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Original Article

Pharmacology Section

Antimicrobial Prophylaxis in Lower Uterine Segment Caesarean Section: A Prospective Observational Data-based Study

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ABSTRACT

Introduction: Any major surgery like lower uterine Caesarean Section (CS) can be hazardous due to postoperative nosocomial infection. Pregnant mothers are at greater risk during such surgical intervention as compared to vaginal delivery. Prophylactic antibiotic administration is a standard practice across the globe to prevent such anticipated postoperative infection.

Aim: To evaluate the prophylactic antimicrobial use with regards to the choice of antimicrobials, dose, route, timing and duration, any possible Adverse Drug Reaction (ADR) as well as to assess the frequency of the postoperative morbidity due to infection (if any).

Materials and Methods: A prospective observational data-based study was conducted in the Department of Pharmacology in collaboration with Department of Obstetrics and Gynaecology, Burdwan Medical College and Hospital, Burdwan, West Bengal, India, from February 2016 to October 2017. Study was conducted on 1944 pregnant women of reproductive age group planned or scheduled for elective/emergency lower segment CS, but otherwise healthy and received prophylactic antimicrobials for the surgery. They were prospectively observed regarding the treatment they received with focus on antimicrobial agents from the period of antimicrobial prophylaxis during their stay at hospital till their discharge. Demographic data, vital signs, indication of CS, postoperative infections and ADR if any were recorded in predesigned proforma. The study population was divided into two groups: group A included 995 mothers, who received ceftriaxone sodium (1 g intravenously) and metronidazole (15 mg/kg) infusion and group B included 949 mothers, who received ampicillin (2 g intravenously), metronidazole (15 mg/kg) infusion and injection gentamycin (5 mg/kg) for 0.5 hour before initiation of CS. The data were statistically analysed by standard statistical software Microsoft excel 2010 and Statistical Package for the Social Sciences (SPSS) sotware version 27.0 (SPSS Inc., Chicago, IL, USA) expressed as mean and standard deviation and percentage. Independent t-test and Chi-square test were used for analysis.

Results: The mean age of group A was 22.36±3.07 years and group B was 22.76±2.47 years. Endomyometritis was documented in 4 (0.4%) from group A and 2 (0.21%) from the group B. Wound infection was present in 3 (0.3%) for group A and five (0.5%) for the group B. Infection related complications like chest infection seen in 7 (0.7%) for group A and in 3 (0.31%) for group B and urinary tract infection was noticed in 6 (0.6%) for group A and 5 (0.52%) for group B. Any incidence of maternal mortality was not evident among the two study groups and statistically insignificant ADR like vomiting and maculopapular rash (p-value=0.324) was observed in both the study groups with the use of abovementioned antimicrobial therapy.

Conclusion: Prophylactic use of ceftriaxone plus metronidazole and combination of triple antimicrobial therapy of ampicillin, metronidazole, and gentamycin therapy at the usual standard dose were commonly used antimicrobials at the present set up and they are safe and equally effective in decreasing considerably the incidence of post caesarean maternal infection thereby reducing their morbidity and mortality.

Keywords: Adverse drug reaction, Antibiotic use, Neonatal infection, Pregnancy, Preoperative

INTRODUCTION

Lower uterine segment CS is the most common surgical procedure done in delivery of new born where normal delivery is hazardous to mother or contraindicated [1]. The average rate is greater than 20% in the developing countries. Based on DLHS-3 (District Level Household and Facility Survey) data, the CS delivery rate in India is 9.2%. However, a substantial interstate variation of CS exists in India [1]. Women undergoing caesarean delivery have a 5 to 20-fold greater risk of infection compared with vaginal delivery [2].

Nosocomial infection, or infection acquired in hospital is a major health problem in a hospital and especially in the maternity departments [3]. There is considerable variation in the type of infections encountered depending upon the standard of set up. Endomyometritis remains the most common infectious complication associated with caesarean delivery its incidence varies from 5-85%, depending on the patients' population surveyed [3]. The common infectious complications include fever, wound infection, endometritis, bacteraemia, Urinary Tract Infection (UTI), and other serious infections (including pelvic abscess, septic shock, necrotising fascitis, and septic pelvic vein thrombophlebitis) [2]. These complications not only results in increased hospital stay but also increase in the cost of care.

The term prophylactic antimicrobial implies the short term use of antimicrobial agents to reduce contamination of the operative field, as opposed to a therapeutic antibiotic used to eradicate established infections. Prophylactic antimicrobials are proved to be effective in lowering postoperative infections both in women at high risk (in labour after membrane rupture), and low risk (non labouring with intact membrane) [4]. They are often administered after umbilical cord clamping. Administration of drug shortly after cord clamping is considered to be as effective as administrating the drug preoperatively [5].

Currently, the choice of antimicrobials and the timing of administration is a matter of debate, i.e., choosing between narrow or broad-spectrum antimicrobial group agroup and between preincision or after clamping of the umbilical cord. The fact that broad spectrum

antimicrobials given before incision might mask neonatal infection and is the reason behind triggering these debates. Another matter of concern is that the selection of wrong antimicrobials which may result in the neonate being confronted to resistant strains of bacteria, which might lead to a unpleasant neonatal outcome or the need for costly neonatal septic screening and infection work-ups [6]. The drugs used must be effective against the prevalent organisms, broad spectrum, with minimum toxicity and easy to administer. Ledger WJ et al., (1975) have outlined guidelines for the use of prophylactic antibiotics in gynaecological surgery [3].

Antimicrobial resistance development results mainly from the inappropriate use of antimicrobials, incomplete courses of antimicrobial therapies and the unnecessary use of broader spectrum regimens. Adherence to both treatment and prophylaxis guidelines likely assists in reducing infection and antimicrobial resistance [7]. Documented guidelines regarding antimicrobial prophylaxis for lower segment CS have not been established in the hospital where the study was conducted. Therefore, the present study was aimed to evaluate the pattern of prophylactic antimicrobial use, any ADRs associated with it and to assess the frequency of the postoperative infection (if any) in a tertiary care hospital, Burdwan, West Bengal, India.

MATERIALS AND METHODS

The present prospective observational data-based study was conducted in the Department of Pharmacology in collaboration with Department of Obstetrics and Gynaecology, Burdwan Medical College and Hospital, Burdwan, West Bengal, India from February 2016 to October 20170. Study was conducted after receiving approval from the Institutional Ethics Committee (memo mo. BMC/PG/4451 dated 11.12.2015).

Inclusion criteria: Pregnant women of reproductive age group planned or scheduled for elective/emergency lower segment CS, but otherwise healthy and received prophylactic antimicrobials for the surgery were included in the study.

Exclusion criteria: Those who received antimicrobials for any associated conditions in preceding two weeks of surgery, with co-morbid conditions like diabetes mellitus, renal impairment, autoimmune diseases like Grave's disease, pernicious anaemia etc., tuberculosis, Human Immunodeficiency Virus (HIV) infections or prophylaxis for rheumatic fever and those on chemotherapy, radiotherapy, long term steroids, or immunosuppressants were excluded from the study.

Study Procedure

A total of (N=1944) participants were recruited based on convenience sampling. After receiving written informed consent from the study participants, they were observed regarding the treatment they received with focus on antimicrobial agents from the period of 1st dose of antimicrobial prophylaxis during their stay at hospital till their discharge. Relevant data were collected in a predesigned proforma. Data regarding patients' demographic profile, diagnosis, indication for CS, laboratory investigations parameters like Haemoglobin (Hb%), blood group, sugar, Venereal Disease Research Laboratory (VDRL), HIV (I and II), Hepatitis B surface Antigen (HBsAg) were recorded.

Total participants were divided into two groups:

Group A: A total of 995 mothers received ceftriaxone sodium (1 g intravenously) and metronidazole (15 mg/kg) infusion.

Group B: Other 949 mothers received the ampicillin (2 g intravenously), metronidazole (15 mg/kg) infusion and injection gentamycin (5 mg/kg) for 0.5 hour before initiation of CS.

The antimicrobials and the relevant laboratory investigations were documented in the case report form prescribed by the attending obstetrician as felt necessary. All patients before CS received single dose of antibiotics 0.5 hours before commencement of the CS as per choice of the treating obstetrician. None of the mothers received any subsequent dose of any kind of antibiotics until any suspicion regarding postoperative infection developed during recovery stage after CS.

Standard postoperative medical care was given to all the mothers included in the present study. The treating doctor did not participate in the study. The investigator by no means interfered, modified or influenced the prescribing pattern of the treating doctor. Those mothers who developed postoperative infection were treated aggressively with other drugs which were not documented during the present study. Any postoperative infection and ADR on occurrence were noted and documented in a predesigned proforma. Demographic parameters like residence, occupation, education, parity and gestational age were recorded. Preoperative vital parameters like temperature, pulse rate, blood pressure, and body weight were also recorded. Causality assessment was done according to World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) scale [8]. The WHO-UMC system takes into account the clinical-pharmacological aspects of case history, with a less prominent role of previous knowledge and statistical chance [9].

STATISTICAL ANALYSIS

At the end of all the relevant data collection, the demographic data, clinical parameters and postoperative status of the mothers were statistically analysed by standard statistical software Microsoft excel 2010 and SPSS software version 27.0 (SPSS Inc., Chicago, IL, USA) expressed as mean and standard deviation and percentage. Intergroup comparison was analysed by Chi-square test. A p-value of <0.05 was considered to be statistically significant.

RESULTS

A total of (N=1944) mothers undergoing CS were included, where 407 (21%) subjects underwent elective CS and 1537 (79%) subjects underwent emergency CS. No participant was excluded or lost to follow-up from the study after their recruitment. The demographic profile of the study participants are depicted in [Table/Fig-1] which were comparable among the two groups.

Parameters		Group A	Group B	p-value
Age (years)#, Mean±SD		22.36±3.07	22.76±2.47	0.0519
Residence# n (%)	Rural	708 (71.16)	677 (71.39)	0.9432
	Urban	287 (28.84)	272 (28.61)	
Occupation† n (%)	Employed	164 (16.48)	190 (20)	0.1623
	Unemployed	831 (83.52)	759 (80)	
Education† n (%)	Illiterate	286 (28.74)	277 (29.19)	0.6828
	Primary	473 (47.54)	461 (48.58)	
	Secondary	147 (14.77)	118 (12.43)	
	University	89 (8.95)	93 (9.8)	
Parity#, Mean±SD		1.33±0.62	1.36±0.57	0.0598
Gestational age (weeks)#, Mean±SD		38.033±0.906	38.032±0.9123	0.9969

[Table/Fig-1]: Demographic profile of study participants.
#Independent t-test, †Chi-square

The preoperative parameters with respect to the vital signs of the patients were recorded, which showed no statistically significant differences between the two groups (p-value >0.05) [Table/Fig-2].

Parameters	Group A	Group B	p-value†
Oral temperature (°F)	97.487±0.0789	97.488±0.07898	0.9379
Pulse rate (per minute)	82.405±7.46	82.54±7.56	0.7919
Systolic blood pressure (mmHg)	124.68±16.546	124.28±16.1	0.4808
Diastolic blood pressure (mmHg)	82.969±9.879	83.663±11.082	0.635
Body weight (kg)	44.0664±2.648	43.948±1.750	0.113

[Table/Fig-2]: Vital sign parameters before Caesarean Section (CS).
†Unpaired t-test; Values presented as mean±SD

The various clinical conditions due to which CS among the study participants were done are depicted in [Table/Fig-3].

Variables	Group A n (%)	Group B n (%)
Obstructed labour	828 (83.21)	794 (83.66)
Post Caesarean Section (CS)	160 (16.08)	152 (16.01)
Breech	1 (0.1)	1 (0.1)
Pregnancy induced hypertension	2 (0.2)	1 (0.1)
Cephalopelvic disproportion	1 (0.1)	0
Foetal distress	3 (0.3)	1 (0.1)

[Table/Fig-3]: Indications of Caesarean Section (CS).

Following prophylactic antibiotic administration before conduction of CS the pattern of postoperative infection observed among the two groups observed were mentioned in [Table/Fig-4]. The findings were not statistically significant (p-value >0.05) when compared between the two groups.

Variables	Group A n (%)	Group B n (%)	p-value†
Endometritis	4 (0.4%)	2 (0.21%)	0.4473
Wound infection	3 (0.3%)	5 (0.52%)	0.4378
Chest infection	7 (0.7%)	3 (0.31%)	0.2326
Urinary tract infection	6 (0.6%)	5 (0.52%)	0.8229

[Table/Fig-4]: Pattern of postoperative infections among both the study groups.
†Chi-square test

Swab sample were taken from wound and blood for culture and sensitivity test. In all (n=35, 1.80%) postoperative infective cases considering both the study groups, *Staphylococcus aureus* was isolated, which were sensitive to Amikacin. There was no incidence of maternal mortality and the prompt and vigorous treatment had led to uneventful recovery in all cases. In all patients, there were no signs or symptoms suggestive of pelvic abscess thrombophlebitis, burst abdomen or septicaemia or disseminated intravascular coagulation. The incidence of ADR was very low and has no statistical significance was seen as shown in [Table/Fig-5]. When causality assessment was done according to WHO-UMC scale, all ADRs observed could be termed as 'possible' link with the antibiotic used [8].

Adverse Drug Reaction (ADR)	Group A n (%)	Group B n (%)	p-value
Vomiting	3 (0.3%)	5 (0.5%)	0.324
Maculopapular rash	1 (0.1%)	2 (0.2%)	
Total	4 (0.4%)	7 (0.7%)	

[Table/Fig-5]: Incidence of Adverse Drug Reaction (ADR).

DISCUSSION

The present study was conducted in a tertiary care hospital to evaluate the effectiveness of prophylactic antibiotics on expecting mothers, those who have undergone CS due to various indications and received chemoprophylaxis in the form of injection ceftriaxone and metronidazole infusion in group A participants and injection ampicillin, metronidazole and gentamycin in group B participants prior to delivery. The selection of the antibiotics was solely done by the treating obstetricians and the investigator did not interfere or influence the treatment protocol. The treating obstetricians neither included during analysis of the study data nor offered authorship of the present publication.

The postoperative infections as observed in the present study were very less in number 35 (1.80%) and there was no statistically significant difference in this regard among the two study groups. These findings resembles with published literature of Alekwe LO et al., and Westen EH et al., where they have demonstrated that prophylactic antibiotics were effective in decreasing the frequency of post-CS infections with odds ratio was 1.21 (95% CI 0.97-1.51) [7,10]. Nazrina S et al., in their study also commented that single dose of third generation cephalosporins are advantageous over multiple other antimicrobial therapy in CS cases and this findings was also substantiated by Kumari R et al., where the selection of ceftriaxone was established as one of the best choice of the treating physician [11,12]. However, on the contrary studies done by Rizk DE et al., and Chan AC et al., showed no statistically significant decrease in post-CS infection following administration of prophylactic antibiotics using cefuroxime, ampicillin, metronidazole and sulbactam and this may be explained by other unforeseen confounding variables in their studies [13,14]. In the present study, the results showed no difference between the two drug regimens and they were similar in reducing postoperative infectious complications. These findings were consistent with other studies conducted by Alekwe LO et al., and Shinde R et al., [7,15].

Also, it is evident that the outcome of this study was seemingly better than other studies in reducing postoperative infections [15-17]. This may be explained by the fact that most of these studies were conducted in unscheduled emergency CS which carry the most important potential risk factors for sepsis, like prolonged duration of labour with ruptured membranes and repeated vaginal examination, and this may permit access of the potential pathogens to the uterine cavity, so that eventually the incision is made in a contaminated site [13,14].

In the present study, few incidences of chemoprophylaxis failure was noted with regard to risk factors for endomyometritis {Group A-4 (0.4%), group B- 2 (0.21%)}, or wound infection {{Group A-3 (0.3%), group B-5 (0.52%)}, among the study participants which was statistically insignificant. The authors believe that those patients who fail prophylaxis may have an incipient infection at the time of caesarean delivery, which may limit the effectiveness of antimicrobial prophylaxis, inspite of the fact that all patients with infectious focus were excluded from the study at the very beginning or may have some sterilisation errors of the instruments used during operations at different time interval. These findings were comparable with the study published by Mudanur S et al., and Bhattachan K et al., where wound infection noted 1 (2%) and 3 (3%) cases only [18,19].

Although no serious maternal and foetal side-effects occurred as the result of the use of the drugs, nevertheless, the possibility of untoward side-effects always must be considered when a decision is made to use prophylactic antibiotics, and it must be pointed out that there is a risk of anaphylactic reactions and there were case reports of this in the literature published by Alekwe LO et al., [7]. The goal of antibiotic therapy is to achieve sufficient tissue levels at the time of microbial contamination, and the ideal drug should be long acting, inexpensive, and have a low side-effect profile [20]. The incorrect selection of alternative antibiotic may lead the neonate and mothers being exposed to resistant strains of bacteria, which may worse the neonatal and maternal aftermath.

Limitation(s)

As the study was conducted in a single centre, where a standard antibiotic chemoprophylaxis was given as a routine procedure, therefore not much variability was observed. Other antibiotics used in treating any complicated cases arising due to any infection during the study period was not assessed. The pharmco-economic aspect of the study drugs was not analysed.

CONCLUSION(S)

Use of ceftriaxone and metronidazole combination found to be equally effective with insignificant adverse effect profile, when compared to ampicillin, metronidazole and gentamycin i.e., triple antibiotic therapies, when administered as chemoprophylaxis.

Author's contributions: Concept, design of study, literature search and conduct of study was done by Tapan Ganguly and Swapan Kumar Mandal. Data acquisition, data analysis and statistical analysis was done by Swapan Kumar Mandal, Tapan Ganguly and Kanai Lal Karmakar. Manuscript preparation was done by Arunava Biswas, Supreeti Biswas and Swapan Kumar Mandal. Manuscript editing and manuscript review was done by Supreeti biswas, Arunava Biswas and Saikat Kumar Dalui.

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