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SCHOOL OF MEDICINE

A RCT comparing the effectiveness of a single dose of antimicrobial prophylaxis versus multiple doses during emergency caesarean section in Rwanda

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A DISSERTATION AS PART FULFILLMENT OF THE REQUIREMNTS FOR THE DEGREE OF MASTER OF MEDICINE, OBSTETRICS AND GYNECOLOGY, UNIVERSITY OF RWANDA.

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LIST OF ABBREVIATION

SSI: Surgical Site Infection

THRiVE: The "Training Health Researchers into Vocation Excellence in East Africa"

WHO: World Health Organization

C/S: Cesarean section

HIV: Human Immunodeficiency Virus

CDC: Center for Disease Control and Prevention

MD: Multiple doses

SD: Single dose

HRH: Human Resource for Health

PI: Principle Investigator

ABSTRACT

Background: Cesarean section is one the most common surgeries done worldwide and surgical site infection (SSI) is one of the main complications resulting in major morbidity ad mortality post cesarean. Prophylactic antibiotics are the main intervention to prevent post-cesarean SSI. However misuse of antibiotics is a very common practice especially in environments where other factors may increase the risk of postoperative infection.

Objectives: To determine whether a single dose of antimicrobial prophylaxis is as effective as multiple doses in prevention of post emergency cesarean section SSI in low resource maternity settings.

Methods: A randomized clinical trial of single dose Ampicillin vs multiple doses in the setting of emergency cesarean was conducted in a large rural hospital in Rwanda (Ruhengeri Hospital) where approxiamtelly1800 Cesarean deliveries are performed annually. All patients undergoing emergency cesarean section were assessed for eligibility for inclusion in the study and written informed consent was obtained. Participants were randomized into two different study arms with aid of computer generated sets of random allocation through block randomizations; the first study arm was composed of women receiving one dose of 2 g Ampicillin 15 to 60 minutes prior to skin incision and the second arm (B) was composed of women receiving 2 g prior to skin incision then extended dosing of 1g Ampicillin every 8 hours over 72 hours. Participants were followed for 30 days post cesarean section for surgical site infection.

Results: Three hundred and one participants were analyzed (154 in the group of multiple dose and 147 on the single dose group). Demographic and clinical data were collected by chart review and patient phone interviews were performed on Days 3, 7, 15 and 30. There were 8 surgical site infections in Group A and 4 in Group B (p=0.089). The overall prevalence of surgical site infections was lower than expected (4.00%). Enrolment of 550 participants would have been needed to demonstrate a difference between groups considering the low rate of SSI observed in our study. Most of SSIs were diagnosed on day 7 (66.6% of all cases of SSI) and only 22.2% of cases were diagnosed at discharge(day 3). On day 15 only one case was diagnosed and no new cases were diagnosed on day 30.

Conclusion: The rate of SSI was low at 4.00% compared to what we estimated from the prior literature. The difference observed with a P value of 0.204 in the two groups was still in the equivalence margins though our study considers the use of single dose of antibiotic as adequate and preferable. However, our findings suggest the need of a larger sample as the majority of SSI were seen in the group of single dose even though the difference in number of cases seen was not significant.

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INTRODUCTON

The rate of cesarean section has increased worldwide which has also affected the rates of surgical complications including post-cesarean infections. Of infections, surgical site infection, which involves the skin incision and uterine incision, is more frequent and threatening to cause adverse outcomes. Surgical site infection (SSI) following cesarean section is a major cause of morbidity and mortality, increasing both the duration of hospitalization and hospital costs(1).

The increase in cesarean sections and the associated complications related to infections has attracted interest of researchers to examine various aspects related to antimicrobial prophylaxis. The main areas of interest for researchers have been involving the timing of administrating antibiotics, types of antibiotics and single dose versus multiple doses.

Currently there is no doubt about the role of antibiotics in preventing post caesarean section infections; the reduction of endometritis by two thirds to three quarters and a decrease in wound infections justifies a policy of recommending prophylactic antibiotics to women undergoing elective or non-elective cesarean sections (2). Globally, the most common intervention to prevent morbidity and mortality associated with maternal infection is the use of antibiotics however, the misuse of antibiotics for obstetrics conditions and procedures that are thought to carry the risk of maternal infections is a common practice which can potentially exacerbate the problem; the 2015 WHO recommendations for the prevention and treatment of maternal puerperum infections recommend a single dose of first generation cephalosporin or penicillin for prevention of post caesarean infections but with weak evidence (3). Considering the timing of giving prophylactic antibiotics, It was previously feared that administrating antibioprophylaxis prior to skin incision could affect the baby in utero, however according to various studies, there is strong evidence that

antibiotic prophylaxis for cesarean delivery given before skin incision rather than after cord clamping decreases the incidence of postpartum endometritis and total infectious morbidities without affecting neonatal outcomes(4). Other important aspect of antibiotic prophylaxis for cesarean section is related to the type of antibiotics used, the most important aspect guiding the choice is to cover common organisms, which are likely to cause postpartum infections especially surgical site infection and endometritis. The antibiotics must be present not only in the plasma but also in the tissues during the surgical procedure, and in most cases a very short prophylaxis, usually using a single bolus is convenient (5). In 2004 E. Ahmed et al. found no difference between a single dose of ceftriaxone versus Ampicillin/Cloxacillin given at the induction of anesthesia(6). An updated recent Cochrane systematic review recommended that a single dose of ampicillin or first-generation cephalosporins, such as cefazolin, should be administered in all women undergoing cesarean delivery and given 15 to 60 minutes prior to skin incision(7). According to various research findings, evidence support the use of pre-skin incision broad spectrum antibiotics(8) and no difference is seen between a single dose prior to skin incision versus extended antibiotic prophylaxis is obvious. In 1988 a multicenter comparative study done in USA compared a single dose of cefotetan versus a multiple dose cefoxitin as prophylaxis in patients undergoing cesarean section and no difference in cases of endometritis or surgical site infection was seen(9). Despite all the evidences about the use of a single dose of antibiotics, resistance to change is being observed in many Hospitals; for example in a teaching hospital, southern Taiwan, dissemination of evidence was done and clinicians were informed about single dose prescription as evidence based best practice and evaluation was made to see how the information has helped clinicians change their practices. The rate of single dose prescription only

increased from 14.2% to 22.4% and the study concluded that knowledge of evidence does not improve practice uniformly; more other interventions were encouraged to improve practice(10).

Even though a number of studies done in high income countries still recommend the use of a single dose prophylaxis, more caution is made in low resource settings. Various aspects including lack of sufficient infrastructures in operating rooms, lack of optimal asepsis, absence of clear antiseptic rules, reuse of disposable materials, challenges in post operative follow up especially after discharge from the hospital and patients level of education to maintain their hygiene, dictate the use of extended antibiotic prophylaxis after emergency cesarean section and even electives cesarean section by many health professionals in low resource settings. There is also inadequate data of antibiotic resistance available further limiting the choice of antibiotics and biasing providers towards the use of antibiotics with broader range.

As a consequence, we lack evidence based standardized protocols to guide the duration of antimicrobial prophylaxis after emergency cesarean section in low resource settings. Considering the consequences of inappropriate use of antibiotics and lack of evidence based consensus about a clear protocol in low resources maternity settings, studies comparing single dose of antibiotics to multiple dosed in uncomplicated emergency cesarean sections are worthy to be done. In 2012 at Bugando Medical Center in Tanzania, a study comparing a single dose of Gentamycin and Metronidazole 30 to 60 minutes prior to skin incision versus extended use of the same antibiotics for 24 hours found no difference in outcome and the use of single intravenous Gentamycin and metronidazole was found superior to extended dose of the same antibiotics(11). The extended systematic use of antibiotics to patients with emergency cesarean section without obvious risk factors have some negative impacts on patient care; it leads to prolonged hospital stay and prolonged intravenous use, expensive and extra cost for patients and hospitals, increase in the

risk of acquiring nosocomial infections and increased risk of developing resistance to commonly used antibiotics. Emin et al, studied the incidence and risk factors of SSI in developing countries and concluded that prolonged antimicrobial prophylaxis and broad spectrum antibiotics may be associated with emergence of resistant bacterial strains(12). Recently some studies carried out in tertiary hospitals in Rwanda have found high prevalence of antimicrobial resistance to commonly used antibiotics; One of those studies found among culture isolates E.Coli and Klebsiella pathogens to be the most common and were resistant to at least one of the third generation cephalosporins, other pathogens also had resistance to other commonly used antibiotics (13). Another study recently done in Rwanda found out that the antibiotics commonly used in Rwanda for the treatment of UTI are no longer effective due to increased resistance of the main isolated organism to common antibiotics (14). Interventions aiming at reducing the risk of resistance and leading to the correct use of antibiotics would be helpful in Rwanda and in other countries where they are no clear protocols. There is no data in Rwanda about the prevalence of surgical site infections post caesarean section. There are limited studies performed in East Africa. A study done in Tanzania at Bugando Medical Center, revealed an incidence of 6.4% among women who received prolonged antibiotic prophylaxis during emergency cesarean section.(ref) A study performed in Nigeria noted a prevalence of 9.1% with single dose antibiotics (15)

In this study, our aim is to test if single dose antimicrobial prophylaxis is as effective as the preferred extended doses of antibiotics for prevention of post caesarean section surgical site infections or if the use of extended antibiotics is justified in high risk poor resource settings. We also sought to determine the baseline incidence of SSI among women receiving antimicrobial prophylaxis and to determine whether there was a difference in other types of infections after emergency cesarean section.

METHODS

A prospective parallel randomized clinical trial with 1:1 allocation ratio was performed. Sample size calculation was calculated based on previous estimates on SSI in the literature. Using the Blackwelder formula for equivalence RCTs, where we hypothesized a difference less than 5% between the two treatments to represent the equivalence. We have used the SSI prevalence found in the previously cited study of 6.4% and we used an incidence. of 10% for single dose therapy based on the previously cited Nigerian study which was 9.1% (16)

The Blackwelder formula used is: $(Z_{0.95} + Z_{0.80})^2 [Ps(1-Ps) + Pn(1-Pn)] / (Ps-Pn-D)^2$

Ps: 6,4% Ps: Estimated Response among women receiving the standard treatment (Multiple dose)

Pn: 10 %; Pn: Estimated Response rate among women receiving the new treatment (Single dose)

D: 5%: Hypothesized difference for equivalence

Using the above prevalence the sample size is 125 for each group and 250 for both groups. We assumed that 10% of patients may be lost to follow up or have incomplete documentation therefore the total sample size was calculated at 275 patients. All the calculation assume alpha is =0,05 and beta is =0,2(power 80%). A statistician who was not involved in enrolling patients used a computer generated random numbers with block randomization. The size of the blocks were only known by the statistician and blinded to those who enroll participants. All the random numbers were sealed in opaque envelopes and kept in a sized box. Each participant picked the next envelope before cesarean section and the envelope was opened at the end of surgery. Each envelope contained a random number corresponding to the to either single dose or multiple dose depending on what the computer had generated.

Three hundred and one women have been recruited, enrolled and analyzed in the study from 1st July 2015 to June 2016.With a 1:1 allocation ratio, 147 women received single dose of antibiotics; 2 gms of Ampicillin 15-60 minutes prior to skin incision and 154 women received 2 gms 15-60 minutes prior to skin incision and continued 1 gm every 8 hours for 3 days. Our study was conducted in Ruhengeri Hospital, a large rural hospital in Rwanda. It has a maternity department where approximately 5000 women deliver annually with around 1500 deliveries being cesarean sections.

Eligibility criteria included all women admitted in maternity at Ruhengeri Hospital during the study period who agreed to be enrolled in the study after written informed consent. Women who had signs of ongoing infections such as chorioamnionitis, fever during labor, premature rupture of membranes for more than 18 hours and those who have had failed instrumental delivery at complete dilatation were excluded. All study participants received 2 grams of Ampicillin in labor ward prior to entering the operating room in order to meet the required 15-60 minutes before skin incision. While the participants were in operating room, the provider was given the sealed opaque envelope that designated what the follow up antibiotic regimen would be. The envelope was opened after the surgery was completed so that the surgeon was blinded to the regimen during the surgery.

All participants were educated about the signs of surgical site infections which were defined as fever, tenderness and swelling of the wound or loss of continuity with pus discharge. Participants were evaluated for any sign of SSI on day of discharge (day 3), then followed by phone interviews on day 7, 15 and day 30. All patients were requested to come back to the same hospital if any problem during the follow up was to occur. Secondary outcomes included endometritis and any other type of postpartum infection. Participants were also educated about

signs of endometritis, which were defined as fever, tender abdomen and full smelling discharge. Participants were requested to consult if any of the above symptoms were observed during the follow up period.

Statistical analysis

A questionnaire containing the social demographic and clinical characteristics was used at the time of enrollment and during follow up. Data on social demographic and clinical characteristics were extracted in the file at the time of enrollment and at discharge on day 3.The source of data during follow up on Day 7,15 and 30 were obtained through interview on phone and all patients were requested to comeback to Ruhengeri Hospital whenever they have any concern; Patients were also allowed and given the contact of the PI whom they can call whenever they have any issue. Note that patients were educated about signs of SSI and other infection and were interviewed about them during the follow up. The follow up was made possible by using the phone call directly to the patient or the husband in case of the participants had no phone or community health worker in charge of the patient.

Data were entered through epi data, and then extracted into stata 13 for analysis. Descriptive statistics were used to test whether the population in both groups were similar and incidence of SSI in both group was calculated on day 3 at discharge, on day 7, day 15 and on day 30. The overall incidence of SSI in each group was used to calculate the difference and P value considered for the significance of the observed difference. The equivalence margin above 5% was initially set as the required difference to confirm the difference in both groups within the 95% confidence interval.

RESULTS

Baseline characteristics in our study population

A total 618 patients were assessed for eligibility. Among them, 20 participants declined to participate in the study and 50 were excluded because they were not meeting the inclusion criteria or did not receive timely antibiotics. The rest of excluded participants (275) were secondary to the provider not being willing to participate in the study or too much work overload .A total of 301 women were enrolled ,randomized and analyzed; 154 in the group of multiple dose and 147 in the group of single dose, basic social demographic and clinical characteristics were similar in both groups as shown on table 1.

Incidence of Surgical Site Infection in both groups

Among the women who received a single dose of ampicillin, only 8 women (5.5 %) developed SSI during the 30 days of follow up, whereas only 4 women (2.6%) developed SSI among those who received multiple doses of antibiotics. The overall prevalence of SSI in our population was 4.00%, which was surprisingly low compared to the baseline assumptions, which were based on the literature available from other African countries. Most of new cases of SSI were diagnosed on day 7.Only 2 cases of SSI were diagnosed at the time of discharge while no cases were newly diagnosed on day 30. See table 2 and table three

Others factors thought to have an impact on the risk of post caesarean surgical site infections

Logistic regression was performed to analyze other cofactors that might have an impact on our primary outcome. Among others we considered the age categories of the patients, education

level, parity, previous cesarean sections, indications of caesarean section, level of the surgeon who did the c/s however no statistically significant tendency was noticed among the infected women. The absence of any tendency might be due to the low incidence of cases during our study. Table 4 demonstrates few of analyzed covariates with a small tendency to have an impact but lacking statistical value.

DISCUSSION

Our study demonstrated that there was no difference in the incidence of SSI between single dose and multiple dose antibiotic regimens. In this study, the sample size was calculated based on the literature which found a prevalence of SSI in African countries ranging between 6% to 10%; (11,17,16).

The total number of analyzed participants was 301 women, 154 in the multiple dose group and 147 in the single dose group. Basic characteristics which could have an impact on the outcome were similar in both groups and they included age category, parity, HIV status, previous history of SSI, indication of Cesarean section, previous history of cesarean, duration of cesarean section, when the cesarean section was performed (day or night) and the level of the Surgeon performing the cesarean section. The total rate of SSI for a period of 30 days of follow up in our study was surprisingly small than expected as it was found to be 4.00%. This low rate of SSI in our population corresponds to the findings in other studies but mainly done in middle-income countries or developed countries and not in low resource settings (18–21) .The low incidence found in our study might be due to the adoption of rigorous protocols for antibiotic prophylaxis as well as hospital asepsis. In one study implementation of interventions aiming at reducing the rate of SSI reduced SSI by 63.5% in their population (22)

While the overall incidence of SSI was 4.00%, the rate of SSI at discharge, which was day 3 in our study, was only 25 % of all cases of SSI while the majority of new cases were seen on day 7 where total of 8 cases corresponding to 66.6% of all cases of SSI. Only one case was discovered on day 15 and no new cases of SSI were discovered on day 30 of follow up. This findings show that most of cases of SSI post cesarean section develop when women are already discharged and a surveillance system or education about the signs and symptoms of SSI should be emphasized while discharging women. The low rate of SSI at discharge was similarly found in other studies (23).

Among the 147 women who received single dose of Antibiotics 8 of them; 5.5% developed SSI and this incidence correspond to the rate of SSI in other studies (11,24).Surprisingly enough the rate of SSI among women who received multiple dose of antibiotics for 3 days was only 4 cases;2.6%. Due to the low incidence of SSI in our study the observed difference in both group was not above the required difference to confirm the difference and deny the equivalence of both intervention the P value was 0.204 though not statistically significant. Considering the low occurrence of SSI in our population a sample size of approximately 500 women would be necessary to confirm the difference in both groups. With the few number of cases of surgical site infections; only twelve both interventions are equivalent in outcome The difference in number of cases observed is still in equivalence margins and does not show any statistically significant difference

Some of the challenges which are basically our study limitation were initially due to providers: a number of doctors who were supposed to enroll participants in the study were biased about the use of single dose of antibiotics as they preferred to stick on their routine use of multiple dose and failed to recruit many eligible participants in our study. Another challenge in our study was

related to unexpected low prevalence of SSI, which was found in our study and leaving suspense from our conclusion. The surveillance of participants after discharge was done using phone call and this practice which is efficient for SSI may not be sensitive enough to recognize other types of infectious morbidity which may arise after C/S though our secondary outcome which was mainly endometritis was not considered in the analysis.

Our study provided information about the rate of surgical site infection in a Hospital where the timing of prophylactic antibiotics prior to skin incision and regular weekly operating room sterilization is respected. The overall rate of 4.00% is low compared to the general prevalence of SSI in developing countries however this is possible as even lower incidence are found in some studies done in well equipped Hospitals.

WHO recommend the use of a single dose of first generation cephalosporin or penicillin to be used in preference to other types of antibiotics but based on very low quality evidence (3) and most of other studies still prefer a single dose of antibiotics for prophylaxis than extended dose. In our study we have compared both options and we did not find any statistically significant difference between the two interventions and we still encourage the use of single dose of antibiotics however due to the low number of SSI than we expected and the tendency to have more cases in the group of single doses; we encourage to conduct a powerful multicenter study or a study with a huge sample size proving the absence of any difference in both groups.

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Table 1. **Social demographic and clinical characteristics in the two groups**				
		SD	M D	P value
Age	Categories			.144
	Less than 20	6(4.5%)	6(4.2%)	
	20-35yra	119(90.2%)	120(84.5%)	
	36 and above	7(5.3%)	16(11.3%)	
Level of education				.028
	No formal education	32(22.4%)	24(15.8%)	
	Primary	83(58%)	82(53.9%)	
	Secondary	22(15.4%)	36(23.7%)	
	University	6(4.2%)	10(6.6%)	
History of SSI				.749
	Yes	1(.89%)	1(.89%)	
	No	111(99.10%)	111(99.10%)	
HIV status				.088
	Negative	66(45.5%)	83(54.5%)	
	Unknown	(49.10%)	50(44.64%)	
Diabetes				.728
	Negative	18(12.4%)	17(11.1%)	
	Positive	0(0%)	0(1.3%)	
	Unknown	127(87.6%)	136(88.9%)	
Indication for CS				.166
	Failure to progress	27(19.0%)	23(23.2%)	
	Fetal distress	33(23.2%)	31(20.4%)	

	Breech	14(9.9%)	12(7.9%)	
	Others	68(47.9%)	86(56.6%)	
CS intervention duration				.446
	0-2 hours	107(95.53%)	110(98.21%)	
	More than 2 hours	5(4.46%)	2(1.78%)	
Time spent in labor before CS				.770
	0-1 hours	62(43.4%)	74(49.0%)	
	1-5 hours	56(39.2%)	46(30.5%)	
	More than 5 hours	25(17.5%)	31(20.5%)	
Previous CS				.77
	None	96(65.8%)	91(59.5%)	
	Previous CS	38(26.0%)	45(29.4%)	
	2 Previous CS	9(6.2%)	11(7.2%)	
	>than 2 CS	3(2.1%)	6(3.9%)	
Survey done day /night				.27
	Day	87(60.4%)	84(55.3%)	
	Night	57(39.6%)	68(44.7%)	
stage of labor by the time of CS				.977
	Latent	78(54.9%)	84(55.3%)	
	Active	61(43.0%)	64(42.1%)	
	Full dilatation	3(2.1%)	4(2.6%)	

Flow Diagram of patients in our study

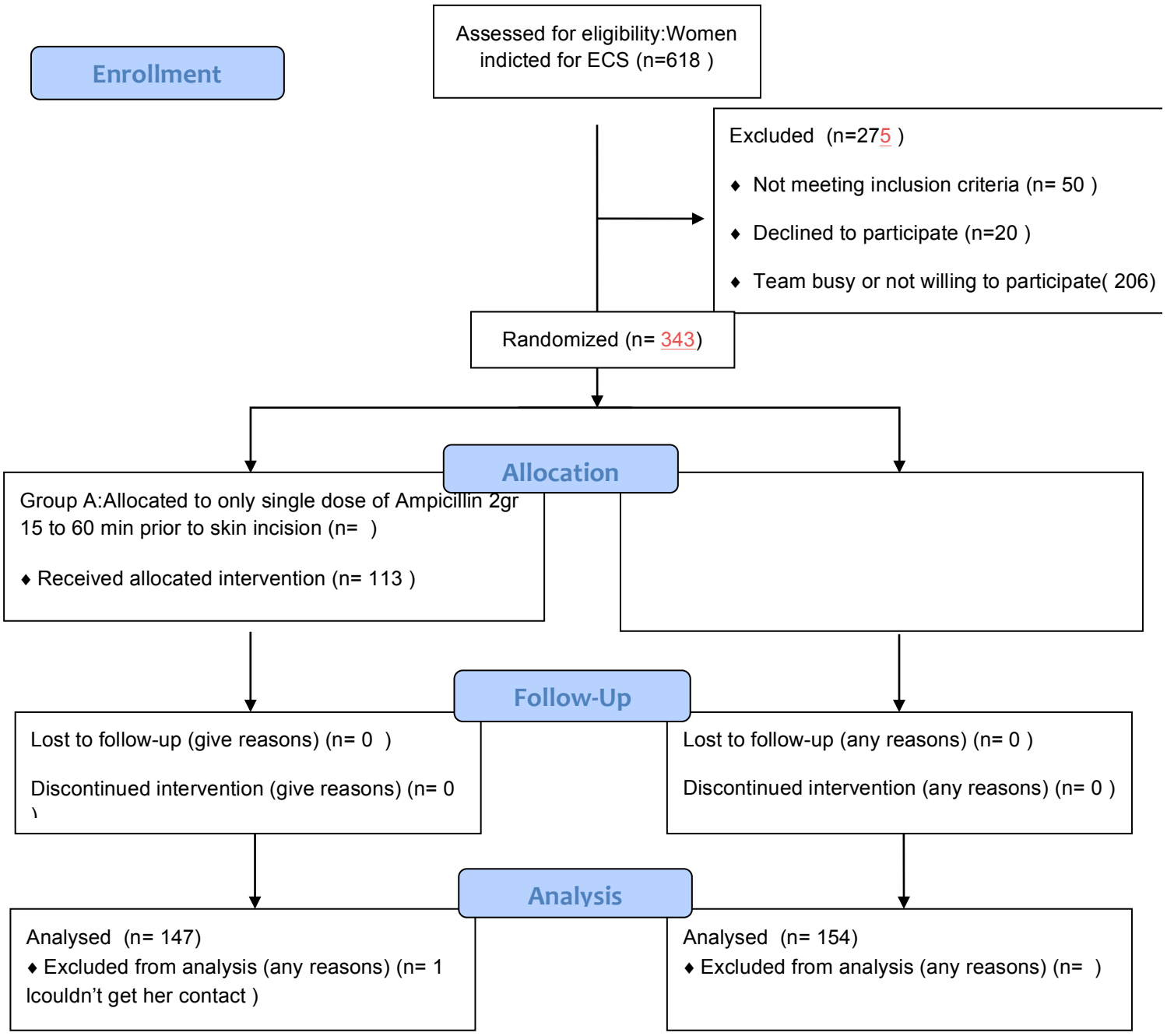

Table 2: Incidence of SSI in single versus multiple dose users within a period on 30 days

	Regimen			
	Single dose	**Multiple dose**	**Total**	P value
				.204
None Surgical site wound infection	138(94.5%)	150(97.4%)	288(96%)	
Surgical site wound infection	8(5.5%)	4(2.6%)	12(4.0%) Overall incidence	

Table 3 : **Incidence of SSI on day 3, 7, 15 and 30 in both groups**

Status of the patient		**Regimen**		
		Single dose	**Multiple dose**	P Value
Day 3				.224
	No SSI	144 (97.9%)	154(100%)	
	SSI	3 (2.04 %)	0(0.0%)	
Day7				.20
	No SSI	140 (97.22)	150 (97.38%)	
	SSI	4 (2.77%)	4(2.6%)	
Day 15				.083
	No SSI	139(99.28%)	150(100%)	
	SSI	1 (0.71%%)	0 (0%)	
Day 30				.078
	No SSI	139(100%)	150(100%)	
	SSI	0(0%)	0(0.0%)	

Table 4: Multiple logistic regression on predictors of SSI

Regimen	OR	95% CI	P-Value
Education	1.574	[.554-4.471]	.395
Wealth index	5.031	[.983-25.751]	.052
Indication	.444	[.247 - .798]	.007
Day or night	.361	[.082- 1.591]	.178
Surgeon	.010	[.272-7.233]	.066