr GJ. Antibiotic prophylaxis for cesarean section. Cochrane Database Syst Rev. 2002(3): CD000933.
15. Shakya A, Sharma J. Comparison of single versus multiple doses of antibiotic prophylaxis in reducing post-elective caesarean section infectious morbidity. Kathmandu Univ Med J (KUMJ). 2010; 8(30): 179-84.
16. Westen EH, Kolk PR, Velzen CL, Unkels R, Mmuni NS, Hamisi AD, et al. Single? dose compared with multiple day antibiotic prophylaxis for cesarean section in low? Resource settings, a randomized controlled, noninferiority trial. Acta Obstet Gynecol Scandinavica. 2015; 94(1): 43-9.
17. Lyimo FM, Massinde AN, Kidenya BR, Konje ET, Mshana SE. Single dose of gentamicin in combination with metronidazole versus multiple doses for prevention of post-caesarean infection at Bugando Medical Centre in Mwanza, Tanzania: A randomized, equivalence, controlled trial. BMC pregnancy and childbirth. 2013; 13(1): 123.
18. Dahlan MS. Besar Sampel dan Cara Pengambilan Sampel dalam Penelitian Kedokteran dan Kesehatan Edisi 3. Jakarta: Salemba Medika; 2010.