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Original Research Article

Comparison of Single Dose versus Multiple Doses of Antibiotic Prophylaxis in Elective and Emergency Caesarean Section

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Abstract:

Background: Infectious complications after caesarean delivery (CD) are a substantial cause of maternal morbidity, increase in hospital stay and treatment cost. The spectrum of these complications' spreads from fever, wound infection, endometritis, urinary tract infection, and some serious complications like pelvic abscess, septic shock and septic pelvic vein thrombophlebitis. To prevent these prophylactic antibiotics have been used however the use of antibiotics should be judicious. Aim was to compare the efficacy of single dose versus multiple doses of antibiotics in elective caesarean section.

Methods: This study was conducted in a tertiary care hospital from December 2019 to May 2020. It was a prospective case control study. Sample size was 162; patients were randomly allocated in two groups A and B by card method. Subjects in arm A received ceftriaxone 1 g and metronidazole 500 mg intravenously within 60 min before incision. A repeat dose was planned to be given if blood loss exceeded 1500 ml because this factor has been shown to increase infectious morbidity during surgery. Subjects in arm B received the same preoperative prophylaxis as arm A. They then received metronidazole 500 mg intravenously every 8 h for 48 h, followed by cefuroxime 500 mg twice a day for 5 days and metronidazole 400 mg three times a day for 5 days. The participants were examined for indicators of infection beginning 24 h post-caesarean section, then every 12 h for 72 h until discharge. Following discharge, they were monitored and followed up via phone calls SMS and enquiries made on presence of any symptoms of infectious morbidity by the researchers for 2 weeks.

Result: There was no statistical difference in the incidence of wound infection (6.6% versus 7.4%; p = .882) and febrile morbidity (11.8% versus 11.1%, p = 0.807). However, clinical endometritis (0.0% versus 6.1%, p = 0.028) was statistically significant with none reported in the single-dose arm.

Conclusions: Single dose antibiotic prophylaxis was found to be comparable to multi-dose antibiotics in our study. Hence it is advocated that single dose antibiotic can be given in elective caesarean section as it is cost effective and as efficient as multi-dose regimen, ensures complete compliance and minimizes side effects and cut-down nursing workload. Keywords: Cefuroxime, Caesarean delivery, Fever, Multi-dose, Prophylactic antibiotics, Single dose, Urine culture and sensitivity, Urine routine microscopy.

Keywords: antibiotic prophylaxis, single dose, multiple dose.

Introduction

Caesarean section describes the delivery of a foetus through a surgical incision made in the anterior uterine wall. [1] Medical advancement has transformed this technique into one with a very low risk of maternal mortality. [1,2] It has become the most common major obstetric surgical procedure performed worldwide, constituting about 25% of all deliveries in many countries. [3,4] Delivery by caesarean section is associated with a 5- to 20-fold greater risk of postpartum infections, ranging from endometritis to urinary tract infection and wound infection, compared with vaginal delivery. [5] Preoperative prophylactic antibiotics are intended to reduce the size of the bacterial inoculums and to change the characteristics at the operative site during the brief time that host defences are impaired by the trauma of surgery. [6] Studies have shown that compared with placebo, prophylactic antibiotics administered alongside caesarean section significantly reduces the rate of maternal postpartum fever, wound infection, endometritis, urinary tract infections, serious infectious morbidity, death and length of hospital stay. [7] Evidence from randomized controlled trials suggests that for caesarean section, shortterm antibiotic prophylaxis is comparable in efficacy to long-term antibiotic prophylaxis. [8,9] Most of these studies were done in high-income nations. Studies have shown increased cost, higher work load on medical staff and risk of antibiotic resistance with the use of long-term antibiotic prophylaxis with no additional benefit in

preventing postpartum infections compared with short-term antibiotic prophylaxis. [10,11] Environmental factors, such as the source, storage and quality of the antibiotics; drug abuse and development of antibiotic resistance have made a short-term antibiotic regimen less desirable in the tropics.

Most obstetricians in Nigeria seem unwilling to adapt to the evidence-based recommended single-dose regimen for surgical prophylaxis despite high awareness, perhaps from the fear of increased postoperative infection in our environment even when there is no evidence to justify this strong, long-held belief. [12] This practice negates the principle of surgical prophylaxis as an approach to prevent infections, because a therapeutic regimen is administered. We aimed to close the knowledge gap on the effectiveness of single-dose compared with multiple-dose antibiotic prophylaxis to prevent post-caesarean section infectious morbidity.

We included emergency caesarean deliveries, which represent the majority of caesarean section cases in the tropics; these cases have not been widely studied in other research done in the tropics.

We determined the efficacy and safety of single-dose compared with multiple dose antibiotic prophylaxis to prevent post-caesarean section infections.

Methods

Study design

This was a prospective, pragmatic, open-label randomized clinical trial.

Study population

The study comprised pregnant women who had caesarean delivery, either electively or due to an emergency

Table 1: Sociodemographic characteristics of the study participants

Factors	Group Single dose (n = 76) N (%)	Multiple doses (n = 81) N (%)	total	$\chi 2$	p
Age (years)				7.432	0.167
15-19	0(0.0)	2(2.5)	2(1.3)		
20-24	9(11.8)	3(3.7)	12(7.6)		
25-29	23(30.3)	32(39.5)	55(35.0)		
30-34	22(28.9)	25(30.8)	47(29.9)		
35-39	17(22.4)	17(21.0)	34(21.7)		
40-44	5(6.6)	2(2.5)	7(4.5)		
Mean age ± SD	30.50 ± 4.82	30.62 ± 4.63	30.59 ± 4.65		
Level of education				30.266	<.001
No formal education	0(0.0)	6(7.4)	6(3.8)		
primary	9(11.8)	8(9.9)	17(10.8)		
secondary	14(18.4)	41(50.6)	55(35.0)		
tertiary	53(69.8)	26(32.1)	79(50.4)		
occupation				7.363	.025
skilled	32(42.1)	23(28.4)	55(35.0)		
unskilled	14(18.4)	50(61.7)	64(40.8)		
professional	30(39.5)	8(9.9)	38(24.2)		

Study duration

The study was conducted between December 2019 to May 2020 at the Department of Obstetrics and Gynaecology LBKMCH, SAHARSA, BIHAR

Inclusion criterion

The inclusion criterion was pregnant women scheduled for caesarean section, either electively or due to an emergency, with no added risk for infection.

Exclusion criteria

The exclusion criteria were pregnant women with known allergy to cephalosporin's or metronidazole, maternal sepsis, prolonged labour, use of antibiotics in the preceding 2 weeks, prolonged rupture of membranes (>24 h), preoperative haemoglobin < 20 g/dL, weight > 100 kg, sickle cell disease and diabetic with poor glucose control.

Interventions

Women who met the inclusion criterion were counselled and provided their consent to participate in the study. A focussed history was obtained from the participants using a structured questionnaire

The study subjects were assigned randomly to one of the two parallel study arms: A or B. Subjects in arm A received ceftriaxone 1 g and metronidazole 500 mg intravenously within 60 min before incision. A repeat dose was planned to be given if blood loss exceeded 1500 ml because this factor has been shown to increase infectious morbidity

during surgery. Subjects in arm B received the same preoperative prophylaxis as arm A. They then received metronidazole 500 mg intravenously every 8 h for 48 h, followed by cefuroxime 500 mg twice a day for 5 days and metronidazole

400 mg three times a day for 5 days. The participants were examined for indicators of infection beginning 24 h post-caesarean section, then every 12 h for 72 h until discharge. Following discharge, they were monitored and followed up via phone calls SMS and enquiries made on presence of any symptoms of infectious morbidity by the researchers for 2 weeks. Those with possible symptoms were invited to the hospital for an evaluation. Wound infection was defined as partial or total dehiscence or the presence of purulent discharge from the Wound with localized swelling, warmth and tenderness with or without microbiological evidence. Clinical endometritis was considered as the presence of fever; tachycardia, uterine tenderness or offensive lochia with or without microbiological evidence. [14]

Postoperative fever was defined by temperature of greater than 38°C at least 4 apart on two or more occasions, excluding the first 24 h after caesarean section. [2] When infectious morbidity was suspected, history was taken and general physical examination performed to localize the potential source of infection. A full septic work up was done including full blood count and differentials, in addition to a blood film for malaria by thick and thin film preparation and urine collected for analysis, microscopy, culture and sensitivity. If endometritis was suspected, an endocervical swab was collected for microscopy, culture and sensitivity.

Wound culture was done for suspected wound infection. Participants with confirmed infectious morbidity evaluated in the laboratory were treated with a full course of therapeutic antibiotics/antimalarial as needed. The primary outcome was wound infection, while the secondary outcomes were clinical endometritis and postoperative fever.

Sample size determination

The sample size was calculated using the formula for sample size determination in a randomized controlled study on

the assumptions that 16.2% of the patients in the multiple dose (control) arm would develop wound infection based on the findings of a previous study.15 The fraction of subjects in the single-dose (test) arm expected to exhibit the primary outcome (wound infection) was set at 32.4% (double the rate in the single-dose arm), and the attrition rate was set at 10%. Based on these values, a sample size of 162 subjects would provide 80% power at the 95% confidence interval (CI).

Randomization

A computer-generated random sequence was used to allocate eligible study participants into either group to maintain balance between each arm. Sequentially numbered opaque sealed envelope was used to ensure concealment of group allocation. The envelopes where opened after surgery because preoperative prophylaxis was the same for both arms. Subsequent administrations of antibiotics were done by the ward nurses. The pre-defined primary and secondary outcomes of interest were ascertained by the assessors, namely, the consultants/senior registrars in the managing team of each enrolled subject. This was an open label, randomized control study because the participants, investigators and assessors were aware of the study arm to which each subject belonged.

Data analysis

The data were collected and then analysed with SPSS Statistics version 22 (IBM Corp., USA). A p-value $< .05$ was considered to be statistically significant. The outcomes were analysed with the per protocol approach, meaning that the participants were analysed in the group in which they were randomized, with exclusion for loss to follow-up. Categorical variables were analysed using the chi-square test or Fisher's exact test (where appropriate); continuous variables were analysed using Student's t-test. Baseline analysis involved comparing the baseline characteristics between the two study arms. Hypothesis testing was done to determine whether there was a significant difference in the cumulative incidence of post-caesarean infectious morbidity, with wound infection as the primary outcome of interest.

Ethical considerations

Ethical approval for the study was obtained from the ethical committee of the college. Written informed consent was obtained from the participants according to the Declaration of Helsinki.

Results

During the study period, there were 162 eligible women who underwent caesarean section. Four women in the single-dose arm opted out of the study while one was lost to follow-up before the 2-week postoperative follow-up. This gave an attrition rate of 3.1%. The overall mean age (± standard deviation (SD)) of the participants was 30.59 ± 4.65 years. There was not a significant difference in the mean ages of the two groups ($p = .167$). Most of the study participants (97.5%) were married. In both arms, most of the caesarean sections were performed as elective surgery (59.2%

for the single-dose arm and 53.7% for the multiple-dose arm, p = .544). Repeat caesarean section occurred in 94 (59.5%) participants. While spinal anaesthesia was used in all participants in the single-dose arm, there was no statistically significant difference in the choice of anaesthesia between the arms (p = .246). P fannenstiel incision was the predominant choice of abdominal incision, performed in 145 (92.4%) of the caesarean sections Outcomes of antibiotic use among the study participants.

Table 2:

factors	Single dose, n+76 n (%)	Multiple dose n=81 n (%)	Total	$\chi 2$	p
Postoperative wound infection				0.051	0.822
yes	5 (6.6)	6 (7.4)	11 (7.0)		
no	71 (93.4)	75 (92.6)	146 (93.0)		
Postoperative febrile morbidity				0.013	0.807
yes	9 (11.8)	9 (11.1)	18 (11.5)		
no	67 (88.2)	72 (88.9)	139 (88.5)		
Postoperative clinical endometritis				**4.848**	0.028
yes	0 (0.0)	5 (6.1)	5 (3.2)		
no	76 (100.0)	76 (93.9)	152 (96.8)		
Postoperative need for therapeutic antibiotics					
yes	5 (6.6)	12 (14.8)	17 (10.8)	2.847	0.092 Yes 5
no	71 (93.4)	69 (85.2)	140 (89.2)		

Discussion

This study was a randomized clinical trial in which single dose of ceftriaxone and metronidazole given within 60 min before skin incision was compared with an additional 5 days of prophylactic antibiotics for women undergoing caesarean section (either electively or due to an emergency). The single- and multiple-dose study arms were similar in terms of demographics and operative characteristics, with no significant differences between the Arms. There were no significant differences in the rates of postoperative infections (wound infections, febrile morbidity and clinical endometritis) between the study arms. The findings in this study are consistent with the overall incidence of wound infection (primary outcome) was 7% (6.6% in the single-dose arm and 7.4% in The multiple-dose arm). This is similar to the findings reported by Alekwe et al. [16] The authors compared treatment with just two doses of antibiotics with antibiotics administered for 7 days, with an overall wound infection rate of 8.4% (6.4% for two doses versus 10.5% for 7-day treatment). However, our wound infection rate was higher than the 4.5% overall wound infection rate in a similar study done in Abuja, Nigeria comparing short-term versus long term antibiotic prophylaxis for caesarean section. [17]

We compared our results with the following studies. In a study by Nagarashi et al, [26] incidence of febrile morbidity was 4.1% in single dose group versus 3.5% in multi dose group, which was not statistically significant. [8] In a study by Prathima et al, among elective caesarean delivery, one patient in single dose group and no patient in multi-dose group developed fever. [9] Again among emergency caesarean deliveries 3 and 4 patients developed fever in single and multi-dose group respectively, and neither result was statistically significant (p=0.45 and 0.83).

Though SSIs are not life threatening in most cases, they tend to prolong the length of hospital stay, increase hospital cost and in some cases, re-admission for women trying to cope with both the postoperative period and new baby. [18] The global estimate of SSI was 0.5-15%. [19]

In a study by Babeeta et al, incidence of SSI was 8% in single dose group and 10% in multi-dose group (p value of >0.05), the difference was not statistically significant. [20] In another study conducted by Ansari et al on post-operative evaluation of wound infection, the incidence of wound infection was 2% in single dose group and 3% in multi-dose group. [21] Another similar study conducted by Shah et al, concluded that there was no statistically significance in the rate of infections in both the groups. [22] Lyimo et al, conducted a similar study which showed the incidence of surgical site infection (12/250) 4.8% in single dose when compared to 16 /250 (6.4%) in multiple doses group. [23] In a study by Westen et al, in the single dose group (n-89) six women (6.7%) developed a wound infection compared with nine (10.3%) in multi-dose (n-87), which was non-significant. [16] In contrast to our study, a study conducted by Abro et al showed 17/208 (8.2%) patients had SSIs. Ten patients (9.6%) were in the single dose group and seven (6.7%) were in multi-dose group (p=0.004). [24] This difference was statistically significant. They concluded that multiple doses of prophylactic

antibiotics over 24 hours should be used instead of single dose in surgical prophylaxis in clean-contaminated and contaminated procedures. Similar to this study, Roex et al conducted a study which showed 3/66 (4.5%) in single dose and 0/77 (0.00 %) in multi dose group developed wound infection. The multi-dose group showed fewer post-operative infections. The difference was statistically significant ($p<0.05$). [25]

Similar to our study, most of the studies say that there is no statistically significant difference in wound infection in both the groups, but contrast to this, few studies say multi-dose is better than single dose.

Conclusion

Therapeutic concentration of antibiotic in serum, tissues and wound during cesarean is assured by antibiotic prophylaxis. Choice of antibiotic should be such that it should cover the common bacteria that may be encountered during surgery. The drug administration should be done for the shortest period to minimize the development of resistance and the adverse effect of the drug. Single dose antibiotic prophylaxis was found to be comparable to multi-dose antibiotics in our study. Since the single dose antibiotic is as efficacious as multi-dose regimen, it is advocated that single dose prophylactic antibiotic can be given in elective cesarean section as it is cost effective and efficient as multi-dose regimen, ensures complete compliance, minimize side effects and cut-down nursing work-load. Many other studies were found to collaborate, our findings. It is a well-known fact that multi-drug resistance is the result of injudicious use of antibiotics; however, in-spite of the medical fraternity being well aware of this fact indiscriminate use of antibiotics is prevalent in our practice. We need to drive home the fact that a blunderbuss antibiotic therapy is not necessary for all routine cases, especially, where good sterility can be maintained. This study was done to set practical example to curtail over-judicious use of antibiotics in our own institution and we were glad to note that it indeed brought down the use of multiple antibiotics in planed surgeries.

Recommendations

Over-judicious use of multi-dose antibiotics should be discouraged to decrease and prevention of drug resistance. In institutions with good sterility conditions single dose antibiotic policy should be in place for planned clean surgeries. Hesitation to adopt this policy is prevalent in many institutions hence small studies of the nature of our study can be undertaken in various institutions to instil confidence amongst practicing surgeons to adopt single dose antibiotic prophylaxis in planned surgeries. Institutions should have a clear drug policy for various type of surgeries. Quality control department in the institutions should ensure adherence to the institutional drug-control policy.

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