
Addition of azithromycin to the routine pre-cesarean prophylaxis against infection, effective or not?

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Abstract

Purpose: There is debatable data regarding the addition of azithromycin to the routine antibiotic prophylaxis of post-cesarean section (CS) infection. In this work, we tried to evaluate its potential benefit to protect against both post-cesarean maternal and fetal infections.

Methods: The study included 230 women who were intended to have selective CS at Mansoura university hospital. They were randomly subdivided into 115 women that received azithromycin plus standard cephalosporin and another 115 women that received standard cephalosporin alone. The main outcome is evaluation of post-cesarean section infection as endometritis, wound sepsis, etc... across the puerperal period.

Results: In comparison between the test group and the control group, there was significant reduction of re-admission during puerperium (0% vs 6.5%, $p=0.01$). Endometritis manifestations were significantly reduced, including: puerperal Fever $>38^{\circ}\text{C}$ (4.3% versus 15.2%), uterine tenderness (3.2% versus 11.9%), abdominal pain (1.1% versus 14.1%), offensive vaginal discharge (2.1% versus 13%) and purulent drainage from uterus (2.1% versus 9.8%). Wound infection manifestations were significantly reduced, including; erythema around incision (2.1% versus 8.7), induration around incision (3.2 versus 12%) and purulent discharge from incision site (1.1% versus 9.8%). Also, the need for further antibiotic during puerperium was significantly reduced (3.2% versus 11.9%). There was no significant difference between the 2 groups regarding neonatal outcomes.

Conclusion: Azithromycin plus the standard cephalosporin administered to women in selective CS reduces maternal infections and maternal episodes of fever, with no clear benefit on the neonatal outcome.

Keywords: Azithromycin, Post-cesarean section infection

INTRODUCTION

Cesarean delivery is considered as one of the major procedures for saving both maternal and fetal lives. The incidence of cesarean deliveries, both repeat and primary, has risen lately in Egypt to be doubled between 2005 and 2014, and reach according to Egypt demographic and health survey to 52% of all deliveries. Egypt now is in the third rank worldwide between countries with the highest rates of caesarean section after Dominican Republic and Brazil(1).

Post-partum infection globally represent one of the leading direct causes of maternal morbidity and mortality which in turn elongate

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the length of hospital stay and add burden to the healthcare costs. Caesarean delivery is counted as one of the major risk factors for postpartum infection (2). Compared to planned vaginal delivery, women who underwent elective caesarean section had double to triple risk to be re-hospitalised for wound complications and/or infections (3).

Surgical site infection (SSI) and endometritis are the main two sub-groups of the post-caesarean section infections. SSI refers to skin and subcutaneous infection at the site of the incision. Endometritis refers to infection of the endometrial lining of the uterus with/without its wall (4).

The American College of Obstetricians and Gynecologists (ACOG) recommendations 2011 endorsed the use of an antimicrobial prophylaxis within 60 minutes from the onset of the caesarean incision and to be as soon as possible in cases of unscheduled caesarean deliveries. The appropriate antimicrobial coverage can be effectively provided by the first generation cephalosporin or aminoglycosides combined with clindamycin in cases of hypersensitivity to cephalosporins (5). According to Cochrane review 2014, penicillins are equivalent to cephalosporins as regard to their prophylactic activity (6).

A single dose of one gram of cefazolin provides the adequate and the broad spectrum antimicrobial coverage for normal and overweight women. However, the dose should be adjusted for more obese women (5).

Adding azithromycin to the routine pre-caesarean cephalosporin prophylaxis against infection may add great benefits to ladies delivering by CS. Having a longer half-life (68 hours) with its higher tissue concentrations and less transplacental passage compared with other antibiotics plus its antimicrobial activity against both aerobes and anaerobes, as well as Ureaplasmas, all making azithromycin a valuable addition to the prophylaxis against the post caesarean section infections. It significantly decreases the risk of endometritis and SSI when added to the routine pre-caesarean cephalosporin prophylaxis (7&8).

Material and Method

Study design

This study was carried out as a prospective randomized non-blinded controlled trial.

Study subject

The estimated sample size is 230 patients who were intended to have selective CS (this number including 10% increase to the estimated minimal sample size). The estimated sample size was calculated with a level of confidence of 95%. Those patients were randomly subdivided into two groups: test group includes 115 women who received Azithromycin plus standard cephalosporin, and control group includes 115 women who received standard cephalosporin alone.

Setting

Obstetrics and gynecology department, Mansoura university hospitals (tertiary hospital), Mansoura University, Egypt. (Figure 1).

Inclusion criteria

Women > 28 weeks viable gestation, women undergo unscheduled / selective cesareans with either labor (spontaneous or induced) or ruptured membranes.

Exclusion criteria

Vaginal delivery, elective or scheduled cesarean prior to labor or membrane rupture, known Azithromycin (or other macrolide) allergy, clinical chorioamnionitis or any other active bacterial infection (e.g. pyelonephritis, pneumonia, abscess), fetal demise or major congenital anomaly, significant liver disease, significant renal disease or on dialysis, active congestive heart failure or pulmonary edema, active diarrhea at time of delivery, and immunosuppressed patients.

Drug administration

All patients were received the standard routine cephalosporin (1gm ceftriaxone) before the surgical incision. Azithromycin (500 mg) was given concurrently with the standard cephalosporin bolus in the test group.

Outcome measures

Endometritis and/or wound infection and/or post-cesarean infections (occurring within 4-6 weeks of delivery) defined as follows: Endometritis is the presence of two or more of the following signs with no other recognized cause: fever $> 38\text{ C}$, abdominal pain, uterine tenderness, or purulent drainage from uterus. Wound infection is the presence of either superficial or deep incisional surgical site infection characterized by cellulitis/erythema and induration around the incision or purulent discharge from the incision site with or without fever. Other infections include pelvic septic thrombosis, abdominal or pelvic abscess, pyelonephritis, pneumonia or maternal sepsis.

Results

In this work we tested the effect of addition of azithromycin to the standard pre-cesarean section cephalosporin prophylaxis (the test group), in comparison to the standard pre-cesarean section cephalosporin prophylaxis alone (the control group). There was no significant difference regarding the socio-demographic, obstetric data and conditions among studied groups (Table 1 and 2).

Endometritis, wound infection needed antibiotics and re-admission during puerperium were significantly reduced in the test group in comparison to the control group ($P= 0.006, 0.02$ and 0.01 respectively) (Table 3).

On comparison between the 2 studied groups we found that puerperal Fever $>38\text{OC}$, uterine tenderness, abdominal pain, offensive vaginal discharge and purulent drainage from uterus were significantly increased in the control group. Also, we found that the need for further antibiotic during puerperium was significantly increased the same group. (Figure 2, and Table 4).

On comparison between the 2 studied groups (Figure 3, and Table 5) we found that erythema around incision, induration around the incision, purulent discharge from the incision site, need for further antibiotic during puerperium and white blood cells count (WBCs) at 7th day postpartum were significantly increased in the control group receiving cephalosporin alone.

There was no significant difference regarding neo-

natal outcomes between both the test and the control groups. (Table 6).

Discussion

Cesarean section (CS) has dramatically increased over the last decade in Egypt to reach up to institution based rate of 67.3% (9). Although it is considered as an important lifesaving operation for both mother and child in many situations, however, this does not omit the fact that it is one of the most important risk factor for postpartum maternal infection which can increase maternal morbidity and mortality (10). Current recommendations for antibiotic prophylaxis in cesarean delivery include the standard administration of a broad-spectrum antibiotic before the skin incision (11). Unscheduled CS represent about 60% to 70% of all caesarean deliveries and up to 12% of women undergoing selective cesarean section delivery had puerperal infection when the standard pre-incision prophylaxis was used (12). These two facts point the importance of availability of more effective antibiotic regimens for protection against post CS infections.

The current study aimed to evaluate the efficacy of addition of Azithromycin with its strong antibacterial and bacteriostatic effects against atypical pathogens (13) to the standard cephalosporin (ceftiaxone) which has strong antibacterial effect against *E. coli* and Enterobacteriaceae in reducing the risk of post-cesarean infection compared to cephalosporin alone among women undergoing unscheduled cesarean delivery.

186 ladies undergoing unscheduled CS were included in the current study. They were subdivided into two groups, study group: included 94 subjects that received Azithromycin (500 mg) plus standard cephalosporin (ceftiaxone 1 gm), and control group: included 92 subjects that received standard cephalosporin (ceftiaxone 1 gm) alone.

There was no significant difference regarding the socio-demographic, obstetric data and conditions among studied groups (Table 1 and 2).

In our study there was significant reduction of re-admission during puerperium among the test group in comparison to the control group (0% vs 6.5%, $p=0.01$). Also, all signs and symptoms of endometritis (including; puerperal Fever $>38\text{OC}$,

uterine tenderness, abdominal pain, offensive vaginal discharge and purulent drainage from uterus) were significantly reduced among the test group in comparison to the control group. Also, all signs and symptoms of wound infection (including; erythema around incision, induration around incision, purulent discharge from incision site, need for further antibiotic during puerperium and WBCs at 7th day postpartum) were significantly reduced among the test group in comparison to the control group.

In accordance with our findings, Tita et al. found the adjunctive azithromycin prophylaxis for caesarean delivery in 1019 cases (study group) showed a significant protective effect against maternal endometritis, wound infection (2.4% vs 6.6%, $p < 0.001$) and serious maternal adverse events (1.5% vs 2.9%, $p = 0.03$) in comparison of addition of placebo in 994 control cases. This effective prophylaxis may be explained by its ability to cover against ureaplasma species, which are reported to be frequently associated with post CS infections (14).

In the same context, Ward and Duff 2016 evaluated the effect of addition of azithromycin to a first generation cephalosporin drug (cefazoline) before skin incision on prevention of postpartum endometritis in comparison to cefazoline alone after cord clamping. Although the difference in the timing of administration and the cephalosporine generation used, but their findings were consistent with ours as regard the significant protection against postpartum endometritis in azithromycin group (8).

Harper et al., 2017 and Skeith et al., 2017 tested the cost effectiveness of addition of azithromycin to the routine cephalosporin given as a prophylaxis against post-partum infections in both scheduled and non-scheduled CS. The research group found addition of azithromycin is both effective in reduction of post-partum infectious complication plus being of less cost compared with the cost of treatment of such complications (15 and 16).

In contrast, Johnson et al., 2019 in a retrospective study found addition of azithromycin to cephalosporines add no value in prevention of post-partum infections. Being a retrospective study and included only 100 participant making this study need further research to stand in front the growing evidence of the efficacy of addition of azithromycin to the routine prophylaxis in cases of selective CS(17).

In the present study, there was no significant difference between the 2 groups regarding neonatal outcomes in accordance with Tita and his colleagues (14) and Ward and Duff(8). In contrast, Oluwalana and his colleagues found azithromycin administered to women in labor reduces maternal and neonatal infections as otitis and conjunctivitis probably due to the effect on colonization of *Staphylococcus aureus* and *Streptococcus* species in the newborns, because these bacteria are major causes of both conditions. This contrast in the results can be explained by the fact that Oluwalana compared administration of azithromycin in test group with giving only placebo in the control group, both were delivering vaginally(18). We recommend performance of larger trials designed to assess the effect of prophylactic use of azithromycin on severe morbidity with studies that allow doing cultures for ureaplasma and other bacteria.

Ethical approval

The study was approved by the Mansoura Faculty of Medicine Institutional Research Board (MFM-IRB).

Conflict of interest

The authors declare that they have no conflict of interest.

Availability of data and material are confirmed.

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Figure 1:Consort flow of the study.

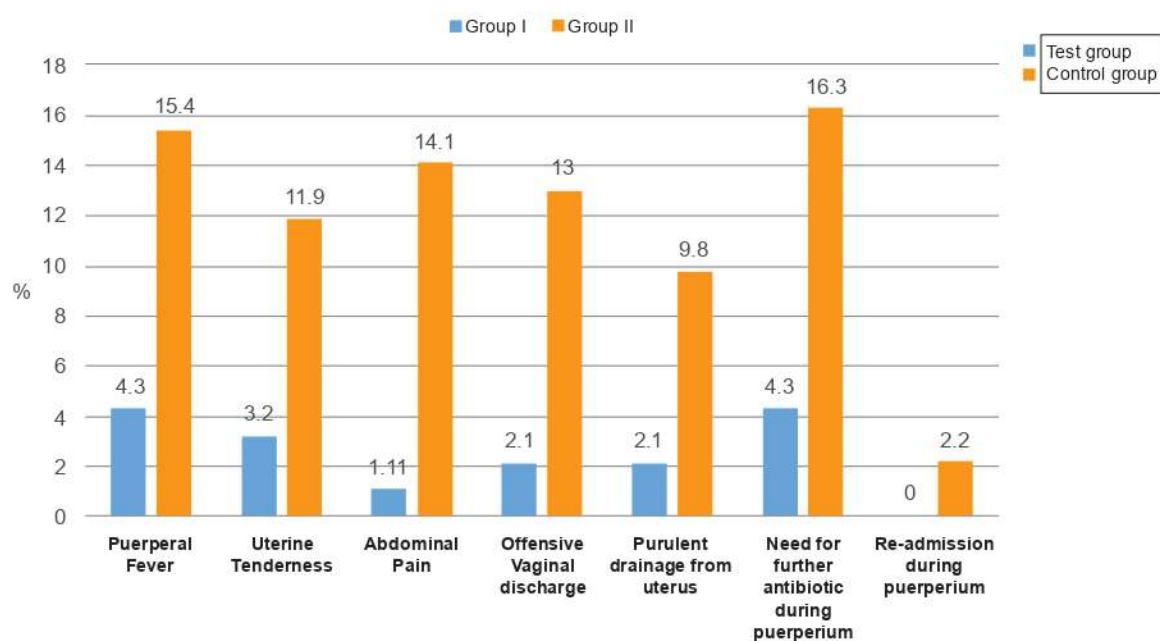
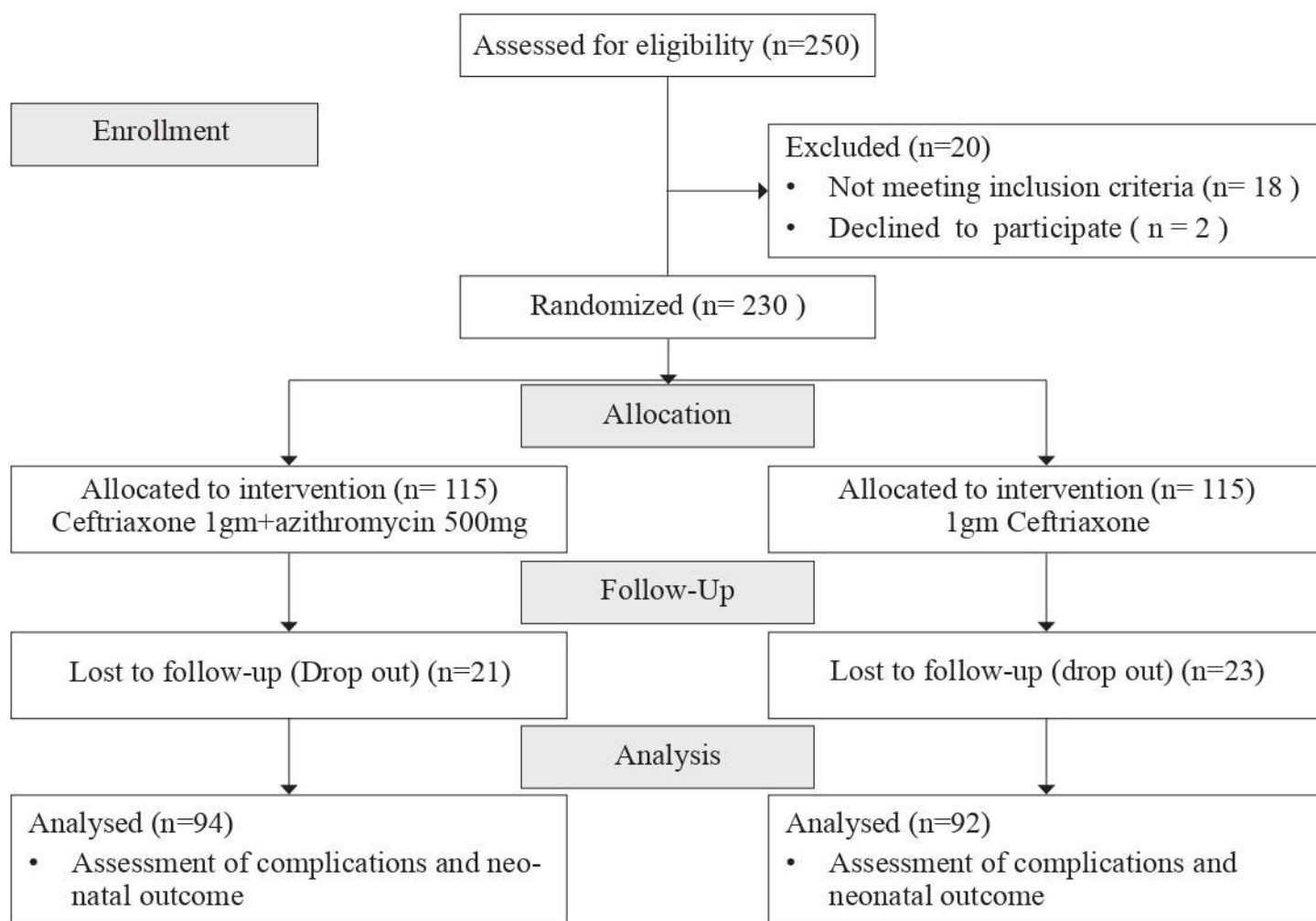
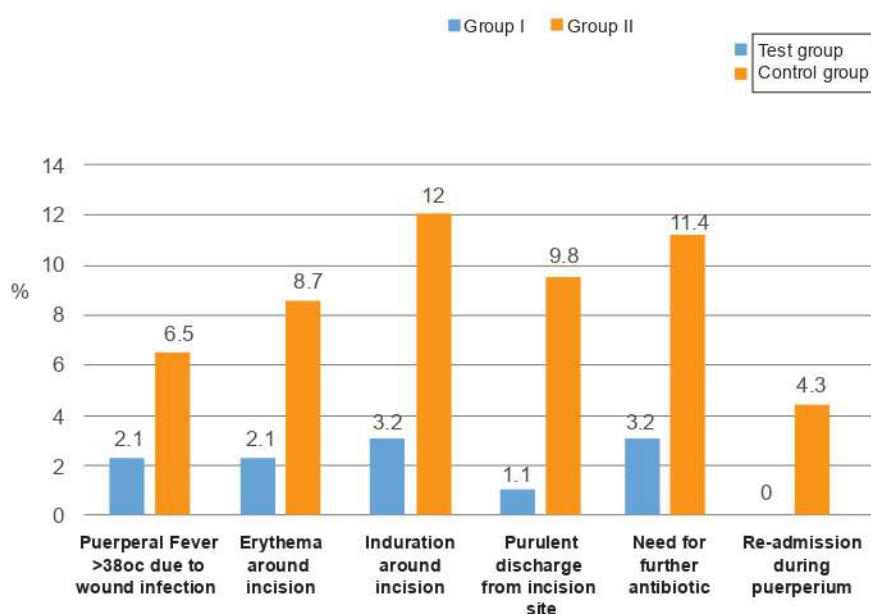


Figure 3: Wound infection distribution among studied cases**Table 1:** Socio-demographic & obstetric data among studied groups.

	Test group N=94(%)	Control group n=92(%)	Test of significance
Age/years Mean±SD	27.44±5.06	27.59±4.97	t=0.22 P=0.83
Gravidity			$\chi^2=0.35$ p=0.95
• Primigravida	12(12.8)	13(14.1)	
• 2 nd	14(14.9)	16(17.4)	
• 3 rd	34(36.2)	31(33.7)	
• >3	34(36.2)	32(34.8)	
Parity			$\chi^2=1.25$ p=0.74
• Nullipara	12(12.8)	13(14.1)	
• Primipara	18(19.1)	19(20.7)	
• 2 nd	38(40.4)	41(44.6)	
• ≥3	26(27.7)	19(20.7)	
Gestational age/weeks Mean±SD	39.15±0.98	39.13±0.99	t=0.13 p=0.89
Mode of previous deliveries :			$\chi^2=2.37$ p=0.12
• Vaginal	8(9.8)	3(3.7)	
• Cesarean	74(90.2)	78(96.3)	

χ^2 : Chi-Square test t: Student t test *statistically significant p: probability of error

Table 2: Maternal and fetal condition during labor among studied groups.

	Test group N=94(%)	Control group n=92(%)	Test of significance
Current Cs Non-elective	94(100.0)	92(100.0)	
Previous CS	74(78.7)	78(96.3)	$\chi^2=2.37$ p=0.12
Breech presentation	4(4.3)	2(2.2)	FET P=0.68
Labor pain	85(90.4)	85(92.4)	$\chi^2=0.23$ P=0.63
Acute fetal distress	2(2.1)	3(3.3)	FET P=0.68
Rupture membrane	27(28.7)	23(25.0)	$\chi^2=0.57$ P=0.62
Anesthesia(spinal)	94(100.0)	92(100.0)	

χ^2 :Chi-Square test FET: Fischer exact test *statistically significant p: probability of error

Table 3: Comparison between endometritis, wound infection needing antibiotic and re-admission during puerperium among studied groups.

	Test group N=94(%)	Control group n=92(%)	Test of significance
Endometritis needing antibiotic	4(4.3)	15(16.3) [#]	$\chi^2=7.36$ p=0.006*
Wound infection needing antibiotics	3(3.2)	11(11.9) [§]	$\chi^2=5.13$ p=0.02*
Re-admission during puer- perium	0(0.0)	6(6.5)	$\chi^2=6.34$ p=0.01*

[#]of them 2 cases with pelvic collections & need surgical intervention

[§]:4 of them need also admission for 2 weeks

χ^2 :Chi-Square test *statistically significantp: probability of error

Table 4: Endometritis distribution among studied groups.

Endometritis	Test group N=94(%)	Control group n=92(%)	Test of significance
Puerperal Fever >38°C due to endometritis	4(4.3)	14(15.2)	$\chi^2=6.39$ p=0.01*
Uterine Tenderness	3(3.2)	11(11.9)	$\chi^2=5.13$ p=0.02*
Abdominal Pain	1(1.1)	13(14.1)	$\chi^2=11.41$ p=0.0007*
Offensive Vaginal discharge	2(2.1)	12(13.0)	$\chi^2=7.96$ p=0.004*
Purulent drainage from uterus	2(2.1)	9(9.8)	$\chi^2=4.89$ p=0.02*
WBCs at 7th day postpartum(K/UL) mean±SD	10.08±2.42	11.54±3.82	t=3.13 p=0.002*
Need for further antibiotic during puerperium	4(4.3)	15(16.3)	$\chi^2=7.36$ p=0.006*
Re-admission during puerperium	0(0.0)	2(2.2)	FET P=0.24

χ^2 : Chi-Square test *statistically significant FET: Fischer exact test
p: probability of error

Table 5: Wound infection distribution among studied groups.

Wound infection	Test group N=94(%)	Control group n=92(%)	Test of significance
Puerperal fever >38°C due to wound infection	2(2.1)	6(6.5)	$\chi^2=2.18$ P=0.13
Erythema around incision	2(2.1)	8(8.7)	$\chi^2=3.94$ P=0.04*
Induration around incision	3(3.2)	11(12.0)	$\chi^2=5.13$ P=0.02*
Purulent discharge from incision site	1(1.1)	9(9.8)	$\chi^2=6.95$ P=0.008*
WBCs at 7th day postpartum(K/UL) mean±SD	10.08±2.42	11.54±3.82	t=3.13 p=0.002*
Need for further antibiotic during puerperium	3(3.2)	11(11.9)	$\chi^2=5.13$ P=0.02*
Post-operative hospital stay(48 hours)	94(100.0)	92(100.0)	
Re-admission during puerperium	0(0.0)	4(4.3)	FET P=0.057

χ^2 : Chi-Square test *statistically significant FET: Fischer exact test
p: probability of error

Table 6: Neonatal Outcome distribution among studied groups..

Neonatal Outcome	Test group N=94(%)	Control group n=92(%)	Test of significance
Death	0(0.0)	0(0.0)	
NICU admission	11(11.7)	13(14.1)	$\chi^2=0.24$ P=0.62
Causes of NICU admission Meconium aspiration Jaundice	n=11 4(36.4) 7(63.6)	n=13 5(38.5) 8(61.5)	$\chi^2=0.01$ P=0.91
Respiratory distress	2(2.1)	3(3.3)	FET P=0.68
Necrotizing enterocolitis	0	0	

χ^2 :Chi-Square test FET: Fischer exact test p: probability of error