Research article

A randomized control trial of single dose versus multiple doses of IV antibiotic prophylaxis in caesarean delivery

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Abstract

Objectives

To determine the effectiveness and safety of single doses antibiotic against conventional multiple doses regimen on clinically detectable maternal and neonatal infectious morbidity.

Method

This is a randomized, non-blind clinical trial on women undergoing caesarean section. By block random sampling, 369 women, who were enrolled in this study, 185 (50.1%) randomly received single dose of antibiotics and 184 (49.8%) received multiple postoperative doses of antibiotics. All potentially infected cases were excluded. These patients were followed up prospectively for infectious and neonatal complications till discharge and verbal enquiry or direct observation done during suture removal. The effectiveness was measured in terms of febrile morbidity, surgical site infection, endometritis, urinary tract infection, other infection along with duration of hospital stay. Chi-square analysis (Fisher's Exact Test) of variance were performed with equivalence margin was set at 5% (p value).

Results

The incidence rates of post-caesarean infections were 1.8% and 3.2% in single dose and multiple dose regimens respectively with the incidence rate ratio of 0.3 [95% CI 0.065-1.63) p-value=0.284]. There were no statistically significant differences in febrile morbidity (p=0.28), wound infections (p=0.123), perinatal outcome (p> 0.05) and median duration of hospital stay (p=0.329) in both arms.

Conclusions

Single combined prophylactic antibiotic usage immediately after cord clamping is equally effective as multiple conventional regimen following the caesarean deliveries in prevention of infectious morbidities and duration of hospital stay, with benefit of reducing staff workload along with reduced medication costs and the emergence of drug selective resistant bacteria.

Key words: Caesarean section, surgical wound infection, antibiotic prophylaxis

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Introduction

Infection is one of the most common complications of caesarean delivery. Women undergo caesarean section have a 5-20 fold greater chance of getting an infection compared with women who give birth vaginally[1]. Usage of prophylactic antibiotic is proved to be effective in lowering post-operative infections[2-4]. The 60-70% reduction in endometritis and the 30-65% reduction in wound infection rate prompted the Cochrane library to recommend prophylactic antibiotics to women who undergo both elective and non-elective caesarean delivery[1]. The antibiotic prophylaxis in women who undergo caesarean delivery also has been proven to be beneficial in decreasing infectious morbidities and length of hospital stay[5].

The potential benefit from prophylactic antibiotic should always be balanced against the possible damage like drug resistance. Now it has been much concerned globally and nationally regarding the misuse of antibiotics leading to a high incidence of resistance, cost effectiveness or suboptimal treatments[6-7].

An attempt to reduce antibiotic usage is timely necessary because injudicious use of antibiotics not only adds to financial burden, burden on hospital resources in terms of human resource, time and equipment, but also exposes women to undesirable side effects ranging from mild nausea and rash to severe life threatening drug reactions. More over the antibiotics compromise immunity suppress host defenses and subject to further risk of acquiring infections. The duration of prophylaxis should be as short as it could be, in order to avoid the danger of occurrence of resistant strains and to avoid unnecessary patient discomfort and unnecessary expenses. Hence serious efforts should be made to minimize unnecessary prolongation of antibiotics.

Given the ever-increasing economic and health burden of caesarean deliveries in Sri Lanka and the need for convenient and less costly regimens, this study was designed to compare the effectiveness of single dose of cefuroxime plus metronidazole and conventional multi-dose regimen for infection prophylaxis in caesarean section.

Methodology

This was a randomized controlled, non-blind trial, which was carried out in the Teaching Hospital Jaffna. Study population was women undergoing caesarean delivery – both elective and non-elective and had consented for the study were eligible for inclusion, but the study exclude those with history of allergy, prior antibiotic usage within two weeks, pyrexia>38° Celsius or obvious evidence of clinical infection or chorio-amniotis, known medical illness that might cause pyrexia or separate indication for use of antibiotics [known immunodeficiency syndromes, chronic disease of cardiovascular, renal, hepatic or gastrointestinal system or severe anemia (Hb <8g/dl)].

The primary outcome measured was clinically detectable postoperative infectious morbidity, defined as fever, wound infection, endometritis, urinary tract infection or serious infection (such as bacteremia, septic shock, septic thrombophlebitis, necrotizing fasciitis and death) after caesarean section.

The duration of hospital stay, adverse events of treatment (eg allergic reactions, antibiotic-associated diarrhea, development of bacterial resistance and any infant outcomes reported are considered as secondary outcome.

Procedure: Stratified block randomization was done by using computer generated table and sequentially numbered sealed opaque envelopes coded with the appropriate treatment regimen groups (group A – only single dose of IV cefuroxime 1.5g and IV Metronidazole 500mg immediately after cord clamping and group B (multiple dose) – IV cefuroxime 750 tds and Metronidazole 500mg tds were continued for up to 24 hours following the caesarean section) was prepared by the supervisor (not by principal investigator). Each mother was randomized into two by the investigator according to the predetermined randomized allocation sequence.

Post operatively, group B mothers were allowed oral cefuroxime 750mg tds and Metronidazole 400mg tds for 7 days completion, within 6 hours, mobilized out of bed within 12 hours. Urinary catheter was removed within 12-24 hours. Dressings were removed in 36-48 hours followed by bath. Full blood count was checked on second post-operative day. Education regarding nutrition, hygiene and wound care were given to all. Uncomplicated mothers were discharged on third post-operative day with verbal and written advice to report if sign or symptom of infection developed. They were called for follow up and stitch removal (if prolene)

on seventh to eighth post-operative day. Later until postpartum completions of 42 days all mothers were followed up weekly through over the phone.

If any mother who developed post-operative febrile morbidity, wound infection, endometritis, urinary tract infection, pneumonia or other serious infection were documented and treated promptly.

Sample size: We liked to estimate the population proportion with a tolerance of (e) =0.02.
If we assumed surgical side infection rate after caesarean section is 0.1 as it is prior information 20 with 95% confidence interval

N = Z/2 * P(1-P) where N=n1 +n2 e 2
= 1.96*(0.1) * (0.9) (0.02) 221
= 441
(n1=221 and n2= 221)

Total number of women required for the study was 442.

This was inflated by 20 to accommodate any dropouts or crossover between groups.

Therefore total number of women required for the study was 530.

Statistical analysis: Data were statistically described in terms of mean +/- standard deviation (+/- SD), median and interquartile range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using t test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Fisher's exact test was used instead when the frequency was less than 5. p value less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22 for Microsoft Windows.

The study was approved by the Ethical Review Committee of University of Jaffna and an informed consent was obtained from all women who agreed to participate in the study.

Results

A total of 465 pregnant women were assessed for eligibility. Of these, 90 participants were excluded from the study according to the exclusion criteria. Out of eligible 375 pregnant women 188 randomly received single dose regime and 187 received multiple dose regime antibiotic for 7 days (dose regime has been explained in methodology). 2 participants in single dose regime declined to participate post operatively and 4 participants from both arm lost the follow-up (Figure 1).

There is homogeneity among the study participants in terms of their baseline characteristics in both arms (p-value >0.05) Table 1.

As showed in Table 2 there were no statistically significant differences in outcome parameters between the two treatment groups. Primary outcome post-operative infections developed in 8 (2.1%) patients p=0.284, among them two patients (1.8%) were from the single dose group and six patients (3.2%) from the multiple dose group.

Three patients (1.6%) in the multiple dose group developed wound infection, but none of the patients in single dose group developed wound infection during the study period. All are culture positive superficial infections and treated according to sensitivity tests. None of these differences were statistically significant.

There were no reported culture positive endometritis, urinary tract infection or other evidence of infection. None of the patients suffered adverse drug effects during our study period. Perinatal out come as recorded in the hospital discharge record, showed no statistically significant differences between the two treatment groups.

Variables that were associated with any infectious morbidity are shown in Table 3. It disclosed statistical significance of important risk factors for post-operative infection.

Performance under general anesthesia (OR 10.2, 95% 10.2-99.08, p=0.124), corticosteroid exposure (OR 2.19, 95% CI0.09-2.33, p=0.295), usage of nylon for skin closure (OR 3.7, 95% CI: 0.90-15.1, p=0.073), interrupted suturing technique (OR 1.4, 95% CI: 0.24-7.57, p=0.643) appear to be risk factor;

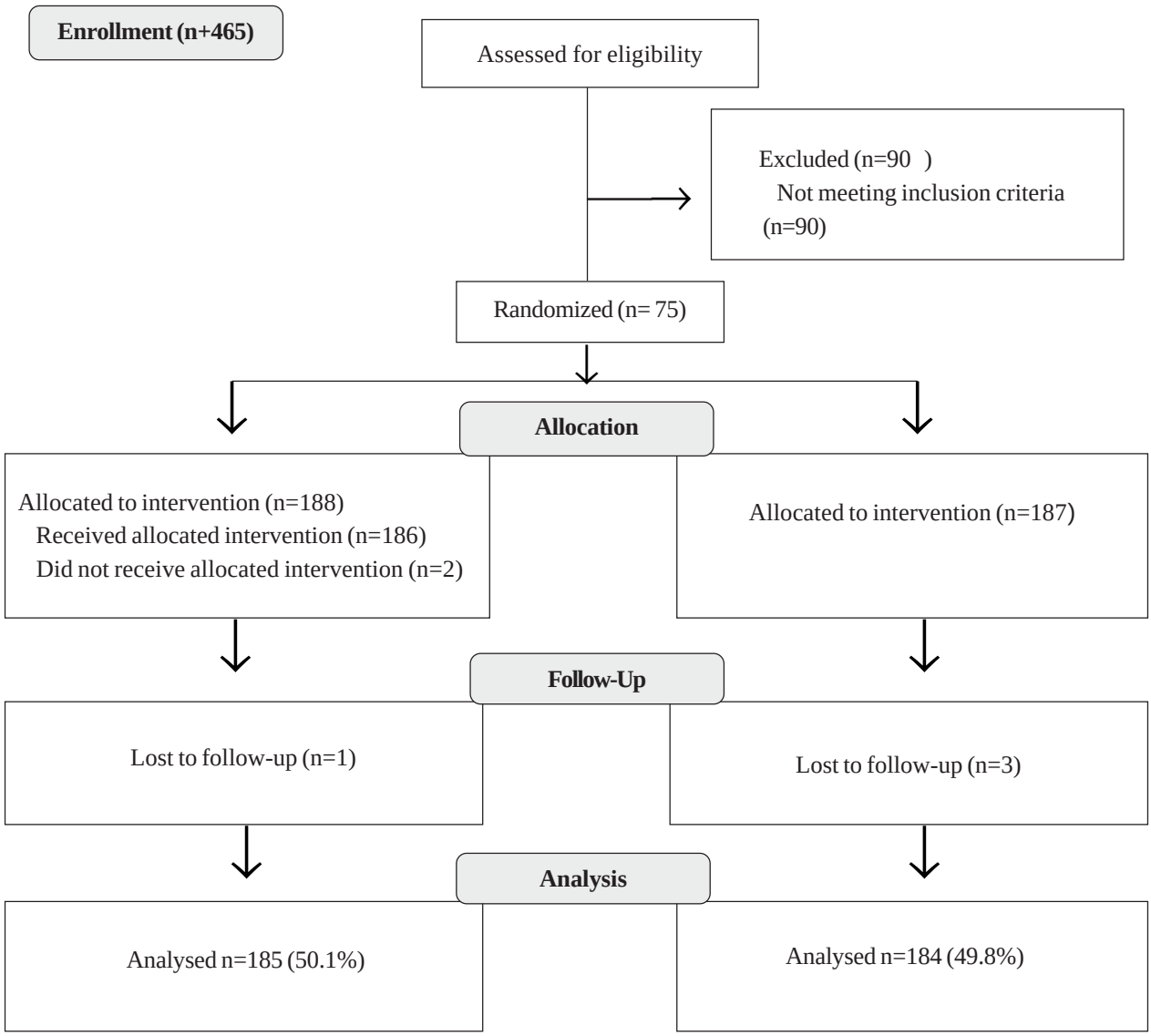

Figure 1. **Flow diagram of the study participant.**

Table 1. Distribution of characteristics in study participants

Variable	Randomized study group		P - value
	Single dose arm n=185 (50.1%)	24 hours usage arm n=184 (49.8%)	
Age (years) mean +/- SD	29.72 ± 5.012	29.46 ± 5.389	0.639
BMI (Kg/m^2), mean+/- SD	26.44 ± 4.169	25.96 ± 3.933	0.261
Gestational age (wks), mean +/- SD	38.9 +- 1.55	38.9 +- 1.75	0.802
Multiparity, n (%)	81 (44.02%)	69 (37.5%)	0.244
VE>/= 6 n (%)	34 (18.3%)	36 (19.5%)	1.000

Continued

Variable	Randomized study group		P - value
	Single dose arm n=185 (50.1%)	24 hours usage arm n=184 (49.8%)	
ROM >/= 6h, n (%)	30 (16.2%)	29 (15.7%)	0.948
Type of CS- Non elective n (%)	69 (37.2%)	71 (38.5%)	0.371
Anesthesia- GA, n (%)	3 (1.6%)	3 (1.6%)	0.655
Duration of surgery > 30 min, n (%)	51 (27.5%)	47 (25.5%)	0.724
Grade of the operator Consultant	9 (4.8%)	7 (3.8%)	0.799
Blood loss >500ml, n (%)	6 (3%)	1 (0.5%)	0.12
BW of the baby (kg), mean +/- SD	2.84 + -0.66	2.9 + -0.61	0.827
Type of pregnancy (in %) Singleton	178	178	1.000

n – number, SD – standard deviation, VE – vaginal examination, ROM – rupture of membrane, CS – cesarean section, post op – post operative, IQR – interquatile range, BW – birth weight of the baby.

Table 2. Distribution of post-operative infectious morbidity in study participants

Post-operative outcome	Randomized study group		P - value
	Single dose arm n=185 (50.1%)	24 hours usage arm n=184 (49.8%)	
All post op. infection, n (%)	2 (1.8%)	6 (3.2%)	0.284
Wound infection, n (%)	0 (0%)	3 (1.6%)	0.123
Endometritis, n (%)	0 (0%)	0 (0%)	
UTI, n (%)	0 (0%)	0 (0%)	
Other infection, n (%)	0 (0%)	0 (0%)	
Adverse drug reaction, n (%)	0 (0%)	0 (0%)	
Neonatal Outcome			
NICU admission	10 (5.4%)	11 (5.9%)	0.629
Neonatal death	4 (2.1%)	6 (3.2%)	0.791
Still birth / IUD	1 (0.5%)	2 (1%)	0.369
Duration of post op. hospital stay, median (IQR)	4 (2-2)	3 (2-2)	0.329

n – number, UTI – urinary tract infection, NICU – neonatal intensive care unit, IUD – death in utero, IQR – interquartile range.

Table 3. Distribution of risk factors among arms complicated with infectious morbidity and non-complicated arm [(n=8) p=0.284, IRR=0.3 95% CI=0.06- 1.63]

Variables	Infectious morbidity		P value	OR	95% CI
	Not complicated	Complicated			
Corticosteroid usage					
Not given	314	6	0.295	2.19	0.09-2.33
Given	48	2			
Vaginal Examination					
<6 or not done	69	1	0.526	0.59	0.2- 13.76
>/= 6	292	7			
ROM					
<6h or intact	303	7	0.627	0.749	0.09-6.2
>/= 6h	58	1			
Type of CS					
Elective CS	219	6	0.715	0.5	0.109-2.75
Non Elective CS	142	2			
MOA					
RA	356	7	0.124	10.2	10.2-99.08
GA	5	1			
Operator grade					
Consultant	16	1	0.316	0.3	0.03-2.76
MO	346	7			
Blood loss					
<500 ml	354	8	1.000	0.97	0.96-0.99
>500 ml	7	-			
Duration of surgery					
<30 min	263	8	0.116	0.971	0.95-0.99
> 30 min	98	0			
Skin closure					
Sub cuticle	296	6	0.643	1.4	0.24-7.57
Interrupted	66	2			
Suture material					
Vicryl	285	4	0.073	3.7	0.90-15.1
Nylon	77	4			

incidence rate ratio (IRR), CS – cesarean section, RA – regional anesthesia, GA – general anesthesia, h – hours, min – minute, MO – medical officer, ROM – rupture of membrane, CI – confident interval, OR – odd ratio. MOA – mode of anesthesia.

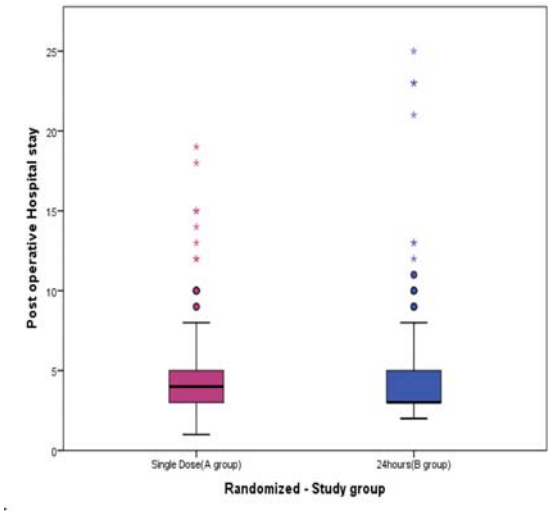

Figure 2. **Distribution of post-operative hospital stay.**

Except performance under general anesthesia, others were not significant statistically.

But ruptured membrane more than six hours (OR 0.749, 95% CI: 0.09-6.2, p=0.627), six or more vaginal examinations prior to the cesarean (OR 0.59, 95% CI: 0.2-13.76, p=0.526), non-elective cesarean (OR 0.5, 95% CI: 0.109-2.75, p=0.715), and blood loss greater than 500 ml (OR 0-97, 95% CI: 0.96-0.99, p=1), operator grade (OR 0.3,95% CI0.03-2.76, p=0.316) appear to be protective without any statistical significance.

The duration of hospitalization was the same in the two groups of patients, with a median stay of four days for the single dose group and three days for the multiple dose group without any statistically significant difference p=0.329.

Discussion

Prophylactic antibiotics are given to help prevent infection. Burke and colleagues in 1961 were the first to describe the role of antibiotics in reduction of rates of wound infection in animal models when administrated before skin contamination[8]. The later development regarding benefits of using prophylactic antibiotics in the prevention of serious infection and febrile morbidity after cesarean section have been well documented in the literature. But the recommendations about single-dose prophylaxis are not uniformly practiced.

In the multicenter trials evaluated by Hopkins L, Smaill F in the Cochrane review compared various trials that compared different antimicrobial agents, comparison between the routes and the number of doses of drugs given[9]. The Table 4 shows comparison of any single dose systemic regimen (pre, post, intra-operative) vs. any multiple dose regimen in terms of wound infections.

Table 4. Comparison of wound infections in other studies

Study	Treatment n/N (%)	Control n/N (%)	Peto odds ratio
Galask	4/162 (6.4%)	4/79 (5%)	0.45
Roex	7/66 (4.2%)	2/72 (2.7%)	3.58
Tassi	3/100 (3%)	1/100 (1%)	2.67
Varner	3/20 (15%)	1/9 (11%)	1.37
Von Mandach	17/536 (3.1%)	20/516 (3.8%)	0.81
Jakobi	0/50 (0%)	1/50 (2%)	0.14
Hawrylyshyn	1/64 (1.5%)	1/60 (1.6%)	0.94
Hartert	1/81 (1.2%)	0/58 (0%)	5.56
McGregor	4/46 (8.6%)	4/24 (16%)	0.46
Mc Gregor	5/195 (2.5%)	3/91 (3.2%)	0.76
Parsons	0/90 (0%)	1/62 (1.6%)	0.09
Present	16/300 (5.6%)	14/300 (4.6%)	0.857

Although antibiotic used and route of administration varies in different above studies, the overall results indicated that multiple dose does not offer any added benefit when compared with single dose regimen which is similar to our study primary outcome evaluated in Table 2.

Hospital stay was almost the same in both groups which means that single dose versus multiple doses of antibiotic does not affect the hospital stay and is related to number of days required for wound healing. This has also been confirmed by Tchabo et al who reported no significant difference in the incidence of post-operative infection and mean duration of hospital stay when compared single dose antibiotic verses multiple dose antibiotics[10].

Regarding neonatal outcomes, we found there was no statistical significant difference between both groups in the occurrence of clinically detectable neonatal death, still birth or neonatal ICU admission. Similar results was reported by Thigpen et al. 2005[11], Hamit et al. 2009[12], and Sullivan et al. 2009[13].

Our study findings are corroborated by previous studies, which show that single dose antibiotic regimens are as effective as conventional multiple doses for prevention of infectious morbidity following cesarean section. This study did not address the cost-analysis of cefuroxime and metronidazole and their potential for emergence of resistant organisms. Both are vast areas, not within the scope of this small clinical trial.

Conclusion and recommendations

Since the differences in the rates of febrile morbidity and wound infection were not statistically significant, and there were no urinary tract infection, endometritis or other infections in women who received either single dose or multiple doses of prophylactic antibiotics for caesarean section in this study, it may be argued that both single and multiple dose regimen protected equally against post-caesarean section infectious morbidity and that a single prophylactic dose prevents unneces-sary long course of antibiotics and susceptibility to antibiotic resistance.

Though the objective of this study did not include cost effectiveness of either regime, the cost of antibiotic therapy is apparently reduced in the single dose group. Therefore, when considering medication cost and drug-susceptibility pattern of the common bacteria causing surgical-site infection in our setting, single dose regime for prophylaxis is the rational choice. However, prophylactic antibiotics should not replace proper pre- and intra operative preparation and meticulous surgical technique.

In addition, the use of single dose regime reduces workload to the nurses, especially at night when few nurses are on duty in the ward. The shortage of health care workers is a well-known problem in many resource limited settings especially in peripheral units of our country.

Limitations

All participates called for follow up and stitch removal (if prolene) on seventh to eighth post-operative day. Later until postpartum completions of 42 days all mothers were followed up weekly through over the phone.

We were unable to follow up the patient directly until the whole postpartum period.

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