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ORIGINAL RESEARCH ARTICLE

Adjunctive post caesarean antibiotic prophylaxis with oral Cephalexin and Metronidazole - A randomised controlled trial

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ABSTRACT

Background: Antibiotic prophylaxis is a concept, used frequently in medical practices, which refers to the use of antibiotics before different surgery procedure. The practice of using antibiotic before operating any kind of surgery is performed under the supervision of the physicians and this practice is capable enough to save life of numerous patients. **Methods:** A single centered Interventional, Randomized Controlled Trial study was done at Department of Obstetrics and Gynecology, R.G. KarMedical College and Hospital, Kolkata over a period of one and a half year from February 2020 to July 2021. Template was generated in MS excel sheet and analysis was done on SPSS software. **Results:** In Group A – 41 out of 86 participants (47.67%) belonged to the age group of 18 – 24 years, In group B, the minimum age was 16 years and maximum age was 39 years. in Group A – 40 out of 86 subjects (46.51%) are of normal BMI where as in Group B – 39 out of 88 (44.32%) are of normal BMI. The second most common category was underweight BMI. In Group A – 35 out of 86 participants (40.69%) were primigravida and in Group B -36 out of 88 people (40.90%) were primigravida. Fetal distress was found to be the commonest indication in both groups with Group A demonstrating 40 out of 86 (46.51%) and Group B having 42 out of 88 participants (47.72%). Group A - out of 86 study subjects, wound

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infection wasfound in 6 participants (6.97%). However, in Group B 20 out of 88 people (22.7%) were found to have wound infections. The endometritis in Group A with antibiotics was 2.32% that is only 2 out of 86 people and Group B was 4.54% that is 4 out of 88 participants. **Conclusions:** Appropriate use of postoperative antibiotic reduces the rate of surgical site infections, reduces the health care costs and burden on both patients and health care workers. Standardization of antibiotic regimen Post Caesarean section is the need of the hour.

Keywords: Antibiotic prophylaxis, cephalexin, metronidazole, post caesarean

INTRODUCTION

Caesarean deliveries account for 17.2% of all the deliveries occurring in India (NFHS – 4)[1.] The three principal complications occurring with Caesarean deliveries include – infection, hemorrhage and thromboembolism.[2] Maternal morbidities may result from a number of infections, including surgical site infections (SSI), endometritis, and urinary tract infections; rarely, pelvic abscess, septic pelvic phlebitis, and pneumonia. Caesarean deliveries have been associated with a 5 – 20 fold increased risk of infections as compared to vaginal deliveries.[3]

The prevention of surgical site infection has been a longstanding battle emerging from the early 18th century. Ignaz Phillip Semmelweis[4], known as the 'savior of mothers', was the first to introduce the concept of hand washing to reduce puerperal mortality due to puerperal fever. This was even before Robert Koch's postulates, Joseph Lister's work on antisepsis and Louis Pasteur's germ theory of disease. In 1960, using animal models, Burke demonstrated that if antibiotics were given before wound contamination, therate of infection decreased[5]. Since the mid nineteenth century, there has been a tremendous growth in knowledge to both reduce the incidence of postoperative infections, puerperal mortality and morbidity and knowledge and use of antibiotics.

Antibiotic prophylaxis reduces the risk of endometritis by 43% and surgical site infection by 38% as shown by Bollig C et al.[6] Post- operative wound infections and endometritis, increase the length of hospital stay, increases time and man power required and total health care cost in a resource limited setting like India.

Concerns about the emergence of resistant strains of common bacteria, emergence of strains with increased virulence have resulted in increased scrutiny of use of antibiotics. In addition, awareness about the potential long term adverse effects on infant such as increased risk of asthma, type 1 Diabetes, Cerebral Palsy, gut dysbiosis and role of gut microbiota and link to chronic disease later in life have come to the forefront.[7]

Surgical Site infections are estimated to occur in 10- 12% of the patients in spite of pre incisional antibiotic prophylaxis with Cephalosporin.[8] Most hospitals in the world, use a single dose Cefazolin pre incision prophylaxis for prevention of surgical site infections.[9] Recent study by Valent on obese women, shows a significant reduction in postoperative morbidity with use of Oral Cephalexin and Metronidazole.[10] The use of Azithromycin as an extended spectrum antibiotic has proved to be beneficialdue to its effect against Ureaplasma organisms[11]. Though

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pre incision antibiotic prophylaxis has been studied extensively, the need and use of post Caesarean antibiotic prophylaxis and general consensus on the type of antibiotic to be usedis still unanswered. Moreover, most of the studies are performed in developed countries with good asepsis.

The rate of Caesarean section has risen from 2.9% in 1992 to 17.2% in 2015-2016 India and in West Bengal from 3.3% to 28.3% in 2015-2016 (NFHS -4)[1]. 12% of the Caesarean sections are complicated by infections[8] – that is one in every 8 women who undergo Caesarean delivery. Thus, a fine balance has to be achieved between reducing maternal morbidity and preventing irrational use of antibiotics. In a developing country like India with increasing Caesarean rates, suboptimal hygiene conditions and overburdened resources – does the use of oral Cephalexin and Metronidazole Post Caesarean delivery prove to be an added advantage in reducing maternal morbidity?

With this background, this study intends to evaluate if the addition of Cephalexin and Metronidazole as a post-operative antibiotic regimen reduces the risk of wound infection post Caesarean section and thus would help in reducing surgical site infections, standardize a post-operative antibiotic regimen eventually reducing health care costs and reduce the burden on women undergoing Caesarean deliveries in a resource limited setting in India

Method and Materials:

Type of study: Hospital based Interventional study

Study design: Randomized Controlled trial study

Study setting: Hospital based study in Department of Gynecology & Obstetrics, R.G. Kar Medical College & Hospital, Kolkata, West Bengal, India

Place of study: Department of Gynecology & Obstetrics, R.G. Kar Medical College and Hospital.

Period of study: February 2020 to July 2021, 18 months

Study population: All women undergoing Emergency Caesarean section in R.G Kar Medical College and Hospital (Fulfilling the inclusion criteria of the study)

Sample size

The study conducted by Amy Valent et al. in 2017[10], comparing the effect of Cephalexin and metronidazole on surgical site infections, showed a statistically significant difference. The SSI rate was 6.4% in the antibiotic group vs 15.4% in the placebo group. Accounting for the low resource setting, the level of asepsis followed and the poor nutritional status of the study population – we can hypothesis the rate of surgical site infection was to be 20%. Keeping the alpha error = 0.05, 80% as the power of the study with atreatment ratio of 1:1, the sample size calculated is 90 in each arm (Total = 180). Sample size is calculated using the following formula:- $n= (Z\alpha/2+Z\beta)\ 2 * [p1\ (1-p1) + p2\ (1-p2)] / (p1-p2)2$

where $Z\alpha/2$ is the critical value of the Normal distribution at $\alpha/2$ (e.g., for a confidence level of 95%, α is 0.05 and the critical value is 1.96), $Z\beta$ is the critical value of the Normal distribution at β (e.g., for a power of 80%, β is 0.2 and the critical value is 0.84) and p1 and p2 are the

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expected sample proportions of the two groups.
Therefore, the sample size thus calculated is 90 in each arm with a total of 180

Inclusion criteria :

- Singleton pregnancies
- Gestational Age > 24 weeks
- Consenting individuals

Exclusion criteria:

- Known allergy to Ceftriaxone, Cephalexin or Metronidazole
- Urinary tract infection
- Superficial thrombophlebitis
- Known allergy to Penicillin (as a 10% cross reactivity is seen)
- Subsequent vaginal delivery
- Antibiotic usage within 7 days before randomization
- Chorioamnionitis or other infections requiring post-operative antibiotictherapy
- Rupture of membrane exceeding 6 hours
- Diabetes or gestational diabetes, on oral steroids
- Patient with known immunodeficiency syndromes

Study variables

Independent variables like Age, Educational status, Employment status, BMI of individual, Gravidity, Indication of Caesarean section and Gestational Age.

Dependent variables like Superficial Wound Infection, Deep Wound infection and Endometritis.

Laboratory methods and facilities – Only applicable to subjects that had superficial or deep wound infection and endometritis. In such a case – a wound swab of the discharging wound, a complete blood count was sent to the Microbiology and Pathology Department of R.G Kar Medical College and Hospital.

Follow up – All patients are kept in the post-operative room for 12 hours after which they are shifted to the ward. Senior residents and junior residents observe the wound on Day 5 of Caesarean section. Prior to that, patients' vitals and features of endometritis will be assessed for the duration of stay in the hospital. Wound swab for culture and sensitivity and complete blood count were sent in case of wound discharge

Statistical Analysis:

Data was entered into SPSS 26 (SPSS Inc Chicago IL USA). Analysis was based on intention to treat. Continuous variables have been assessed by Student's t test and Mann Whitney U test depending on the data normality. Categorical data has been assessed by chi square test. P value <0.05 has been considered to be statistically significant.

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Ethical clearance: The study will be conducted only after obtaining written approval from the Institutional Ethics Committee. Written informed consent was taken from every study patient or their logical representative

Results

A hospital based Interventional study was carried out in Department of Gynecology & Obstetrics, R.G. Kar Medical College & Hospital, Kolkata, West Bengal, India amongst all women undergoing Emergency Caesarean section (Fulfilling the inclusion criteria of the study) from the period February 2020 to July 2021. Sample size in group A was 86 and in group B was 88.

Table 1: Comparison of age, educational status, employment status, BMI, Gravidity and gestational age of both groups.

Age Range	Group A (n = 86)	Group B (n = 88)	P-value
<17 years	10 (11.62%)	12 (13.63%)	0.9737 (not significant)
18 – 24 years	41 (47.67%)	46 (52.27%)	
25 – 31 years	25 (29.06%)	22 (25%)	
32 – 38 years	10 (11.62%)	7 (7.95%)	
39 – 45 years	0	1 (1.13%)	
Mean Age	23.54 years	23.52 years	
StandardDeviation	4.99	4.61	
Educational Status			
Illiterate	12 (13.95%)	14 (15.90%)	0.8675 (not significant)
Primary School	35 (40.69%)	29 (32.95%)	
Middle School	29 (33.72%)	32 (36.36%)	
High School	8 (9.30%)	10 (11.36%)	
Graduate or higher	2 (2.32%)	3 (3.40%)	
Employment Status			
Unemployed	52 (60.46%)	58 (65.90%)	0.5544 (not significant)
Employed	34 (39.53%)	30 (34.09%)	
BMI			
Underweight	28 (32.56%)	33 (37.5%)	0.9041 (not significant)
Normal	40 (46.51%)	39 (44.32%)	
Overweight	13 (15.11%)	11 (12.5%)	
Obese	5 (5.81%)	5 (5.68%)	
Gravidity			
Gravida 1	35 (40.69%)	36 (40.90%)	0.965
Gravida 2	31 (36.04%)	29 (32.95%)	

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Gravida 3	14 (16.28%)	16 (18.18%)	(not significant)
Gravida more than 3	6 (6.98%)	7 (7.95%)	
Gestational Age			
24 – 28 WEEKS	1 (1.16%)	0 (0%)	0.760 (not significant)
28-32 WEEKS	2 (2.33%)	1 (1.14%)	
32- 36 WEEKS	12 (13.95%)	14 (15.90%)	
36 – 40 WEEKS	61 (70.93%)	58 (65.90%)	
>= 40 WEEKS	10 (11.63%)	15 (17.04%)	
Mean gestational age	37.23	37.33	

In the present study, In Group A – 41 out of 86 participants (47.67%) belonged to the age bracket of 18 – 24 years. In Group B, 46 out of 88 (52.27%) belonged to the age group 18 – 24 years. The second most common age bracket was found to be 25 - 31 years. In Group A was 16 years and maximum age was 34 years. In group B, the minimum age was 16 years and maximum age was 39 years. In both groups, the mean age was 23.54 and 23.52, with a standard deviation of 4.99 and 4.61 in Group A and Group B respectively. With a 95% CI, the p value was 0.9737 which is >p=0.05 and hence it is not statistically significant. Both groups are thus comparable on age characteristic.

Group A shows 35 out of 86 subjects (40.69%) were of primary school education. Group B shows 29 out of 88 (32.9%) were primary school level educated whereas maximum 32 out of 88 (36.3%) were middle school level educated.

In group A 52 out of 86 (60.46%) of the people are unemployed. Whereas, in Group B – 58 out of 88 people are unemployed (65.9%).

It is seen that in Group A – 40 out of 86 subjects (46.51%) are of normal BMI where as in Group B – 39 out of 88 (44.32%) are of normal BMI. The second most common category was underweight BMI.

In Group A – 35 out of 86 participants (40.69%) were primigravida and in Group B -36 out of 88 people (40.90%) were primigravida. This was followed by second gravida. Less than 7 percent of the participants in both the groups were 4th gravida or beyond.

In Group A - 61 out of 86 participants (70.93%) were between 36 – 40 weeks and in Group B 58 out of 88 (65.90%) were between 36 – 40 weeks. (Table 1)

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Figure 1: Comparison of indication of caesarean section in both groups.

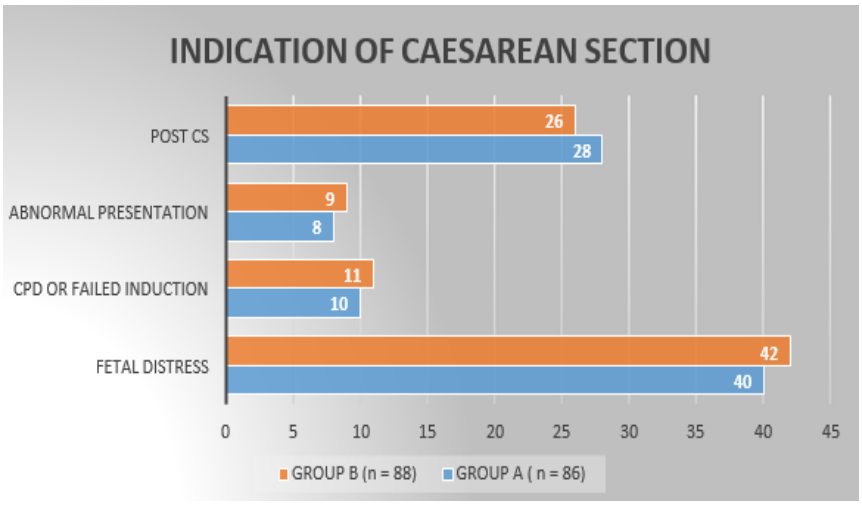

Figure 1 shows the indication of Caesarean sections in both the groups. Fetal distress was found to be the commonest indication in both groups with Group A demonstrating 40 out of 86 (46.51%) and Group B having 42 out of 88 participants (47.72%). Post caesarean section was found to be the second most common presentation in both the groups. With an alpha error of 0.05 and degree of freedom 3, the chi square value calculated is 0.2063 and p value – 0.976 which is more than p = 0.05 and hence not statistically significant. Therefore, both the groups are comparable based on the indication of caesarean section.

Figure 2: Comparison of haemoglobin status in both groups.

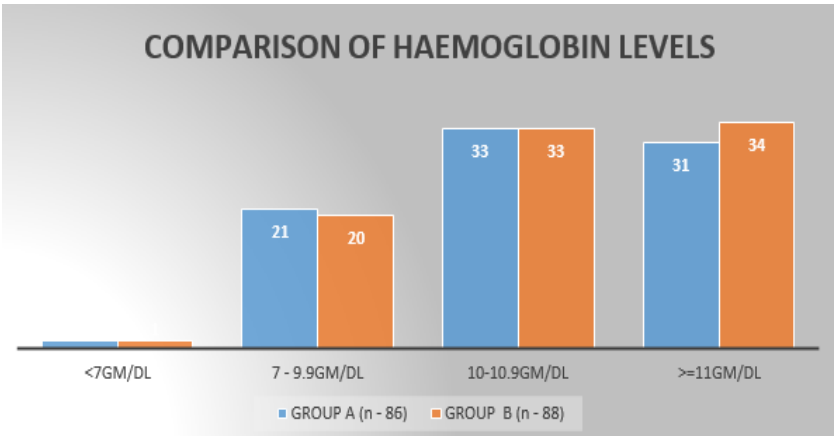

Figure 2 demonstrate the baseline Haemoglobin levels in both groups. 33 out of 86 participants in Group A (38.4%) – had mild anemia (10 - 10.9g) whereas 33 out of 88 participants in Group B (37.5%) had mild anemia. 24.4% in Group A and 22.72% in Group B had moderate anemia. The mean Haemoglobin levels in both groups – was 10.29 gm/dL and 10.31gm/dL respectively. The Haemoglobin levels were obtained from the antenatal cards, the Haemoglobin levels are

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measure in the Department of Pathology, RGKMCH. With an alpha error of 0.05 and a 95% confidence interval, the t test equals a value of 0.1388. The p value thus obtained is 0.8897 which is p>0.05. Thus both the groups are comparable on the basis of anemic status

Table 2: Comparison of wound infection rates, superficial wound infection and deep wound infection with need for secondary suturing of Caesarean wound of both groups.

Wound infection rates	Group A (n = 86)	Group B (n = 88)	P-value
Wound infection	6 (6.97%%)	20 (22.7%)	0. 0035 (statistically significant)
No wound infection	80 (93%)	68 (77.2%)	
Superficial wound infection			
Total	5 (5.81%)	18 (20.4%)	0. 0043 (statistically significant)
Redness and swelling	3	12	
Wound discharge serous	2	8	
Purulent discharge	1	3	
Culture positive	0	2	
Deep wound infection			
Secondary suturing	1	2	0. 57 (Not significant)

Table 2 shows the primary outcome – that is wound infectionin both the groups. In Group A - out of 86 study subjects, wound infection was found in 6 participants (6.97%). However, in Group B 20 out of 88 people (22.7%) were found to have wound infections. Thus, addition of oral cephalosporin and metronidazole reduces the incidence of Superficial Wound infections.

Table 3: Comparison of endometritis between both groups.

Wound infection rates	Group A (n = 86)	Group B (n = 88)	P-value
No endometritis	84 (97.67%)	84 (95.45%)	0. 422 (Not significant)
Endometritis	2 (2.32%)	4 (4.54%)	

Table 3 shows the incidence of endometritis in both the groups. The endometritis in Group A with antibiotics was 2.32% that is only 2 out of 86 people and Group B was 4.54% that is 4 out of 88 participants.

DISCUSSION

A randomized controlled trial involving 174 participants (86 and 88 in both the arms) was conducted in R.G Kar Medical College from February 2020 to July 2021. The study participants

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were enrolled after proper consent and in adherence to the inclusion criteria mentioned above. The following is the brief discussion on the study.

The socio demographic characteristics of the present study include a mean age of 23.54 and 23.52 years in both the groups. Most of the participants were in the category of 18 – 24 years. The lower age in India corresponds to the NFHS – 4 survey 2015- 2016 which stated that the median age of marriage was 18.6 years.[1] The effect on surgical site infection can be seen both ways – a higher prevalence of anemia in the younger age group, however the incidence of comorbidities like diabetes affecting wound healing would be reduced.

The educational status – primary and middle school was the most common education level in both the groups. 60.46% and 65.9% participants in both the groups were unemployed. Thus, proper education about wound careand risk of wound infection is necessary.

In present study, 40.69% and 40.9% of the study participants were primi- gravida. The most common indication being fetal distress, followed by post Caesarean section. Emergency Caesarean itself predisposes to SSI as compared to Elective Caesarean section. A differentiation between elective and emergencyCaesarean section was not conducted in the present study as all the participants were of emergency Caesarean section.

In present study, 63.95% of participants in Group A and 61.36% of the participants in Group B have anemia in pregnancy. Out of this 38.4 % and 37.5% of the participants have mild anemia in the range of 10 – 10.9 gm/dL.

The prevalence of anemia in pregnancy is in accordance with the NFHS- 4[1] finding of 62% anemia in pregnancy in West Bengal. Hemoglobin is required for oxygen delivery at surgical site and better collagen synthesis and remodeling. These findings are supported by Kelly Yerba et al 2020[11]. However, both the groups are comparable based on Haemoglobin levels and iron and folic acid supplementation were provided to all study participants postnatally.

In present study, the primary outcome considered was surgical site infection after a 48 hour post-operative course of oral Cephalexin and metronidazole. Therate of surgical site infection in the group that received post-operative oral Cephalexin and metronidazole was 6.97% vs 22.7% in the group that did not receive any post-operative antibiotic. This is statistically significant; showing that oral Cephalexin and metronidazole was effective in reducing the incidence of surgical site wound infection. Among the secondary outcomes, there was no statistically significant difference between endometritis.

These findings are similar to the study conducted by Amy Valent et al .in 2017[10] among obese women undergoing Caesarean section (6.4% vs 15.4%). However, the study was conducted in a developed country with better aseptic precautions and was specifically routed for obese patients who themselves are a risk factor of Caesarean delivery and infections.

The risk of reduction in surgical site infection is similar to studies by Meyer et al. 2003[12], Smaill and Gyte et al. 2010[13] in the Cochrane database, David Chelmow et al. 2000[14] and Tita et al. in 2008[15]. These studies used various combinations of Cephalosporins and extended spectrum antibiotics. Tita et al. further stated that the routine use of extended spectrum antibiotics decreased the risk of post-operative infections as opposed to Cephalosporins alone.

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The secondary outcome was reduction in the risk of endometritis – which was not statistically significant in the study. Many of the studies including Constantine et al 2008[16], Baqueel et al 2013[17], Smaill and Gyte 2010[18], Andrews et al 2003[19] show a significant decrease in the risk of endometritis. In contrast, studies by Valent et al 2017[10], A Shakya et al 2010[20] and Azizi et al 2014[21] showed no significant reduction in the rate of endometritis with different combinations of Cephalosporins with and without metronidazole.

The reason for this in the present study can be attributed to the fact that all the patients in the present study have all received pre incision antibiotic with Inj Ceftriaxone. The pre-incision antibiotic decreases the risk of endometritits by 43% as documented by Bollig C et al[6]. Secondly, endometritis is a clinically challenging diagnosis.

The antibiotics chosen for the study are oral Cephalexin and metronidazole. This was chosen as it has a broad spectrum of activity covering both aerobic and anaerobic organisms. It has proven efficacy in treatment of abdominal infections. Post caesarean infections are usually polymicrobial. The main pathogens are anaerobes like Bacteroides, Clostridium, and Fusobacteriumspp. and gram-negative aerobes Escherichia coli, Klebsiella, Enterobacter, and Proteus where these drugs are effective. Furthermore, metronidazole has anti-inflammatory properties and also effective against Mycoplasma and Ureaplasma.

Both the drugs have good oral bioavailability, are cost effective and are well tolerated. A time period of 48 hours was chosen due to the stages of woundhealing. In the first 48 hours, there is hemostasis by initial clot formation, inflammation, infiltration by neutrophils and after 48 hours, there is replacement by granulation tissue. This period is critical for the proper deposition of fibroblasts, basement membrane organization, and collagen formation. Because regulation of this inflammatory phase is important for the remodeling periods of healing, we chose a 48-hour course of prophylactic antibiotics to provide coverage while re-epithelialization occurs.

As side effects of Cephalexin and Metronidazole were minor, specified minor side effect analysis was not undertaken. Also, even though there is low risk of transmission of antibiotics via breast milk; studies in the past have not demonstrated any effect with Cephalexin or combination. Long-term childhood or adverse neonatal outcomes specific to cephalexin-metronidazole exposure cannot be determined, as outcome measures were not evaluated for this study protocol. Recognizing the maternal and neonatal benefit of breastfeeding, the lack of known neonatal adverse effects, and maternal reduction in SSI, the benefit of this antibiotic regimen likely outweighs the theoretical risks of breast milk exposure.

CONCLUSIONS

A significant reduction in the incidence of post operative wound infections has been observed – 6.97% vs 22.7 % with and without cephalexin and metronidazole in this study. In our study, the incidence of superficial wound infection also shows a significant reduction - 5.81% vs 20.4%. However, there is no significant difference in the incidence of deep wound infection. No significant difference in the rates of endometritis has been noted in our study. Cephalexin and metronidazole have been chosen for its broad spectrum of activity, low cost and easy availability.

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Use of oral Cephalexin and Metronidazole reduces the incidence of wound infection post Caesarean sections.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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