Original Article

Single Dose Versus 72-Hour Course of Ceftriazone for Antibiotic Prophylaxis in Preventing Post-Caesarean Wound Infection: A Randomized Control Trial

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Abstract

Background: Single dose antibiotic prophylaxis has been established as the standard for prevention of post-caesarean wound infection in most developed centers across the world. However, this is not the case in most developing countries including Nigeria where various multiple dose regimens are still being used due to paucity of locally generated evidence, and anecdotal suggestions of a higher risk of infectious morbidity in our environment. **Objectives:** This study was aimed to determine whether there was a significant difference in the incidence of post-caesarean section wound infection between a single dose and a 72-hour course of intravenous ceftriazone for antibiotic prophylaxis in selected patients undergoing both elective and emergency caesarean section. **Materials and Methods:** A randomized controlled trial was carried out among 170 consenting parturients scheduled for elective or emergency caesarean section who met a set out selection criteria, between January and June 2016. They were divided randomly into two equal groups, A and B, of 85 each using the Windows WINPEPI software version 11.65 (Copyright J.H. Abrahamson, 22 Aug 2016) for randomization. Group A patients received a single dose of 1 g, whereas Group B patients were given a 72-hour course (1 g daily) of intravenous ceftriazone. The primary outcome measure was the incidence of clinical wound infection. The secondary outcome measures were the incidences of clinical endometritis and febrile morbidity. Data were collected using a structured proforma and analyzed using Statistical Package for Social Sciences version 21. **Results:** The overall incidence of wound infection was 11.2%; Group A had 11.8%, and Group B had 10.6%. Endometritis was 20.6%; Group A had 20% and Group B had 21.2%. Febrile morbidity was 4.1%; Group A had 3.5% and Group B had 4.7%. There was no statistically significant difference in the incidence of wound infection (relative risk [RR] = 1.113; 95% confidence interval [CI] = 0.433, 2.927; $P = 0.808$), endometritis (RR = 0.943; 95% CI = 0.442, 1.953; $P = 0.850$), and febrile morbidity (RR = 0.745, 95% CI = 0.161, 3.415; $P = 0.700$) between the two groups. Group A showed similar risk of developing wound infection compared to Group B ($P > 0.05$). **Conclusion:** There was no significant difference in post-caesarean wound infection and other infectious morbidity between patients that received a single dose, and those that received a 72-hour course of ceftriazone for antibiotic prophylaxis. This suggests that single dose antibiotic prophylaxis with ceftriazone is similar to multiple dose regimens in efficacy with likely cost-effective advantage.

Keywords: *Caesarean section, ceftriazone, endometritis, febrile morbidity, wound infection*

Introduction

Antibiotics have become a very important tool in modern surgical practice since first discovered almost a century ago.[1] Despite this importance, however, antibiotic use in surgery has evolved over the years. There is now a focus on regulating antibiotic use in surgical practice. This is in the light of increasing risks of antibiotic resistance, general side effects of antibiotics, and even cost effectiveness of treatment.[2] Caesarean section, being the most common surgical procedure performed in most countries today,[3] has not been immune to these changes.

The importance of antibiotic prophylaxis in prevention of post-caesarean wound infection has been reported in several studies.[2,4-6] A few studies, such as that by Bagratee *et al.*,[7] have even suggested that antibiotics prophylaxis may not be required in caesarean section.

In many developed countries, narrow spectrum, single dose antibiotic prophylaxis has long been adopted for most caesarean

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sections.[2,4,8] However, in many developing countries including Nigeria, there is no specific national guideline on antibiotic prophylaxis during caesarean section. Various multiple dose regimens, sometimes extending to seven days, are generally used due to anecdotal suggestions of a higher risk of post-operative infectious morbidity in our environment.

A recent systematic review and meta-analysis of studies comparing single versus multiple doses of antibiotics for caesarean section in low and middle-income settings, however, cautioned that there was insufficient evidence to conclude that there is no difference in infectious morbidity between both single dose and multiple dose groups.[9] They observed that the quality of evidence was still low, and further, well designed randomized controlled trials were needed to reach a valid conclusion.

This study aimed to determine if there was a significant difference in the wound infection rates between a single dose and a 72-hour course of ceftriazone for antibiotic prophylaxis in patients undergoing caesarean section.

Materials and Methods

The study was an equivalence, open label, randomized controlled trial. The sample size for the study was calculated to be 170 participants using the formula $2(Z_{\alpha/2} + Z_{\beta})^2 P(1 - P)/(p1 - p2)^2$,[10] where $Z_{\alpha/2} = Z_{0.05/2} = Z_{0.025} = 1.96$ (from Z table) at type 1 error of 5% and 95% confidence interval (CI), $Z_{\beta} = Z_{0.20} = 0.84$ (from Z table at 80% power), $p1$ and $p2$ were the incidences in both study groups set at 5% and 20%, and P was the pooled incidence ($p1 + p2/2$) = 0.125.

Consenting women scheduled for elective or emergency caesarean section in the antenatal clinic and delivery suite, with low risk for infectious morbidity, were recruited for the study. Exclusion criteria included patients with premature rupture of membranes, already on antibiotics prior to surgery, diabetes mellitus and human immunodeficiency virus, anemia, and active phase of labor. They were divided randomly into two equal groups A and B of 85 each. The Abrahamson WINPEPI software was used to generate a table of random numbers allocating study participants from 1 to 170 randomly to groups A and B (done by a statistician). Envelopes numbered 1–170 with their allocated study groups were then placed in a box, and picked out at random by trained research assistants for each patient as they were recruited into the study. Group A patients received a single dose of 1 g, and those in Group B, a 72-hour course (1 g daily) of intravenous ceftriazone. The first dose was given about 15–30 min before skin incision[11] in both groups. Caesarean sections were performed by residents and consultants within the department using standard surgical techniques under standardized, strict aseptic protocols. The primary outcome measure was the incidence of clinical wound infection. The secondary outcome measures were the incidences of clinical endometritis, and febrile morbidity. Patients were assessed for signs of clinical wound infection from the third to the 14th day postoperatively. These included presence of purulent discharge, indurations, wound dehiscence, and wound tenderness.[12] They were also assessed for clinical endometritis from the 5th to the 14th day postoperatively (defined as uterine tenderness with or without offensive lochia or abnormal vaginal discharge),[12] and febrile morbidity (defined as axillary temperature ≥38.0ºC on two different occasions at least 4 h apart excluding the first 24 h post-delivery) from 24 h to 5 days post-operatively. The patients were assessed by senior residents and consultants not directly involved in randomization of the patients and blinded to the patient's study group to reduce bias. The patients were discharged on the 5th day post-operatively (as per departmental protocol at the time of the study), and counselled to present to the hospital immediately they noticed pain, discharge, bleeding or hardness around the wound site, and also recurrent lower abdominal pain or offensive lochia. They were also called by mobile phone every three days by the research assistants to ask for symptoms, and ensure presentation at the hospital for assessment and treatment. Final assessment was done during the first postnatal visit at 2 weeks (14 days) post-delivery. Data were collected using a structured proforma (designed for the study) containing patients' sociodemographic characteristics, reproductive profile, indications for surgery, patients' weight, and the presence of wound infection postoperatively. The data were analyzed using the Statistical Package for Social Sciences version 21. Chi-square test and Student t test analysis were used to compare categorical and continuous variables respectively. Relationships were expressed using relative risks and confidence intervals. A P-value of ≤0.05 was considered statistically significant. Written informed consent was obtained from each study participant and ethical clearance for the study was obtained from the Health Research Ethics Committee of the Hospital (Assigned number HREC/P05/2015).

Results

The study groups A and B were comparable in terms of booking status, age, educational status, parity, gestational age, weight, type of caesarean section, and indications for caesarean section [Table 1].

The overall incidence of wound infection was 11.2% (11.8% in Group A vs. 10.6% in Group B). There was no statistically significant difference in the incidences of wound infection between both study groups. Study Group A showed similar risk with study Group B of developing post-caesarean wound infection (RR = 1.113, 95% CI = 0.433, 2.927) [Table 2].

There was no statistically significant difference in the risk of endometritis between both study groups [Table 3].

Table 1: Sociodemographic and obstetric characteristics of the study population

Sociodemographic and obstetric characteristics		Study groups		*P*-value
		Group A	Group B	
		f (%)	*f* (%)	
Age (years)	<18	1 (50.0)	1 (50.0)	0.929
	18–34	68 (50.7)	66 (49.3)	
	≥35	16 (47.1)	18 (52.9)	
	Mean ± SD	29.78 ± 5.54	29.25 ± 5.96	
Booking status	Booked	60 (50.4)	59 (49.6)	0.986
	Booked elsewhere	24 (49.0)	25 (51.0)	
	Unbooked	1 (50.0)	1 (50.0)	
Educational status	Quranic only	1 (33.3)	2 (67.7)	0.850
	Primary	9 (40.9)	13 (59.3)	
	Secondary	31 (50.8)	30 (49.2)	
	Tertiary	44 (52.4)	40 (47.6)	
Parity	0	21 (52.7)	19 (47.3)	0.553
	1–4	54 (51.4)	51 (48.6)	
	≥5	10 (40.0)	15 (60.0)	
Gestational age (weeks)	<34	12 (50.0)	12 (50.0)	1.000
	>34	73 (50.0)	73 (50.0)	
	Mean ± SD	37.12 ± 2.88	36.93 ± 2.97	
Maternal weight at delivery (kg)	<90	67 (51.1)	64 (49.9)	0.850
	≥90	18 (46.2)	21 (53.8)	
	Mean ± SD	83.48 ± 12.46	85.13 ± 13.21	
Type of C/S	Elective	35 (50.7)	34 (49.3)	0.876
	Emergency	50 (49.5)	51 (50.5)	
Indication for caesarean section	APH	6 (40.0)	9 (60.0)	0.888
	One previous C/S	21 (52.5)	19 (47.5)	
	Abnormal	5 (41.7)	7 (58.3)	
	Lie/presentation	18 (56.1)	19 (51.4)	
	2 or more previous C/S	23 (56.1)	18 (43.9)	
	Preeclampsia/eclampsia abnormal BPP	12 (48.0)	13 (52.0)	

f = frequency, % = percentage, APH = antepartum haemorrhage, BPP = biophysical profile, C/S = caesarean section, SD = standard deviation

Table 2: Distribution of wound infection in the study groups

Study groups	Wound infection		RR	*P*-value	95% CI
	Yes	No			
	f (%)	*f* (%)			
Group A	10 (11.8)	75 (88.2)	1.113	0.808	0.433, 2.927
Group B	9 (10.6)	76 (89.4)			
Total	19 (11.2)	151 (88.8)			

df = degree of freedom, RR = relative risk, CI = confidence interval

Table 3: Distribution of clinical endometritis in the study groups

Study groups	Endometritis		RR	*P*-value	95% CI
	Yes	No			
	f (%)	*f* (%)			
Group A	17 (20.0)	68 (80.0)	0.943	0.850	0.442, 1.953
Group B	18 (21.2)	67 (78.8)			
Total	35 (20.6)	135 (79.4)			

f = frequency, RR = relative risk, CI = confidence interval

Table 4: Distribution of febrile morbidity in the study groups

Study groups	Febrile Morbidity		RR	*P*-value	95% CI
	Yes	No			
	f (%)	*f* (%)			
Group A	3 (3.5)	82 (96.5)	0.745	0.700	0.161, 3.415
Group B	4 (4.7)	81 (95.3)			
Total	7 (4.1)	163 (95.9)			

f = frequency, RR = relative risk, CI = confidence interval

There was no statistically significant difference in risk of febrile morbidity between both study groups [Table 4].

Discussion

The reported incidence of wound infection in the overall study population was higher than the 9.2% reported by Jido *et al.*[13] in Kano, 9.3% by Ezechi *et al.*[14] in Lagos, and 4.5% reported by Adaji *et al.*[15] in Abuja. It was, however, lower than the 16.2% reported by Morhasson-Bello *et al.*[16] in Ibadan. The Kano study was a retrospective study with no post-discharge follow-up of the patients documented,

whereas the Lagos study was a prospective study, which also had no post-discharge follow-up. The Ibadan study included a significant proportion of high-risk caesarean sections such as premature rupture of membranes and labor complications in their study population. The Abuja study defined wound infection as partial or total wound dehiscence, and/or presence of purulent/serous wound discharge, thus excluding patients with indurations or wound tenderness, who were included in our study. These differences with our study may explain the differences in the reported incidences of wound infection.

The incidence of wound infection in this study and most of the reviewed local studies were, however, higher than several reviewed studies outside Nigeria such as Lyimo *et al*.[17] in Tanzania (4.8% vs. 6.4% in both study groups), Wali *et al*.[18] in Pakistan (4% vs. 8% in both study groups), Kalaranjini *et al*.[19] in India (0.7% vs. 1.4% in both groups), and Dhar *et al*.[20] in Oman (2.66%). These were all prospective studies similar to our study. Their reported low incidences as compared to ours may be due to use of microbiological diagnosis of wound infection as against clinical diagnosis used in our study. It may also suggest a possible higher risk of wound infection in our environment as compared to theirs.

This study demonstrated that there was no statistically significant difference in the incidence of wound infection between the study groups A and B. This was similar to the findings reported by Alekwe *et al*.[12] in Ife, Nigeria, though their study compared different antibiotic agents; ceftriazone in the single dose group, and a combination of ampiclox, metronidazole and gentamicin for seven days in the other group. Our findings were also similar to the reports by Lyimo *et al.*[17] in Tanzania, Shakya *et al*.[21] in Nepal, and Abhilasha *et al*.[22] in India.

They all also reported no significant differences in incidence of wound infection between single and multiple dose antibiotic regimens for antibiotic prophylaxis during caesarean section. There were, however, differences in the methodology of all these studies; Lyimo *et al*.[17] compared a single dose of gentamicin and metronidazole with a 24-hour course of the same antibiotics; Shakya *et al.*[21] compared a single dose of cefazolin and metronidazole, with a 24- to 72-hour course of the same antibiotics depending on hospital protocols in a multicenter study; Abhilasha *et al*.[22] compared a single dose, 24-hour course, and 7-day course of the same antibiotic regimen.

Adaji *et al*.[15] in Abuja compared a 48-hour course of parenteral cefuroxime-metronidazole combination, with a 7-day course of the same antibiotics, which were continued as oral medication for 5 days after completion of the parenteral course. They found no significant differences between the two study groups in terms of post-operative wound infection, thereafter suggesting a need for comparison between a single dose regimen and the 48-hour course of antibiotic prophylaxis.

The findings on endometritis documented in this study were comparable to the report by Alekwe *et al*.,[12] which showed no significant difference between the single and multiple dose regimens as well. However, the incidence of 20% versus 21.6% in our study is quite higher than the 14% versus 15% in the single versus multiple dose groups reported by Alekwe *et al*.[12] The higher incidence in this study may be due to the difference in diagnostic criteria, whereby clinically suspected endometritis was the outcome measure, as against microbiological diagnosis from an endocervical swab specimen used by Alekwe *et al.* In addition, emergency cases formed the majority of the study population in this study, whereas Alekwe *et al*. only studied elective cases.

Whereas Wali *et al.*[18] and Kalaranjini *et al.*[19] also found no difference in postpartum endometritis rates between the single and multiple dose antibiotic groups in their studies, their results were significantly different from this study in that they recorded no cases of endometritis. The other arguments made earlier for the higher wound infection rates in this study, such as differences in the study populations (emergency cases vs. elective cases), as well as clinical versus microbiological diagnosis of endometritis, may also contribute to the differences in the rates of endometritis seen. However, they alone cannot explain the very wide differences (20.6% vs. 0%) that have been noted. This may further buttress the argument that stricter adherence to asepsis and infection control measures may be responsible for the differences observed generally in infectious morbidity.

The findings on febrile morbidity reported in this study were also comparable to the findings of Alekwe *et al*.,[12] which reported no significant difference in febrile morbidity between its single and multiple dose antibiotic groups. They were also comparable to the findings reported by Lyimo *et al*.[17] in Tanzania, Shakya *et al*.[21] in Nepal, and Abhilasha *et al*.[22] in India. They also found no significant differences between the single and multiple antibiotic dose regimens in the post-operative febrile morbidity rates.

The febrile morbidity rates in this study are lower than the 7% versus 6% reported by Alekwe *et al*.[12] It must be pointed out that whereas febrile morbidity may reflect the level of infectious morbidities which include wound infection, endometritis, urinary tract infection, thrombophlebitis, and possible pelvic collection/peritonitis, it is also affected by non-bacterial infections such as malaria and viral infections. Since these non-bacterial infections cannot be accounted for in both study populations, it may be difficult to draw conclusions from the results. The results may, however, suggest similar or even lower microbiological wound infection and endometritis rates in this study compared to theirs.

The incidence of febrile morbidity in this study is, however, higher than the 1% versus 3% reported by Bhattachan *et al*.[23] in Nepal, which correlated with a low wound infection rate of 1% versus 0%, and also higher than the 2.1% versus 1.1% reported by Kalaranjini *et al.*[19] which

also correlated with low wound infection (0.7% vs. 1.4%) and endometritis rates (0% in both groups) in the single versus multiple dose antibiotic groups respectively. This may suggest a higher incidence of infectious morbidity in our environment when compared to these reports.

Single dose antibiotic prophylaxis has the obvious advantage of reduced cost both for the patient and the hospital, and reduced stress of serving medications on already overstretched nursing services in low and middle-income settings like ours. It also mitigates the emerging problem of antibiotic resistance due to inappropriate antibiotic use. This, however, has to be weighed against risk of infectious morbidity.

Limitations

Whereas there was an attempt at blinding to reduce bias, a fully blinded study using placebo agents similar in packaging and appearance to the active drug used and making both regimens look alike may have achieved a better result.

In addition, a small percentage of patients may develop post-caesarean wound infection and endometritis up to 30 days postoperatively, whereas the period of follow up in this study was 14 days.

Conclusion

It may be concluded from this study that single dose, broad spectrum antibiotic prophylaxis is similar to multiple dose regimens currently practiced in low-risk caesarean sections in most Nigerian hospitals. However, further studies with larger sample size and preferably multicenter could help establish stronger evidence for single dose antibiotic prophylaxis in low-risk caesarean sections in Nigeria.

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Conflicts of interest

There are no conflicts of interest.

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