The Efficacy of Two Doses versus 7 Days’ Course of Prophylactic Antibiotics Following Cesarean Section: An Experience from Aminu Kano Teaching Hospital

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Abstract

Background: Postcesarean wound infection is a leading cause of prolonged hospital stay. Considerable debates still exist regarding choice of antibiotics, dose, and duration of use. Objectives: The objective is to compare the efficacy of 2 doses of amoxicillin-clavulanic acid versus a 7 days combination of amoxicillin-clavulanic acid and metronidazole as prophylactic antibiotics following cesarean section (CS). Methodology: It was a randomized controlled trial that was conducted among 160 women undergoing CS at Aminu Kano Teaching Hospital. Women were randomized into two groups. Group I (study group) received 2 doses of 1.2 g amoxicillin-clavulanic acid. Group II (control group) received a 7 days course of amoxicillin-clavulanic acid and metronidazole. The data obtained were analyzed using SPSS version 17. Categorical (qualitative) variables were analyzed using Chi-square test and Fisher’s exact test as appropriate while continuous (quantitative) variables were analyzed using independent sample t-test. P < 0.05 was considered statistically significant. Results: There was no statistically significant association in the occurrence of fever (12.8% vs. 15.8%, P = 0.6), wound infection (6.4% vs. 10.5%, P = 0.36), endometritis (7.7% vs. 11.8%, P = 0.38), UTI (6.4% vs. 5.3%, P = 1.00), mean duration of hospital stay (129.7 vs. 134.2 h, P = 0.48), and neonatal outcomes between the two groups. There was statistically significant difference in the mean cost of antibiotics (₦2883/US$9.5 vs. ₦7040/US$23.1, P < 0.001) and maternal side effects (10.3% vs. 26.3%, P < 0.001) between the study and the control groups, respectively. Conclusion: This study found no statistically significant difference in infectious morbidity, duration of hospital stay, and neonatal outcomes when two doses of amoxicillin-clavulanic acid was compared with a 7 days course of prophylactic antibiotic following CS. The use of two doses of amoxicillin-clavulanic acid has the advantages of reduced cost and some maternal side effects. The two doses were cheaper with minimal side effects.

Keywords: Amoxicillin-clavulanic acid, cesarean section, infectious morbidity, prophylactic antibiotic

Résumé

Contexte: L’infection des plaies post-césariennes est l’une des principales causes d’hospitalisation prolongée. Des débats considérables existent toujours concernant le choix antibiotiques, dose et durée d’utilisation. Objectifs: L’objectif est de comparer l’efficacité de 2 doses d’acide amoxicilline-clavulanique par rapport à 7 jours association d’acide amoxicilline-clavulanique et de métronidazole comme antibiotiques prophylactiques après une césarienne (CS). Méthodologie: c’était un essai contrôleé randomisé mené auprès de 160 femmes subissant une CS à l’hôpital universitaire Aminu Kano. Les femmes ont été randomisées en deux groupes. Le groupe I (groupe d’étude) a reçu 2 doses d’acide amoxicilline-clavulanique de 1,2 g. Le groupe II (groupe témoin) a reçu 7 jours de l’acide amoxicilline-clavulanique et du métronidazole. Les données obtenues ont été analysées à l’aide du SPSS version 17. Catégorie (qualitative) les variables ont été analysées à l’aide du test du chi carré et du test exact de Fisher, selon le cas, tandis que les variables continues (quantitatives) ont été analysées en utilisant un test t pour échantillon indépendant, P < 0.05
était considéré comme statistiquement significatif. **Résultats:** Il n’y avait pas d’association statistiquement significative en cas de fièvre (12,8% vs 15,8%, \( P = 0,6 \)), infection des plaies (6,4% vs 10,5%, \( P = 0,36 \)), endométrite (7,7% vs 11,8%, \( P = 0,38 \)), IVU (6,4% contre 5,3%, \( P = 1,00 \)), durée moyenne de séjour à l’hôpital (129,7 contre 134,2 h, \( P = 0,48 \)) et résultats néonatals entre les deux groupes. Il y avait une différence statistiquement significative dans le coût moyen des antibiotiques (83 2883 / US $ 9,5 contre N 7040 / US $ 23,1, \( P < 0,001 \)) et côté maternel effets (10,3% contre 26,3%, \( P < 0,001 \)) entre l’étude et les groupes témoins, respectivement. **Conclusion:** Cette étude n’a trouvé aucune statistique différence significative dans la morbidité infectieuse, la durée du séjour à l’hôpital et les résultats néonatals lorsque deux doses d’amoxicilline-clavulanic l’acide a été comparé à un traitement antibiotique prophylactique de 7 jours aprè la CS. L’utilisation de deux doses d’acide amoxicilline-clavulanic a avantages du coût réduit et de certains effets secondaires maternels. Les deux doses étaient moins chères avec des effets secondaires minimes.

**Mots-clés:** Acide amoxicilline-clavulanic, césarienne, morbidité infectieuse, antibiotique prophylactique

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**INTRODUCTION**

Surgical site infection (SSI) is one of the most common postoperative complications, occurring in at least 5% of all patients undergoing surgery and 30%–40% of patients undergoing abdominal surgery, depending on the level of contamination.\(^1\) Postcesarean wound infection is not only a leading cause of prolonged hospital stay but also a major cause of the widespread aversion to cesarean delivery in developing countries.\(^2\) The single most important risk factor for postpartum maternal infection is cesarean section (CS). Women undergoing CS have 5–20 times greater risk of infection compared with vaginal delivery.\(^3\)

Infectious complications (infectious morbidity) following cesarean delivery include fever, wound infection, endometritis, bacteremia, urinary tract infection, and other serious infection (including pelvic abscess, septic shock, necrotizing fasciitis, and septic pelvic vein thrombophlebitis) which can sometimes lead to maternal mortality.\(^3,4\) Some of the factors associated with increased risk of infection include; prolonged labor and rupture of membranes, six or more vaginal examinations, postoperative anemia, emergency CS, obesity, and diabetes mellitus.\(^3,5\)

The most important source of micro-organisms responsible for post-CS infection is the genital tract, particularly if the membranes are ruptured.\(^4\) Even in the presence of intact membranes, microbial invasion of the intrauterine cavity is common, especially with preterm labor.\(^6\) The general principle for prevention of any surgical site infection is based on sound surgical technique, skin antisepsis, and antimicrobial prophylaxis.\(^4\) Antimicrobial prophylaxis is not an attempt to sterilize tissues, but a critically timed adjunct used to reduce the microbial burden of intraoperative contamination to a level that cannot overwhelm host defenses.\(^7\) An adequate antibiotic level in the tissue can augment natural immune defense mechanisms and help kill bacteria that are invariably inoculated into the wound at the time of surgery.\(^4\) Even though antibiotic prophylaxis for women undergoing cesarean delivery has been proven to be beneficial in decreasing post-CS infectious morbidity both in high-risk (in labor post membrane rupture), or low-risk patients, (nonlaboring with intact membranes),\(^1,4\) considerable debate still exists regarding choice of antibiotics (whether narrow spectrum or broad spectrum), timing of administration (before skin incision or after cord clamping), dose and duration of use.\(^9\)

Since there are overwhelming numbers of effective drugs available, attempts to define an antibiotic regimen of choice have been problematic. In many respects, penicillins and cephalosporins are good choices.\(^9\) However, despite the use of antibiotics, 10% of CSs are still complicated by infection and 15% by fever.\(^10\)

Despite the above, injudicious use of antibiotics can lead to increased cost of health care, side effects, and development of resistant organisms.\(^11\)

Amoxicilline-clavulanic acid is a broad spectrum antibiotic that is active against most of the organisms implicated in postcesarean infections.\(^11\)

Prophylactic antibiotics for CS can be expected to result in a major reduction in postoperative infectious morbidity. The question that remains, therefore, is which regimen to use.\(^9\) Surveys suggest that there is inconsistent and variable application of the use of prophylactic antibiotics at CSs.\(^4\) Prophylactic antibiotic use differs from treatment with antibiotics in that the former is intended to prevent infection, whereas the latter is intended to resolve an established infection, typically requiring a longer course of therapy.\(^12\)

Many hospitals especially in the developing countries are still using prophylactic antibiotics following CS beyond 24 h despite overwhelming evidence against this practice.\(^1,4,12\) Increasing the duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms so also is the use of combination antimicrobials.\(^13\) Of note, the recent 2014 World Health Assembly expressed serious concern regarding antibiotic resistance due to antibiotic overuse and misuse and urged immediate action to combat antibiotic resistance on a global scale.\(^1,4,15\)

Recent evidence suggests that broad-spectrum antibiotics are more effective in preventing postcesarean delivery infections than narrow range antibiotics, so also is the administration of prophylaxis within 30–60 min prior to skin incision instead of after cord clamping with no untoward effects on the baby.\(^16\)

Even though studies on short courses of antibiotic prophylaxis...
exist in Nigeria, almost all were on elective CS with exclusion of emergency cases.\(^{[11]}\)

The aim of this study was to evaluate the efficacy of 2 doses of amoxicillin-clavulanic acid (study group) versus a 7 days combination of amoxicillin-clavulanic acid and metronidazole (control group) as prophylactic antibiotics following CS.

**Methodology**

The study was a randomized controlled trial conducted among 160 pregnant women at Aminu Kano Teaching Hospital (AKTH) from July 1, to November 30, 2016. Ethical approval was obtained from the hospital ethics committee. Consenting pregnant women admitted for CS who fulfilled the eligibility criteria and were willing to participate in the trial were randomized into two groups: Group I (study group) and Group II (control group).

Consecutive pregnant women who were scheduled for either elective or emergency CS in the obstetric unit of AKTH were included in the study until the required sample size was met. Pregnant women allergic to the drugs, those with established infections before the surgery, those with prolonged rupture of membranes, obstructed labor, those who had more than 6 vaginal examinations, chronic illnesses, on antibiotics within the past 7 days prior to randomization were excluded from the study. Eighty small pieces of paper were marked Group I and another 80 marked Group II. These pieces of paper were mixed thoroughly and each placed in serially numbered 160 opaque envelopes (Randomization) which were kept in a box. Allocation was done by opening a sealed opaque envelope. The sealed envelopes were secured and placed in the theater. The matron in the theater who was otherwise not involved in the study opened the envelopes serially as the patients were brought in until completion of the study. Neither the surgeon nor the participants were aware of the allocation of participants to any particular group prior to opening the envelopes (allocation concealment). A book was kept in theatre where the anesthetist records the serial number, hospital number and patients’ group. The group allocation was only unmasked if the patients developed infectious morbidity that required additional antibiotic therapy or at the end of the study. A standard operating procedure of CS was done under aseptic condition for all the recruited participants.

Group I (study group) comprised 80 patients. Each patient received 2 doses of 1.2 g of amoxicillin-clavulanic acid intravenously. The first dose was administered by the anesthetist within 60 min before commencement of the skin incision and the second dose 12 h after the first dose. No additional postoperative antibiotic was given. Those who developed infectious morbidity were evaluated and treated.

Group II (control group) also consisted of 80 patients. This group received antibiotics post operatively for 7 days (Amoksiklav brand of amoxicillin-clavulanic acid manufactured by Lek pharmaceuticals, and Metronidazole (Unigyl); Unique pharmaceuticals Limited).

The principal investigator and 6 trained research assistants from anesthesia, neonatology, nursing and obstetrics and gynecology units were involved in administering the questionnaire; follow up of the subjects and data collection. After developing the questionnaire, it was reviewed and revised by the authors using critical appraisal checklist for a questionnaire study, and thereafter pretested on 30 participants for validity and reliability (see attached copy).

In this study, primary outcomes measures were maternal febrile morbidity (fever), wound infection, endometritis, and serious infectious complications (such as bacteremia, septic shock, septic thrombophlebitis, necrotizing fasciitis, or death attributed to infection); live or dead baby. Secondary outcome measures were maternal urinary tract infection, adverse effects of treatment on the woman (e.g., allergic reactions, nausea, vomiting, diarrhea, skin rashes, thrush), length of stay in hospital and cost; neonatal febrile illness, neonatal sepsis, infection with resistant organism, special care baby unit (SCBU) admission, and length of admission at SCBU.

Patients in both groups were managed postoperatively. Wound was inspected on day 3 for signs of infection. Patients were assessed daily for above outcomes. Those patients who were well on day five or day seven (depending on the type of skin incision used) were discharged. Patients found to have wound infection were kept on admission for evaluation and treatment. Babies were also followed up for above neonatal outcomes.

After discharge patients were interviewed weekly through telephone and instructed to report to the hospital at any time whenever they developed problems such as fever, foul smelling vaginal discharge or bleeding, discharge from the wound margin, and breast engorgement within two weeks of discharge or to come to the hospital for follow-up at 2 weeks. Patients were followed up for 30 days.

Patients that develop febrile morbidity were evaluated further to determine the possible cause (malaria, UTI, endometritis, or wound infection). Samples were taken for malaria parasite, wound swab m/c/s and urine m/c/s as appropriate.

In this study, febrile morbidity was defined as axillary temperature of ≥38°C obtained on 2 or more occasions at least 4 h apart, excluding the first 24 h after the operation. Digital thermometer was used for recording the temperature.\(^{[17]}\)

Wound infection was based on The CDC’s National Nosocomial Infections Surveillance system which was defined as Infection occurring within 30 days after the operation and at least one of the following: (1) purulent drainage, (2) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision, and (3) at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, fever ≥38°C,
Table 1: General characteristics

| Variable                        | Group I (n=78)       | Group II (n=76)      | Statistical test | P      |
|---------------------------------|----------------------|----------------------|------------------|--------|
| Mean age±SD (years)             | 31.2±5.2             | 31.7±5.1             | t=−0.6           | 0.55   |
| Mean GA at delivery±SD (weeks)  | 39.1±1.2             | 38.7±1.1             | t=1.6            | 0.11   |
| Booking status, n (%)           |                      |                      |                  |        |
| Booked                          | 68 (87.2)            | 69 (90.8)            | χ²=0.51          | 0.48   |
| Unbooked                        | 10 (12.8)            | 7 (9.2)              |                  |        |
| Educational status, n (%)       |                      |                      |                  |        |
| Quranic                         | 3 (3.9)              | 1 (1.3)              | Fisher’s=2.2     | 0.55   |
| Primary                         | 2 (2.6)              | 2 (1.3)              |                  |        |
| Secondary                       | 38 (48.7)            | 33 (43.4)            |                  |        |
| Tertiary                        | 35 (44.8)            | 41 (54.0)            |                  |        |
| Mean number of previous CS±SD   | 1.1±0.9              | 1.1±0.1              | t=−0.2           | 0.85   |
| Mean maternal weight±SD (kg)    | 78.9±19.7            | 76.9±18.6            | t=0.6            | 0.52   |
| Preoperative PCV (%)            | 33.2±2.4             | 33.5±2.5             | t=−0.9           | 0.4    |

SD=Standard deviation, CS=Cesarean section, GA=Gestational age, PCV=Packed cell volume

and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.[7]

Endometritis was defined as fever with concomitant uterine tenderness and foul smelling lochia.[18]

Urinary tract infection was defined as burning micturition with a positive urine culture of ≥10⁵ bacteria per mL.[19] The length of hospital stay was calculated in hours from the time of completion of the surgery to the time of discharge.

Data obtained were entered into excel sheets by 2 separate clerical staff and compared for difference. It was then analyzed using Statistical Package for Social Sciences (SPSS) version 17 (SPSS Inc., SPSS Statistics for Windows, Chicago, IL, USA). Quantitative variables were described using means and standard deviation while qualitative variables were described as percentages. Categorical (qualitative) variables (such as wound infection, endometritis, urinary tract infection, and maternal side effects) were analyzed using Chi-square test and Fisher’s exact test as appropriate while continuous (quantitative) variables were analyzed using independent sample t-test, and the results presented in tables. P < 0.05 was considered statistically significant.

RESULTS

The study was conducted from July 1, and November 30, 2016 among 160 women undergoing both elective and emergency CS at AKTH. Two patients in Group I and four patients in Group II were lost to follow-up before the 30-day period. Seventy-eight patients (97.5%) in Group I and 76 patients (95%) in Group II were successfully followed up and data collected were analyzed.

Table 1 shows the general characteristics of the patients. The mean age of the patients in the study group (Group I) was 31.2 ± 5.2 years while the mean age in the control group (Group II) was 31.7 ± 5.1 years and the difference was not statistically significant (t = −0.6, P = 0.55). The median parity was 2 in both the study and the control groups. The mean gestational age in weeks at the time of CS was 39.1 ± 1.2 and 38.7 ± 1.1 in the study and control groups, respectively, and the difference was not statistically significant (t = 1.6, P = 0.11). Sixty-eight (87.2%) and 69 (90.8%) patients were booked in the study and control groups, respectively. Booking status was not statistically associated with either the study or the control groups, respectively. Overall, educational status was not statistically associated with grouping (Fisher’s exact = 2.2, P = 0.55).

The mean maternal weight in kilograms was 78.9 ± 19.7 and 76.9 ± 18.6 in the study and control groups respectively and the difference was not statistically significant (t = 0.6, P = 0.52). The mean packed cell volume in the study group was 33.2 ± 2.4%, while it was 33.5 ± 2.5% in the control group and the difference was not statistically significant (t = 0.9, P = 0.52). Overall, there was no statistically significant difference in the general characteristics of the patients.

Table 2 shows the various indications for CS. The commonest indication in both groups was previous CS and another indication accounting for 32 (41.0%) and 28 (36.8%) patients in the study and control groups, respectively. Two or more previous CS accounted for 22 (28.2%) and 26 (34.2%) patients in the study and control groups, respectively. Other indications included; bad obstetric history, contracted pelvis, suspected fetal macrosomia, and prolonged infertility, which accounted for 10 (12.8%) and 7 (9.2%) patients in the study and control groups, respectively. Overall, indications for CS were not statistically associated with either the study or the control groups (χ² = 2.2, P = 0.78).

Table 3 shows the operative characteristics of the patients. Fifty-five (70.5%) and 52 (68.4%) patients had elective CS in the study and control groups, respectively, while 23 (29.5%) and 24 (31.6%) patients had emergency CS in the study and control groups, respectively. There was no statistically significant association between the mode of CS and the
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Table 2: Indications for cesarean section

| Variable                  | Group I (n=78), n (%) | Group II (n=76), n (%) | Total       | Statistical test | P   |
|---------------------------|-----------------------|------------------------|-------------|-----------------|-----|
| Previous CS + another indication | 32 (41.0)             | 28 (36.8)             | 60 (38.9)   | χ²=2.2          | 0.78|
| Two or more previous CS   | 22 (28.2)             | 26 (34.2)             | 48 (31.2)   |                 |     |
| Severe preeclampsia       | 4 (5.1)               | 2 (2.6)               | 6 (3.9)     |                 |     |
| Placenta praevia          | 5 (6.4)               | 7 (9.2)               | 12 (7.8)    |                 |     |
| Malpresentation/malposition| 5 (6.4)               | 6 (7.9)               | 11 (7.1)    |                 |     |
| Others                    | 10 (12.8)             | 7 (9.2)               | 17 (11.1)   |                 |     |
| Total                     | 78                    | 76                    | 154         |                 |     |

CS=Cesarean section

Table 3: Operative characteristics

| Variable                  | Group I (n=78), n (%) | Group II (n=76), n (%) | Total       | Statistical test | P   |
|---------------------------|-----------------------|------------------------|-------------|-----------------|-----|
| Type of CS                |                       |                        |             |                 |     |
| Elective                  | 55 (70.5)             | 52 (68.4)             | 107 (69.5)  | χ²=0.1          | 0.78|
| Emergency                 | 23 (29.5)             | 24 (31.6)             | 47 (30.5)   |                 |     |
| Type of anesthesia        |                       |                        |             |                 |     |
| Spinal                    | 68 (87.2)             | 68 (89.5)             | 136 (88.3)  | χ²=0.2          | 0.66|
| General                   | 10 (12.8)             | 8 (10.5)              | 18 (11.7)   |                 |     |
| Type of skin incision     |                       |                        |             |                 |     |
| Pfannenstiel              | 73 (93.6)             | 66 (86.8)             | 139 (90.3)  | χ²=2.0          | 0.16|
| Mid-line                  | 5 (6.4)               | 10 (13.2)             | 15 (9.7)    |                 |     |
| Placental delivery        |                       |                        |             |                 |     |
| Controlled cord traction  | 68 (87.2)             | 62 (81.6)             | 130 (84.4)  | χ²=0.9          | 0.34|
| Manual                    | 10 (12.8)             | 14 (18.4)             | 24 (15.6)   |                 |     |
| Mean duration of surgery±SD (min) | 56.5±11.1   | 54.7±12.3             | 55.6±11.7   | t=0.9           | 0.36|
| Mean EBL±SD (ml)          | 425.0±93.5            | 432.2±114.5           | 428.6±104.1 | r=−0.4          | 0.67|
| Cadre of surgeon          |                       |                        |             |                 |     |
| Registrar                 | 18 (23.1)             | 10 (13.2)             | 28 (18.2)   | χ²=3.6          | 0.17|
| Senior registrar          | 50 (64.1)             | 59 (77.6)             | 109 (70.8)  |                 |     |
| Consultant                | 10 (12.8)             | 7 (9.2)               | 17 (11.0)   |                 |     |

CS=Cesarean section, EBL=Estimated blood loss, SD=Standard deviation

Grouping (χ² = 0.1, P = 0.78). Spinal anesthesia was the commonest form of anesthesia administered in both groups accounting for 68 (87.2%) and 68 (89.5%) patients in the study and control groups, respectively. There was also no statistically significant association between the two groups (χ² = 0.2, P = 0.66). Pfannenstiel incision was the most common form of incision accounting for 73 (93.6%) and 66 (86.8%) patients in the study and control groups, respectively. Furthermore, no statistically significant association (χ² = 2.0, P = 0.16). The most common mode of placental delivery was by controlled cord traction which was done in 68 (87.2%) and 62 (81.6%) cases in the study and control groups, respectively. No statistically significant association between the mode of placental delivery and the two groups (χ² = 0.9, P = 0.34).

The mean duration of surgery in minutes was 56.5 ± 11.1 and 54.7 ± 12.3 in the study and control groups, respectively. There was no statistically significant difference (t = 0.9, P = 0.36). The mean estimated blood loss in milliliter (ml) was 425.0 ± 93.5 and 432.2 ± 114.5 in the study and control groups respectively, and the difference was not statistically significant (t = −0.4, P = 0.67). Most of the surgeries were performed by Senior Registrars which accounted for 50 (64.1%) and 59 (77.6%) cases in the study and control groups, respectively, and there was no statistically significant association (χ² = 3.6, P = 0.17).

Table 4 shows infectious morbidity based on type of CS. Fever was the most common morbidity accounting for 10 (12.8%) and 12 (15.8%) patients in the study and control groups respectively, however, it was not statistically associated with the grouping (χ² = 0.3, P = 0.60). There was no statistically significant association between the rate of wound infection and the study or the control group (5.1% and 6.7%, χ² = 0.2, P = 0.1). Also, the rate of endometritis did not show any statistically significant association between the two groups (7.7% and 11.8%, χ² = 0.8, P = 0.38). Urinary tract infection accounted for 5 (6.4%) and 4 (5.3%) patients in the study and control groups respectively, and it was not statistically associated with the two groups (Fishers exact = 0.1, P = 1.00). The overall rates of infectious morbidity were: Fever 22 (14.3%), wound infection 13 (8.4%), endometritis 15 (9.7%), and UTI 9 (5.8%). No patient developed pelvic abscess and there was no case of pelvic vein thrombophlebitis.
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Control groups, respectively. Four (80%) and 2 (25%) wound infections were diagnosed after discharge in the study and control groups, respectively, and there was no statistically significant association with the two groups (Fishers exact = 3.7, P = 0.10).The mean time of the development of endometritis in days was 5.7 ± 4.1 and 3.2 ± 0.9 in the study and control groups respectively, and the difference was not statistically significant (t = 1.4, P = 0.21). Overall, there was no statistically significant difference in the meantime of development of wound infection and endometritis between the two groups.

Infectious morbidity rates were commoner with emergency than elective CS.

Table 5 shows the mean time of the development of wound infection and endometritis (number of days postoperatively)

Table 4: Infectious morbidity and infectious morbidity based on type of cesarean section

| Variable                      | Group I (n=78), n (%) | Group II (n=76), n (%) | Total, n (%) | Statistical test | P    |
|-------------------------------|-----------------------|------------------------|--------------|------------------|------|
| Fever                         | 10 (12.8)             | 12 (15.8)              | 22 (14.3)    | χ²=0.3           | 0.60 |
| Malaria parasites             | 4 (5.1)               | 5 (6.7)                | 9 (5.8)      | Fisher’s=0.2     | 0.74 |
| Wound infection               | 5 (6.4)               | 8 (10.5)               | 13 (8.4)     | χ²=0.9           | 0.36 |
| Endometritis                  | 6 (7.7)               | 9 (11.8)               | 15 (9.7)     | χ²=0.8           | 0.38 |
| UTI                           | 5 (6.4)               | 4 (5.3)                | 9 (5.8)      | Fisher’s=0.1     | 1.00 |

Infectious morbidity based on type of CS

| Wound infection               |                       |                        |              |                  |      |
| Electro                        | 2 (40)                | 3 (60)                 | 5 (3.2)      | Fisher’s=0.0     | 1.00 |
| Emergency                      | 3 (37.5)              | 5 (62.5)               | 8 (5.2)      |                  |      |
| Fever                          | 5 (55.6)              | 4 (44.4)               | 9 (5.8)      | Fisher’s=0.6     | 0.66 |
| Emergency                      | 5 (38.5)              | 8 (61.5)               | 13 (8.5)     |                  |      |
| Endometritis                   | 3 (50.0)              | 3 (50.0)               | 6 (3.9)      | Fisher’s=0.4     | 0.62 |
| Emergency                      | 3 (33.3)              | 6 (66.7)               | 9 (5.8)      |                  |      |
| UTI                            | 2 (50.0)              | 2 (50.0)               | 4 (2.6)      | Fisher’s=0.1     | 0.76 |
| Emergency                      | 3 (60.0)              | 2 (40.0)               | 5 (3.2)      |                  |      |

UTI=Urinary tract infection, CS=Cesarean section

Table 5: Mean time of development of wound infection and endometritis (number of days postoperatively)

| Variable                      | Group I                  | Group II                 | Total, n (%) | Statistical test | P    |
|-------------------------------|--------------------------|--------------------------|--------------|------------------|------|
| Wound infection               | n=5                      | n=8                      |              |                  |      |
| Mean number of days at diagnosis | 9.8±4.0                  | 5.9±2.9                  | 7.9±3.78     | t=1.9            | 0.11 |
| Diagnosed on admission, n (%)  | 1 (20)                   | 6 (75)                   | 7 (53.9)     | Fisher’s=3.7     | 0.10 |
| Diagnosed after discharge, n (%) | 4 (80)                  | 2 (25)                   | 6 (46.1)     |                  |      |
| Endometritis                  | n=6                      | n=9                      |              |                  |      |
| Mean number of days at diagnosis | 5.7±4.1                  | 3.2±0.9                  | 4.2±2.9      | t=1.4            | 0.21 |
| Diagnosed on admission, n (%)  | 4 (66.7)                 | 8 (88.9)                 | 12 (80)      | Fisher’s=3.7     | 0.10 |
| Diagnosed after discharge, n (%) | 2 (33.3)                | 1 (11.1)                 | 3 (20)       |                  |      |

Table 6: Other maternal outcomes and neonatal outcomes

| Variable                      | Group I (n=78)            | Group II (n=76)          | Total, n (%) | Statistical test | P    |
|-------------------------------|---------------------------|--------------------------|--------------|------------------|------|
| Mean duration of hospital stay±SD (h) | 129.7±46.7               | 134.2±28.1               | 131.9±38.6   | r=−0.7           | 0.48 |
| Mean cost of antibiotics±SD (naira) | 2883±1695                | 7040±1260                | 4934±2407    | r=−17.3          | 0.00*|
| Maternal side effects, n (%)   | 8 (10.3)                  | 20 (26.3)                | 28 (18.2)    | χ²=6.7           | 0.01*|
| Neutonal outcome               |                           |                          |              |                  |      |
| Mean APGAR score±SD            | 8.6±0.5                   | 8.7±0.5                  | 8.7±0.5      | r=−0.5           | 0.58 |
| SCBU admission, n (%)          | 4 (5.1)                   | 3 (3.9)                  | 7 (4.5)      | Fisher’s=0.1     | 1.00 |
| Mean duration of SCBU stay (days) | 4.3±2.8                  | 4.3±2.5                  | 4.3±1.6      | r=−0.0           | 0.97 |

*Statistically significant. SD=Standard deviation, SCBU=Special care baby unit
Table 7: Microbiological pattern of postcesarean wound infection and urinary tract infection

| Organisms            | Group I, n (%) | Group II, n (%) | Sensitivity pattern                  |
|----------------------|---------------|----------------|---------------------------------------|
| Wound infection      | n=5           | n=8            |                                       |
| S. aureus            | 3 (60)        | 5 (62.5)       | Ceftriaxone***, cefuroxime**, augmentin*** |
| Klebsiella species   | 1 (20)        | 1 (12.5)       | Ceftriaxone***, ofloxacin**, cefuroxime** |
| E. coli              | 1 (20)        | 2 (25)         | Ceftriaxone***, levofloxacin**, augmentin*** |
| Pseudomonas          | 0 (0)         | 1 (12.5)       | Ceftazidine**, gentamycin**, levofloxacin**, ofloxacin** |
| No growth            | 1 (20)        | 1 (12.5)       |                                       |
| UTI                  | n=5           | n=4            |                                       |
| E. coli              | 3 (60)        | 3 (75)         | Ceftriaxone***, levofloxacin**, augmentin*** |
| Klebsiella species   | 2 (40)        | 1 (25)         | Ceftriaxone***, ofloxacin**, cefuroxime** |

Each + represents the degree of sensitivity; +++>+++>+ + . S. aureus=Staphylococcus aureus, E. coli=Escherichia coli, UTI=Urinary tract infection

Table 6 shows other maternal outcomes and neonatal outcomes. There was no statistically significant difference in the mean duration of hospital stay in hours between the two groups (129 ± 46.7 and 134.2 ± 28.1, t = −0.7, P = 0.48). The mean cost of antibiotics in naira was 2883 ± 1695 (US$9.5 ± 5.6) and 7040 ± 2407 (US$23.1 ± 4.1) in the study and control groups respectively, and the cost was significantly higher in the control group than the study group (t = −0.7, P < 0.001). Eight (8.3%) patients in the study group and 20 (26.3%) in the control group had maternal side effects mainly nausea and vomiting, and the difference was statistically associated with the groups (χ² = 6.7, P = 0.01). There was no statistically significant difference in the mean APGAR scores between the two groups (8.6 ± 0.5 and 8.7 ± 0.5, t = −0.5, P = 0.58). Four (5.1%) and 3 (3.9%) babies were admitted to the SCBU in the study and control groups, respectively, and the difference was not statistically associated with the groups (Fisher’s exact = 0.1, P = 1). There was no statistically significant difference in the mean duration of admission to SCBU in days between the two groups (4.3 ± 2.8 and 4.3 ± 0.5, t = −0.0, P = 0.97). Most of the babies admitted were as a result of transient tachypnea of the new born and fetal macrosomia. There were no cases of neonatal death, febrile illness, neonatal sepsis, or infection with resistant organisms.

Table 7 shows the microbiological pattern of wound infection and urinary tract infection. The commonest organism responsible for wound infection was Staphylococcus aureus accounting for 3 (60%) and 5 (62.5%) in the study and control groups respectively. Escherichia coli, Klebsiella, and pseudomonas are other organisms implicated in wound infection. One patient with wound infection in the study group had polymicrobial infection with S. aureus and Klebsiella, while two patients in the control group had polymicrobial infection involving S. aureus and E. coli, and S. aureus and Pseudomonas. E. coli was the commonest organism implicated in UTI accounting for 3 (60%) and 3 (75%) in the study and control groups, respectively.

**Discussion**

In this randomized controlled study, there was no statistically significant difference in the general characteristics, indications for CS and operative characteristics between the study and the control groups. This shows that the two groups were comparable and variations in outcome measures would be as a result of difference in antibiotics administered.

The overall incidence of fever was 14.3% (12.8% in the study group and 15.8% in the control group). The study showed no difference in the incidence of fever between the two groups. This is similar to the findings at Ile-Ife where short term (24 h) was compared with long-term (7 days) antibiotic prophylaxis following elective CS.[19] This is also similar to the findings in Ghana which found no statistically significant difference in the incidence of fever when two doses of amoxicillin-clavulanic acid was compared with triple therapy as prophylaxis during elective and emergency CS.[17] This is also similar to other studies.[1,18]

The overall incidence of fever in this study was 14.3%, which is similar to 15% in a Cochrane review of 2002 and the United States (US) review.[10,20] The incidence of fever was higher following emergency CS (8.5%) than elective CS (5.8%) which is similar to a US review which showed that febrile morbidity was documented to be approximately twice as common following emergency procedures, compared with elective CS.[20] Incidence of malaria was not statistically associated with either of the groups (5.1% versus 6.7%), (P < 0.05) which is similar to the findings at Ile-Ife.[19] Also, the incidence of postscearean wound infection was 6.4% and 10.5% in the study and control groups respectively and was not statistically associated with either of the groups (P < 0.005). This is similar to the findings at Ile-Ife.[19] A study conducted in Mozambique on comparison of single combined preoperative antibiotics with a 7 days postoperative regimen (5.2% vs. 6.4%) reported similar findings.[21]

It was noticed with dismay that the group that received antibiotics postoperatively for 7 days had more cases of wound infection. This shows that critical to antibiotic prophylaxis is the timing of administration as demonstrated by several randomized control trials, systematic reviews, meta-analyses, and Cochrane review of 2014.[22-24] All these supported administration of antibiotics prior to skin incision. Microbial contamination of the surgical site is a necessary precursor of SSI. Antimicrobial prophylaxis is not an attempt to sterilize...
tissues, but a critically timed adjunct used to reduce the microbial burden of intraoperative contamination to a level that cannot overwhelm host defenses. Therefore, prophylactic antibiotic administration is most effective before microbial contamination.

There is paucity of literature comparing 2 doses including preoperative dose of amoxicillin-clavulanic acid and extended prophylaxis for 7 days as was done in this study. The overall incidence of wound infection in this study was 8.4% which is similar to a previous study at AKTH (9.1%) and 7.0% at Abakaliki.[24] This is lower than 16.2% at Ibadan[26] and 37% at Ile-Ife,[27] probably because there were more elective cases than emergency cases in this study. It could also be as a result of preoperative antibiotic administration or because of exclusion of cases at increased risk of infection. The incidence of wound infection was higher following emergency than elective CS (5.2% vs. 3.2%). This is similar to the findings of a study at AKTH which showed that only one patient among the group that had elective CS developed wound infection as opposed to eight patients in the group that had emergency CS.[5] It is also similar to an observational study at Ibadan which showed that patients who developed wound infection all had emergency CS.[26]

Eighty percent of those that developed wound infection in the study group were diagnosed after discharge, versus 25% in the control group. This could be as a result of preoperative antibiotic administration leading to late manifestation of infection as opposed to early manifestation of infection secondary to perioperative microbial contamination in the absence of preoperative antibiotic in the control group. Overall, 53.9% of wound infections were diagnosed on admission and 46.1% after discharge. This is different from the findings in a US study which showed that 80% of wound infections were diagnosed after discharge and that postcesarean infection rates peak after the 4th or 5th day postoperatively.[7] This difference could be as a result of the fact that most patients are discharged early in the US and antibiotics were administered after cord clamping as opposed to postoperative administration. This is also different from the findings in Mozambique which showed that wound infection was diagnosed exclusively after discharge, but patients were discharged on the 3rd day.[21] In our center, patients are usually discharged late (5 or 7 days depending on the type of skin incision) making diagnosis of wound infection possible while the patients are still on admission.

The microbiological pattern of postcesarean wound infection showed S. aureus, E. coli, Klebsiella species, and Pseudomonas. S. aureus was the commonest organism isolated from both groups. This is similar to the findings at AKTH[5] and Ile-Ife.[19] Both groups had some polymicrobial infections which is similar to the findings in Ghana.[17] The organisms were mostly sensitive to ceftriaxone and levofloxacin which is similar to sensitivity pattern in a previous study at AKTH and Ghana.[5,17]

The incidence of endometritis in this study was 7.7% and 11.8% in the study and control groups respectively. This is similar to the findings at Ile-Ife and India.[18,19] Again there were more cases of endometritis in the control group, probably demonstrating the effect of timing of administration of antibiotics. A Cochrane review of 2014 found significant reductions in endomyometritis (by 30%–60%) in women who received antibiotics preoperatively as compared to those who received antibiotics after cord clamping.[23] An American study comprising 9,010 cesarean deliveries, compared with women receiving antimicrobial prophylaxis after umbilical-cord clamping; those administered antimicrobial prophylaxis before skin incision had lower rates of postpartum endometritis (2.2% compared with 3.9%).[24] This perhaps shows that the timing of administration is more important than extended prophylaxis. During labor and abdominal delivery, the endometrium and peritoneal cavity invariably are contaminated with large numbers of highly pathogenic aerobic and anaerobic bacteria. Therefore, high serum concentration of antibiotics at the time of microbial contamination may explain the reduction in the incidence of endometritis in the study group where preincisional antibiotic was administered when compared with postoperative administration.

In this study, the incidence of urinary tract infection was 6.4% and 5.3% in the study and control groups respectively. This compared favorably with the findings at Ile-Ife, Ghana, and India.[17-19] In this study urinary tract infection occurred in 5.8% of patients following emergency CS and 3.9% following elective CS. This is similar to a Dutch study where urinary tract infection was diagnosed in 2.5 and 3.4% of women after elective and nonelective CS. The incidence was lowest in elective CS.[26] It is also similar to a Danish study on infections related to CS, where UTI occurred in 1.5% after vaginal delivery, 2.6% after elective CS, and 3.0% after emergency CS.[29]

This study demonstrated no statistically significant difference in the mean duration of hospital stay in hours between the two groups with a mean of 129.7 for the study group and 134.2 for the control group. This is similar to the findings in Mozambique, Pakistan, and India.[1,18,21]

The mean cost of antibiotics per patient was found to be 2883 naira (US$9.5) and 7040 naira (US$23.1) in the study and control groups respectively, and the difference was statistically significant. The mean cost of antibiotics in the control group was more than double that in the study group and is similar to the findings at Ile-Ife and Mozambique.[19,21]

There were more maternal side effects in the control group (26.3%) than in the study group (10.3%). This is not unexpected because the control group received multiple doses of antibiotics for 7 days. The use of short-term antibiotics apart from reducing the cost and side effects also reduces the risk of colonization with resistant organisms and may save nursing time.
There was no statistically significant difference in neonatal outcomes between the two groups. This is similar to the findings of a Cochrane review, and the US study which compared neonatal outcomes following preincisional antibiotic administration with that after cord clamping.\textsuperscript{[23,24]} This is also similar to the findings in Mozambique.\textsuperscript{[21]}

**Conclusion**

This study found no statistically significant difference in infectious morbidity, duration of hospital stay, and neonatal outcomes when two doses of amoxicillin-clavulanic acid was compared with a 7 days’ course of prophylactic antibiotic following CS at AKTH. The use of two doses of amoxicillin-clavulanic acid has the advantages of reduced cost and some maternal side effects.

**Recommendations**

1. Two doses of intravenous 1.2 g amoxicillin-clavulanic acid should be administered as prophylaxis during CS. The first dose should be administered within 30–60 min before skin incision.
2. A further research on the use of a single preincisional dose of 1.2 g amoxicillin-clavulanic acid should be carried out and find out whether it would have the same effects as two doses.

**Limitations**

1. Single centered study, as such, findings could be difficult to generalize.
2. Exclusion of other reasons for CS might mask increased infection rate.
3. The principal investigator was not blinded throughout the period of data collection for logistics reasons. The patients were also not blinded as the study group did not receive placebo for 7 days.

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**Conflicts of interest**

There were no conflicts of interest.

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