



## Comparative Evaluation of Antibiotic Prophylaxis in Caesarean Section before Skin Incision and after Cord Clamping

Authors

**Chanda Rai<sup>1</sup>, Sunita Malik<sup>2</sup>, Harish Chellani<sup>3</sup>, Jagdev Kaur<sup>4</sup>, Harsha Gaikwad<sup>5</sup>**

<sup>1</sup>Senior Resident, Department of Obstetrics & Gynecology, VMMC & Safdarjung Hospital, New Delhi

<sup>2</sup>Professor, Department of Obstetrics & Gynecology, VMMC & Safdarjung Hospital, New Delhi

<sup>3</sup>Professor, Department of Pediatrics, VMMC & Safdarjung Hospital, New Delhi

<sup>4</sup>Professor, Department of Microbiology, VMMC & Safdarjung Hospital, New Delhi

<sup>5</sup>Associate Professor, Department of Obstetrics & Gynecology, VMMC & Safdarjung Hospital, New Delhi

### Introduction

Caesarean section has been invariably associated with the use of antibiotics in post-operative period of a patient. It has been seen that caesarean delivery causes five to twentyfold increase in infection rates as compared with vaginal delivery.

[<sup>1</sup>] Infection remains one of the top five causes of pregnancy related mortality and contributes to maternal morbidity. [<sup>2</sup>] With the upsurge of caesarean rates world-wide, chances of post-operative infections have increased, and here comes the role of antibiotics to help prevent and combat the infections. However, in recent times the injudicious and prolonged administration of antibiotics have led to a surge in the emergence of resistant strains of micro-organisms. With no newer antibiotic coming up for the the next few years, optimum use of antibiotics remains a challenge for us. In our study single prophylactic dose of antibiotic was given pre-operatively to prevent development of surgical site infections in postoperative period. Our dilemma was whether to administer it before skin incision or delaying it till cord clamping to prevent neonatal transfer of

antibiotics which is supposed to mask neonatal infections and their microbial cultures which in turn interferes with proper treatment. According to recent data by Russel antibiotics reaching the baby due to trans- placental transfer can alter their gut flora and affect their developing immune system. [<sup>3</sup>] So this study aims to find out the correct timing of administration of antibiotic and whether a single pre-operative dose of antibiotic is sufficient to prevent SSIs in caesarean deliveries.

### Materials and Methods

A prospective, randomized control study was conducted in the department of Obstetrics and Gynaecology at VMMC and Safdarjung Hospital over a period of one year which has an annual caesarean rate of 17.9% which is slightly higher than the WHO estimate of 5-15%. [<sup>4</sup>] A total of 200 women undergoing caesarean section, elective or non-elective were enrolled and divided into two groups. Women who were allergic to penicillin group of drugs had received antibiotics in the past 24 hours or those with existing infections like preterm rupture of membranes for more than 12

hours, chorio-amnionitis or those with other pyrexia of unknown origin were excluded from this group. Those patients who gave their consent to be a part of the study and to be in follow-up were randomly divided into two groups. Group 1 consisted of 100 patients who were given single prophylactic dose of amoxicillin-clavulanic acid thirty minutes before skin incision, 50 of them were those who got prepared for emergency caesarean section and the other 50 belonged to elective caesarean group. Group 2 consisted of another 100 patients who were administered single dose of amoxicillin-clavulanic acid immediately after cord clamping, 50 each in emergency and elective caesarean group. These women were given test dose of antibiotic about 45 minutes before skin incision. Amoxicillin-clavulanic acid was chosen in this study since it targets  $\beta$ -lactamase producing gram positive bacteria like streptococcus, staph aureus, anaerobes and gram negative bacteria like E.coli, proteus, klebsiella and enterococci known to inhabit the genital tract and cause surgical site infections. Also it is cheap and easily available in our hospital. These women were not given further antibiotic in post-operative period. Patients were assessed in post-operative period for Wound infection Endometritis Urinary tract infection and Other serious complications like bacteremia, septic shock, septic thrombophlebitis or death Attributed to infection. Wound infection was diagnosed by the presence of purulent discharge or wound dehiscence either superficial or deep. A superficial infection was identified as one which involved only skin and subcutaneous tissue whereas a deep wound dehiscence involved both fascia and muscles. A positive microbial culture was not necessary for diagnosing wound infection. Endo-myometritis was identified by the presence of maternal fever  $\geq 100.4$  F on two separate occasions six hours apart exclusive of the first 12 hours following surgery accompanied by uterine tenderness, foul smelling lochia and /or leukocytosis along with positive high vaginal swab culture. Mere high vaginal swab culture

positivity without signs and symptoms of endometritis was not considered as a case of endometritis. UTI meant symptomatic bacteriuria i.e. positive urine culture with symptoms like burning micturition, increased frequency of micturition etc. Other infections like pneumonia, deep vein thrombosis were diagnosed by symptoms along with radiological findings on X-ray or Doppler ultrasound. Investigations were sent on second post-operative day of all patients which included Complete blood count Urine routine and microscopy Urine culture and sensitivity High vaginal swab culture and sensitivity Culture media used were Mc Konkey and blood agar. Infants born to mothers by cesarean section were assessed for neonatal sepsis on the basis of their admission in neonatal intensive care unit (NICU). Those infants who developed sepsis were either positive for sepsis screen with negative blood culture report or were cases of blood culture proven sepsis. A positive sepsis screen took into account two or more positive tests as mentioned below:

- a) Total leucocyte count  $< 5000$  or  $> 20,000/\text{mm}^3$  (age  $> 72$  hours)
- b) Neutropenia (Absolute neutrophil count  $< 1800/\text{mm}^3$ )
- c) Immature neutrophil (band cells) to total neutrophil (I/T) ratio  $> 0.2$
- d) Micro-ESR (ESR  $> 15$  mm first hour)
- e) C-reactive protein- positive

Neonatal sepsis was determined clinically by the presence of tachycardia and/ or tachypnoea as well as leucocytosis. Inclusion of sepsis proforma of neonates in NICU helped to maintain record of the babies sepsis profile which included the duration of stay, the type and duration of antibiotic received, whether the sepsis was of early or delayed onset, whether the baby developed any nosocomial infection and the final outcome of the neonates. These babies were followed up for a period of six weeks to check for any infections or complications which they developed after discharge from the hospital.

### Data Analysis

Qualitative variables were compared by chi-square test or Fischer's test. Quantitative variables were presented as Mean  $\pm$  SD and significance determined by 't' test or non-parametric Wilcoxon Mann Whitney test. P value  $\leq$  0.5 was taken as level of statistical significance. Data was analysed using SPSS statistical software version 14.0.

### Results

Both the groups were found to be comparable on basis of age, parity, socio-economic status, Literacy level, basal metabolic index and indication for caesarean section. Total infection rate, which includes wound infection, endometritis and urinary tract infection, was found to be 14% in both the groups. A patient with either of these infections was considered as 1 case of infection. Group 1 (pre-incision group) showed a total infection rate of 10% as compared to 18% in cord clamping group (p 0.160, seen in table 1). Further analysis of patients in Group 1 revealed that out of 7 patients who had infection in emergency caesarean group, all 7 had wound infection while one had associated UTI. This patient had been operated for NPOL with labour pains lasting for 12 hours, had leaking PV for 11 hours and had undergone vaginal examinations for 7 times. Two patients had developed endometritis along with wound infection. In the elective group, 3 developed wound infection. No case of endometritis or UTI was seen. In Group 2, out of the 13 patients with infection in emergency group, 10 developed wound infection and 2 had associated UTI. 2 patients developed endometritis along with wound infection. One patient had endometritis only, in the elective group, 5 had wound infection only. Table 1 compares the rate of infection in the two groups. Total rate of wound infection was found to be 12.5%, of which Group 1 showed a statistically non significant reduction in wound infection which was 10% in Group 1 as against 15% in Group 2 (p 0.285) as seen in table 1. None of the patients had deep wound dehiscence and elective cases of C-section showed

decreased rate of wound infection. On further analysis of these patients, it was seen that four out of the seven patients in emergency group belonging to Group 1 and 7 out of 15 patients of emergency section in Group 2 were operated for non-progress of labour with labour pains lasting for more than 10 hours on an average, leaking per vaginum for more than 6 hours and they had around 5 vaginal examinations. Five patients with gaped wound in Group 1 and one in Group 2 belonged to the obese category. Two other patients in Group 1 and 3 in Group 2 were moderately anemic with post-op Hb values of  $\sim$ 7g%. Pus culture report showed 4 patients had got their wound infected with staph aureus while 2 were positive for MRSA (methicillin resistant staph-aureus). Another patient had Proteus infection. In the elective cases of caesarean delivery in both the groups, 6 patients had post-op anemia, one due to atonic PPH and the other one was operated for placenta accreta. Another patient with wound infection had gestational diabetes receiving insulin. Pus culture report showed diptheroids in both the cases. Two patients were obese while one case showed sterile wound culture. It was found that 25.49% of all obese patients had developed wound infection which was statistically significant (p0.0027) (table 2). Endometritis showed a non-significant increased rate in cord clamp group compared to pre-incision group (table 1). HVS culture positivity rate of 5% and 11% was seen in Group1 and Group2 respectively (Table 3). Emergency cases in Group1 revealed 3 cases positive for HVS, two showed staphylococcus aureus and one had E coli infection. Out of these 3 patients, two showed clinical signs and symptoms of endometritis. These 2 patients were operated for NPOL and had LPV for more than 10 hours. Both these cases had associated wound infection. Elective group showed two cases positive for Ecoli infection but did not show any clinical feature of endometritis. Group 2 had 7 culture positive cases, 4 of which had E.coli and 3 had staph aureus infection. Four out of these seven patients developed endometritis

in post- op period. All of these patients had LPV for more than 6 hours and one gave history of handling by untrained mid-wife at home. The elective group showed 4 cases positive for Ecoli but without any sign or symptom of endometritis. Urinary tract infection identified as symptomatic bacteriuria showed a non- significant increase in Group 2. The urine culture positivity rate was seen to be 2% in Group 1 and 4% in Group 2 (Table 4). The overall febrile morbidity in our study is 15.5%, out of which 15% cases of fever were seen in Group 1 while 16% of patients developed fever in Group 2 (Table 5). Main cause of fever in both the groups remained wound infection, endometritis and UTI. But few other patients had fever due to several other causes like malaria, typhoid or respiratory tract infections. None of the patients developed septicaemia, thrombophlebitis or any other serious morbidities. In this study the total rate of neonatal sepsis, including clinical sepsis which was culture negative or culture positive, was found to be 9%. Group 1 had 10% of babies developing sepsis while 8% of babies in Group 2 showed evidence of sepsis which was not statistically significant with p value of 0.605 (Table 6). Out of the 10 babies with sepsis in Group 1, there were 7 babies with culture negative sepsis, 3 in emergency and 4 in elective group. All 3 babies with culture positive sepsis belonged to emergency group. In Group 2, 6 babies had culture negative sepsis, 4 in emergency and 2 in elective group. Two babies with culture positive sepsis belonged to emergency group.

### Discussion

Our study showed a non-significant decrease in overall infectious morbidity in the pre- incision group as compared to the cord clamp group. Similar result was observed by Thigpen *et al* who found no significant difference in maternal infectious morbidity whether antibiotics were given before skin incision or after cord clamping.<sup>[5]</sup> However, Sullivan *et al* <sup>[6]</sup> and Costantine *et al* found statistically significant

decrease in total infection rate in the pre- incision group as compared to the cord-clamp group (RR 50;95% CI 0.33 to 0.78, p=0.002).<sup>[7]</sup> Cochrane review involved a meta- analysis of 95 studies involving over 15,000 women.<sup>[8]</sup> They found that prophylactic antibiotics decrease the rate of infectious morbidity post caesarean section by 60-70% as compared to placebo and no significant difference was found whether antibiotics were given before skin incision or after cord clamping. Result was the same for both emergency and elective cases. Our study results also did not find any significant difference in the total infection rate between emergency and elective cases (p 0.182 in Group 1 and 0.137 in Group 2). Our study shows a non-significant 5% reduction in the rate of wound infection in women receiving antibiotic prophylaxis before skin incision as compared to the cord-clamp group. Similar results are shown in the study by Sullivan *et al* and Thigpen *et al* who demonstrated statistically non significant reduction in wound infection in women administered antimicrobials before skin incision (RR 0.40 and RR 0.84, 95%CI 0.45-1.55 respectively).<sup>[6,5]</sup> Constantine did a meta-analysis of three randomized controlled studies involving 749 women; 377 received antibiotics before skin incision and 372 were given at the time of cord clamping. It was seen that pre-operative administration was associated with non-statistically significant 40% reduction in wound infection (RR 0.60;95% CI 0.3-1.21).<sup>[7]</sup> However, Kaimal AJ *et al* found that pre-incision administration of prophylactic antibiotic resulted in 60% reduction in the rate of SSIs which was statistically significant (p0.002).<sup>[9]</sup> Cochrane review in 2010 showed that prophylactic antibiotics in women undergoing caesarean section substantially reduced the incidence of wound infection as observed in 77 studies involving 11,961 women.<sup>[8]</sup> The result was the same for patients given prophylactic antibiotic before skin incision and at the time of cord clamping and also for both emergency and elective caesarean cases. This was similar to our

study results which showed no statistically significant difference in the wound infection rate of patients between emergency and elective caesarean cases of both the groups. This study did not find any statistically significant difference in the rates of endometritis before skin incision and after cord clamping (p 0.407). Thigpen et al too found a similar non-statistically significant reduction in endometritis (RR 0.67, CI 0.42-1.07) between the two groups.<sup>[5]</sup> This was further emphasised by Cochrane meta-analysis which found two-third to three-quarters reduction in the rate of endometritis (RR 0.38;95% CI 0.34 to 0.42, 79 studies, 12,412 women). Their analysis too found similar result in both emergency and elective groups.<sup>[8]</sup> Stephanie M. Owens noted statistically significant difference in the rate of post-partum endometritis when antimicrobial prophylaxis was given prior to skin incision ((RR 0.2, RR 0.47, OR 0.61, respectively).<sup>[10]</sup> Cochrane meta-analysis of 50 studies involving 8141 women showed an average risk ratio 95% CI 0.39 to 0.51 between the skin-incision and cord-clamp group and between the emergency and elective group.<sup>[8]</sup> This is comparable with our results in which fever showed no statistical significance between the two groups. Further review of 61 studies involving 9454 women showed reductions in maternal urinary tract infection (RR 0.55; 95% CI 0.47 to 0.65) with the use of prophylactic antibiotic and did not find any significant difference in result whether the antibiotic was given before or after cord clamping, and for both emergency and elective cases.<sup>[8]</sup> A recent meta-analysis involving 2313 women found a non-significant 41% reduction in endometritis and significant 29% reduction in the rate of total infectious morbidity, with non-significant decrease in the rate of wound infection when antibiotics were given pre-operatively. There was non-significant reduction in the rate of neonatal sepsis, and NICU admission in the pre-operative group.<sup>[11]</sup> In this study the total rate of neonatal sepsis was 9% and the difference in the rate of sepsis between the two groups was found to be

statistically non-significant (p0.605). Cochrane meta-analysis, done in 2010, reviewed 86 studies involving 13,000 women but could not come to a consensus regarding the timing of antibiotic administration. These studies lacked a systematic collection of data regarding drug resistance in the neonates. This has been overcome in our study by a proper systematic collection of the neonates who got admitted in NICU as per the neonatal proforma which helped to maintain complete record of the babies while they were admitted in the NICU. The day of development of sepsis, whether culture positive or culture negative, the organism responsible for sepsis, the total course of antibiotics given, whether it was the first episode of sepsis or recurrent sepsis, the total course of antibiotics given and response of the baby was properly maintained in neonatal proforma. We, therefore, have come to the conclusion that antibiotics whether given before or after cord clamping, did not affect the neonatal outcome.

### Conclusion

This study proves instrumental in determining the fact that antibiotic prophylaxis given mothers undergoing caesarean section does not affect the microbial cultures of neonates nor interferes with neonatal assessment of infection. Single dose of prophylactic antibiotic is sufficient to prevent post-operative infections in both Emergency and elective C-sections. However, therapeutic dose of antibiotics needs to be given in patients who are at high risk e.g. prolonged leaking for more than 12 hours, immune compromised state etc. BMI of 30 or more is associated with increased rates of wound dehiscence. Other factors which increase the rate of wound infection include prolonged duration of labour pains for more than 9 hours, leaking PV for more than 6 hours and post-operative anaemia. Although the absolute rate of total infections and SSIs were found to be less in the pre-incision group as compared to the cord clamp group, no definite conclusion can be drawn regarding timing of antibiotic administration since the results were

non-significant. We recognize that a small sample size and short span of one year was a major constraint and also our study was not sufficiently powered to achieve a significant result. A larger sample size taken over a longer duration of time would address these issues and would help in arriving at a definitive protocol regarding timing of antibiotic administration.

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**Informed consent:** A written informed consent was taken from all the participants in the study.

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