

Efficacy of Pre Incision Intravenous Single Dose of Cefazolin Versus Multiple Doses of Cefazolin for Antibiotic Prophylaxis for Caesarean Section

Babeeta¹, Kulhari Sandeep², Choudhary Deepak³

¹(M.D. Obstetrics & Gynaecology, Postgraduate Institute Of Medical Education And Research, Chandigarh, India)

²(Junior Resident, Pediatrics, Sardar Patel Medical College, Bikaner, India)

³(Junior Resident, Pediatrics, Sardar Patel Medical College, Bikaner, India)

Abstract

Aim : To study the efficacy of pre-incision intravenous single dose of cefazolin versus multiple doses of cefazolin for antibiotic prophylaxis for caesarean section.

Materials and methods: This was an interventional, open label, two armed, randomized study conducted in the Department of Obstetrics and Gynaecology at PGIMER, Chandigarh from July 2013 to October 2014. Two hundred women were enrolled in the study and randomized into two groups. Group A received single dose of cefazolin whereas Group B received multiple doses of cefazolin. Primary outcome of the study was occurrence of SSI and secondary outcomes included the incidence of febrile morbidity, UTI, endometritis and neonatal outcome.

Result: Incidence of SSI occurred was 8% in Group A and 10% in Group B (p-value of >0.05). There was no significant difference observed for secondary outcomes.

Conclusions: Present study indicates that use of pre-incision single dose of cefazolin for antibiotic prophylaxis is equally effective compared to multiple doses of cefazolin given over 24 hours in terms of development of SSI, and other infectious morbidity including fever, UTI and endometritis.

Keywords: Surgical Site infection, Urinary Tract Infection

I. Introduction

Infectious complications that occur after caesarean delivery are important and substantial cause of maternal morbidity and are associated with a significant increase in hospital stay. Postpartum infection remains among the top five causes of pregnancy related maternal mortality and morbidity worldwide¹. A woman who undergoes caesarean section has a 5-20 fold greater risk of postpartum infection than women having a vaginal delivery^{2, 3}. Following caesarean delivery maternal mortality and morbidity may result from a number of infections including endometritis, urinary tract infections and surgical site infections (SSI). Pelvic abscess, septic pelvic phlebitis, and pneumonia, although rare, are also known to contribute to considerable health and economic burdens⁴. The incidence of post caesarean infection varies widely worldwide from 2.5% to 20.5% in developed countries and from 40-75% in developing countries and it varies widely by population profile depending on several risk factors^{5,6}.

Low socioeconomic status, maternal medical disorders, immunosuppression, steroid use, obesity, frequent vaginal examinations and emergency caesarean section are some of the risk factors associated with post caesarean section infection⁷. Like most obstetrical interventions caesarean section is considered a clean-contaminated procedure when scheduled caesarean delivery without labour and/or ruptured membranes occurs and, contaminated when emergency caesarean delivery with labour and/or ruptured membranes occurs⁸. Post caesarean infections are polymicrobial, involving aerobes, anaerobes and ureaplasma. The main source of postpartum infection after caesarean section is the lower genital tract, particularly if the membranes are ruptured, but this still occurs with intact membranes following preterm birth. The most common isolated pathogens are anaerobes and gram negative aerobes. Gram negative aerobes include *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp and *Proteus* spp. The anaerobes include *Bacteroides* spp, *Clostridium* spp, and *Fusobacterium* spp⁹. In a systematic review of over 80 studies on the use of prophylactic antibiotics for caesarean delivery, the Cochrane Collaboration specifically examined the effect of prophylactic antibiotics on the rate of maternal postpartum fever, WI, endometritis, UTI, serious infectious morbidity/death, as well as maternal side effects and length of hospital stay¹⁰. The use of antibiotics was associated with a statistically significant reduction, with an effect size of 40-65%. Endometritis and WI were reduced following both elective and emergency caesarean delivery by 60-70% and 30-65% respectively. Routine use of prophylactic antibiotics reduced the risk of post caesarean section fever and infections by over 50%.Based on the above systematic

reviews; this benefit applies to both non-elective as well as elective procedures. The reduction of endometritis by two thirds to three quarters and decrease in wound infections justify a policy of recommending prophylactic antibiotics to women undergoing elective or non-elective cesarean section (CS). Administration of antibiotic within 30-60 minutes of surgery is considered optimal as this maximizes tissue and blood antibiotic concentrations at surgical site. A systematic review by Baaqeel and Baaqeel in 2013 highlights the important debate on the timing of prophylactic antibiotics for CS and confirms that pre-incisional rather than post cord clamping administration of antibiotics in women undergoing CS significantly reduces the rate of postoperative maternal infectious morbidity without any adverse effects on the newborn, however, the long-term effects on the offspring were not evaluated¹¹. Most institutions in the developed countries are presently using single dose cefazolin as prophylaxis for caesarean section as it is recommended by most international obstetric and gynaecological bodies all over the world, in many countries there is no consensus on which antibiotic regimen to use, especially in low-resource settings where surgery is often performed under poor aseptic conditions¹². In developing countries antibiotics are used more liberally due to concerns of higher incidence of infection associated with surgery even though there is no concrete data to prove the same.

However, multiple dose regimen of antibiotic does not offer any added benefit when compared with a single dose regimen, the single dose being not only less expensive but more likely to ensure universal utilization of prophylactic antibiotics for caesarean section, especially in under-resourced countries and additionally will lower the incidence of antimicrobial resistance¹³. A protocol of prolonged antibiotic use has been followed for caesarean prophylaxis in the labour ward of our institute (PGIMER, Chandigarh) for many years. The precise incidence of infectious morbidity associated with caesarean section at PGIMER is not known, however it is expected to be closer to 20% or even more. There is a need to determine the incidence of post-caesarean infection in our labour ward as well as to compare the use of single dose of prophylactic antibiotics with multiple doses (as is presently followed) for caesarean sections. Therefore this study had been planned to compare a single dose of cefazolin with multiple doses of cefazolin (total 4 doses) for antibiotic prophylaxis for caesarean section.

II. Methods

Participants: This was an interventional, open label, two armed, randomized study conducted in the Department of Obstetrics and Gynaecology at PGIMER, Chandigarh from July 2013 to October 2014. Two hundred pregnant women admitted in Labour ward for elective or emergency caesarean sections were enrolled in the study. All pregnant women who required to undergo emergency or elective caesarean section and consented for the study were eligible for inclusion and the study excluded all pregnant women with fever (temperature of 38°C and above), prolonged obstructed labor, prolonged and premature rupture of membranes (rupture of membrane more than twelve hours). Pregnant women presenting with features of chorioamnionitis (i.e. foul smelling lochia, uterine tenderness associated with fever) and allergies to the antibiotics used or those who had used antibiotics in the 48 hours preceding the operation, on steroids or immunosuppressive agents, uncontrolled diabetes (either on insulin or blood sugar not controlled on diet), heart disease and HIV+ patients were excluded from the study.

Sample size estimation: In this study, the hypothesis was “there is no clinically significant difference between a single preoperative dose of cefazolin and multiple doses of cefazolin given over 24 hours for prevention of post caesarean section infection”. Lyimo et al in their randomized study found that surgical site infection occurred 4.8% in receiving single dose compared to 6.4% in receiving multiple doses¹⁴. If we assume that hypothesized difference to be 2% then sample size needed to reject the hypothesis at $\alpha=0.05$ & $\pi=0.02$ is 100 in each arm.

Randomization and Interventions: Intervention was started after randomization into two groups (Group A and Group B) using a computer generated randomization table after decision for caesarean section had been made and all the eligibility criteria had been ascertained.

Group A was consisting of those patients who received a single dose of 2g cefazolin intravenously 30-60 minutes before operation.

Group B was consisting of those patients who received multiple doses of cefazolin (2g cefazolin intravenously 30-60 minutes before operation followed by 1g every 8 hours for 24 hours i.e. total 4 doses). Caesarean section was performed by the obstetric registrar/consultant according to the routine protocol. Data on parity, BMI, indication of caesarean delivery, number of vaginal examinations, premature rupture of membranes, duration of surgery, blood loss more than 1 liter, type of anesthesia and American Society of Anesthesiologists (ASA) score were recorded¹⁵.

All the studied women were kept under daily monitoring during postoperative hospitalization period and after being discharged from hospital .They were also assessed at post-op day 7-8 (around the time of suture removal) and day 30-35 (telephonically if not able to come for follow-up). Complete blood count including differential and urine culture was performed on 2nd postoperative day. The occlusive dressing applied in the operation theatre was removed on 2nd postoperative day. The women were discharged on 3rd postoperative day in whom there were no signs of infection or complications and asked to return on day 7-8 postop for stitch removal.

The following information was recorded daily during the hospitalization period: vital signs, clinical signs and symptoms of wound infection (such as induration, rise in temperature, erythema, pain and discharge from the wound) and signs and symptoms of infections of other sites. Febrile morbidity was defined as temperature above 38°C at least 4 hours apart on two or more occasions excluding the first 24 hours after delivery. Postoperative superficial and deep incision soft tissue SSI and intraabdominal abscess was defined according to published criteria of Mangram et al (1999)¹⁶.Specimens for both aerobic and anaerobic bacteriologic culture was taken in case of a postoperative wound infection or collection. Endometritis was diagnosed in the presence of at least one of the following conditions¹⁷.

- Culture positive from endometrial fluid
- At least two of the following signs- fever (38°C), uterine tenderness, purulent discharge from the uterus.

In the presence of febrile morbidity or wound infection, after obtaining appropriate cultures from suspected sites of infection a different antibiotic therapy of wider spectrum was initiated typically consisting of amoxicillin, gentamycin and metronidazole until all microbiological investigations were reported back following which modification of antibiotic therapy were made based on culture and sensitivity results.

III. Statistical Analysis

All data were extracted from patient’s files and used to fill in a case record form designed for this study. Mean, standard deviation (SD), median, inter quartile range, frequencies, percentage were analyzed by applying descriptive statistics. Normality of continuous data was checked by using one sample Kosmogrove-Simonov test. If data was normally distributed then independent t test is used to compare the two independent group mean otherwise Mann- Whitney test was used for the same. For categorical data Chi Square test with or without continuity correction was used to analyze the association between group categories. Binomial logistic regression was applied to determine the independent factor for post op surgical site infection, febrile morbidity, endometritis and urinary tract infection. Principle of “intervention to treat analysis “ was used at $p < .05$ level of significance with 95% confidence interval .Microsoft Excel 2010 advanced version of SPSS software was used for data analysis.

IV. Results

This study was conducted in the department of Obstetrics and Gynaecology department PGIMER, Chandigarh from July 2013 to October 2014. Total numbers of caesarean sections carried out during this period (2013-2014) were 1730 with an incidence of 31.5% of all the births, out of which 74.1% were emergency and 25.9% were elective. Out of these, two hundred women were enrolled in the study after applying inclusion and exclusion criteria.

They were randomized by computer generated random number tables into two groups for receiving antibiotic prophylaxis, Group A (single dose cefazolin) and group B (multiple doses of cefazolin).There were 100 women in each group. No participants in either arm were lost to follow-up. There was an even distribution of the participants with respect to demographic and other baseline characteristics in both arms (p -value >0.05) as shown in Table 1.

Table 1: Baseline maternal parameters

Parameters	Group A (N=100)	Group B (N=100)	P value
Age (years) (Mean ± SD)	27.67 ±4.69	27.87 ± 4.37	0.755
Parity (Mean ± SD)	2.01 ± 1.02	2.38 ± 1.20	0.020
POG (weeks) (Mean ± SD)	36.58 ± 2.61	36.41 ± 2.75	0.654
BMI (kg/m ²) (Mean ± SD)	25.22 ± 3.56	24.55 ± 2.76	0.138
No. of vaginal examinations (Mean ± SD)	1.19 ± 1.08	1.14 ± 1.03	0.737
Duration of rupture of membranes(hours) (Mean ± SD)	3.82 ± 3.53	3.75 ± 3.36	0.886

Registered Pregnancies (%)	89	81	0.113
Previous caesarean (%)	28	40	0.073

POG- period of gestation, BMI-body mass index, DOR-duration of rupture

Table 2 : Primary Outcome

Primary outcome	Group A (N=100)	Group B (N=100)	P value
Superficial surgical site infection	8	10	0.614
i) Induration & erythema	1	3	
ii) Discharge serous	3	4	
purulent	2	2	
iii) Wound Dehiscence	2	1	
Deep surgical site infection	0	0	

* Yate's corrected Chi Square test

There were 8 and 10 patients in group A and group B respectively who had surgical site infection as defined by Mangram et al(1999)¹⁶. Induration along with erythema was present at the wound site in 1, three patients had serous discharge, two had purulent discharge, and in another two patients wound had to be opened up to rectus sheath (only skin and subcutaneous tissue) in Group A. Whereas in Group B, there were 3 instances of induration accompanied by erythema, four had serous discharge and two patients had purulent discharge from the abdominal wound. There was only one patient who required opening of the wound up to sheath for abscess formation in Group B. All these events were statistically comparable between the two groups ($p > 0.05$). There were no deep surgical site infections in either group. The only risk factor which correlated an increase in incidence of SSI was the booking status of a patient i.e. a patient was well supervised or not. Those women who developed SSI, a significantly higher number were unsupervised and this difference was highly significant ($p = 0.003$). None of the other risk factors for development of SSI were significantly different between the groups.

Table 3 - Secondary Outcomes

Secondary Outcomes	Group A (N=100)	Group B (N=100)	P value
Febrile Morbidity	5	6	0.756
UTI	7	9	0.614
Endometritis	2	3	0.651
Duration of hospital stay(days)	5.96 ± 3.96	6.27 ± 3.6	0.563
Neonatal sepsis (%)	8	5	0.390
NICU admission	(N=9)	(N=11)	0.927
NICU stay duration (days)(mean ± SE)	11.67±3.81	12.18±3.97	
Antibiotics Cost (Rs) (Mean± SE)	55.38±5.62	205.42±7.03	<0.0001*

UTI- Urinary Tract Infection, * Mann-Whitney U test, SE: Standard Error

There was no difference in the occurrence of Febrile morbidity, Endometritis, UTI, Allergic and other adverse effects of treatment, Side effects due to antibiotics, Maternal length of hospital stay, Neonatal outcome (including neonatal sepsis and NICU stay) in women who received either single dose or multiple dose of antibiotics. An overall infectious morbidity was noted in 18% and 24% women who included SSI, endometritis, UTI, and febrile morbidity alone without any associated complication.

V. Discussion

This study indicates that there is no difference in the occurrence of SSI or other infectious morbidity in women who received either single dose or multiple doses of antibiotics. Previous studies have reported that there is no added benefit of using multiples doses over single dose of antibiotics for prophylaxis of SSI^[18, 19]. For this reason the administration of pre-operative single dose antibiotic prophylaxis for emergency caesarean is recommendable. This is also supported by the 1998 Swedish and Norwegian consensus on the use of antibiotic

prophylaxis in surgery, which states that the choice of antibiotics should be generally conservative. Antibiotics used for therapy should be avoided in prophylactic regimens. In most cases, surgical antibiotic prophylaxis should be given as a single dose, and in no case should the prophylaxis time exceed 24 hours²⁰. Costs of medications are an important parameter especially in resource-limited settings. Multiple doses regime is associated with higher medication cost than single dose regime. In addition, the use of single dose regime reduces workload to the nurses, especially at night when only few nurses are on duty in the ward. This is in agreement with the available published literature reviewed already.

VI. Conclusion

The present study, therefore, indicates that use of pre-incision single dose of cefazolin for antibiotic prophylaxis is equally effective compared to pre-incision multiple doses of cefazolin given over 24 hours in terms of development of SSI, and other infectious morbidity including fever, UTI and endometritis. In addition there is an added advantage of lower cost of antibiotics incurred with use of single dose prophylaxis. The present study was not powered enough to detect the effect of antibiotic prophylaxis on the secondary outcomes such as incidence of endometritis and neonatal sepsis. The incidence of SSI in the present study is relatively higher, as compared to that reported by institutions from developed countries. Frequent and excessive use of antibiotics (over several days) is a potential risk for development of microbial resistance to the antibiotics and their inefficacy for the purpose of prophylaxis against SSIs. Therefore a single dose for antibiotic prophylaxis should be preferred over multiple doses.

Ethical Approval: This trial did not involve new drugs but only determined the efficacy of a single dose regime versus multiple dose regimes; however GCP and Declaration of Helsinki were observed. Clearance for conducting this study was sought from the PGIMER, Chandigarh Ethics Committee. An informed consent was requested from participants after explaining the study aims. For literate women, the consent information was provided before providing a copy of the consent form that each participant was required to sign. For non-literate women, the consent information was read in full, and participants were required to thumb print on the consent form to signify their acceptance to participate in the study. A nurse or doctor who was not part of the study was around to witness the verification counseling process for illiterate women. Authors declare that they have no conflict of interest.

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