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Original Article

A randomized controlled trial to compare antibiotic prophylaxis in elective gynecological surgeries: Single dose of cefazolin versus single dose of cefazolin and tinidazole

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Abstract

Objectives: To evaluate if addition of an anti-anaerobic agent to standard drug-cefazolin for antimicrobial prophylaxis would further decrease postoperative infectious morbidity or not. This is relevant as most of the infections in gynecological surgeries are anaerobic but cefazolin does not protect against anaerobes. **Materials and Methods:** The study design was a parallel randomized controlled trial. Two hundred patients undergoing benign gynecological surgeries were divided into two groups of 100 each. Group A received 2 g cefazolin 30–60 min before incision and Group B received 2 g cefazolin 30–60 min and 1.6 g tinidazole 60–120 min before incision. The patients were followed for any infectious morbidity for 1 month postoperatively. The analysis was done separately for abdominal, laparoscopic, and vaginal surgeries. The analysis was also done for surgeries according to the wound category, i.e. clean and clean-contaminated. **Results:** The two groups were comparable for age and body mass index (BMI). The two groups were comparable for the factors affecting infectious morbidity such as duration of surgery, blood loss, blood transfusions, duration of hospital stay, and need for additional antibiotics. The postoperative infectious morbidity was analyzed in terms of fever, surgical site infection (SSI), and urinary tract infection (UTI). No patient in vaginal and laparoscopic groups suffered from infectious morbidity. In abdominal surgeries group, postoperative fever occurred in 6/74 (8.1%) and 11/74 patients (14.8%) in Groups A and B, respectively (P = 0.38). SSI occurred in 1/74 (1.3%) and 2/74 (2.7%) patients in Groups A and B, respectively (P = 1.0). UTI occurred in 5/74 patients (6.7%) and 2/74 patients (2.7%) in Groups A and B, respectively (P = 0.44). The data were also analyzed for infectious morbidity for clean and clean-contaminated wound categories, and the results were nonsignificant between both groups for each type of wound category (P > 0.05). **Conclusion:** Cefazolin alone is a sufficient antibiotic prophylaxis for benign gynecological procedures.

Keywords: *Anaerobic cover, Antimicrobial prophylaxis, Cefazolin, Infectious morbidity, Tinidazole*

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Introduction

Surgical site infection (SSI) is the most common nosocomial infection (25%) and leads to increased cost and longer hospital stay in up to 5% cases [1]. Other complications such as urinary tract infection (UTI), endometritis, perineal infection, vaginal cuff cellulitis, and sepsis can also occur in the postoperative period following a gynecological surgery. The frequency of all these types of postoperative infections can be reduced with antibiotic prophylaxis (AP) [2]. Prophylactic antibiotics decreases the colonization of those microorganisms which can enter the body at the time of surgical incision to such a level which the patient's immune system can overcome [3].

For a long time, multiple doses of antibiotics were advocated in surgical procedures [4], but recent guidelines suggest that a single dose of AP is as effective in clean,

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and clean-contaminated surgical procedures as are multiple doses of antibiotics [5,6]. Inappropriate and prolonged use of antibiotics which occurs in around 25%–50% of surgeries not only increases the health-care costs but also increases the rate of antibiotic resistance.

Anaerobes are responsible for most of the postoperative infections following gynecological surgeries and despite the fact that cefazolin is the standard antimicrobial prophylaxis, it lacks an anaerobic cover. Thus, there is a need to evaluate if addition of an anti-anaerobic agent to the standard AP would further reduce postoperative infectious morbidity. Having this background in mind, we conducted this study with the hypothesis that addition of anti-anaerobic agent like tinidazole to cefazolin reduces postoperative infectious morbidity in elective benign gynecological surgeries (Primary objective). The secondary objective of conducting this study was to evaluate the need for additional postoperative antibiotics for fever, UTIs, vaginal discharge, and SSIs.

If the results of our study support our hypothesis, then we can achieve lesser infectious morbidity in elective benign gynecological surgeries by the addition of tinidazole to cefazolin as AP. If, however, the results depict no advantage of an additional anti-microbial agent then we can avoid extra drugs, thus achieving cost-saving and reducing microbial resistance. There have been studies in the literature which compare single drug against another drug as anti-microbial prophylaxis agent, but the novelty in our study lies in the fact that there are very few studies in the literature that compare a cephalosporin with a combination of cephalosporin and an anti-anaerobic agent.

Materials and Methods

The study was a parallel randomized controlled trial with 1:1 allocation ratio conducted for 1 year in the Department of Obstetrics and Gynecology, PGIMER, Chandigarh with approval from the Institutional Ethics Committee bearing approval no. INT/IEC/2017/518. The registration no. of the Institutional Ethics Committee is ECR/25/Inst/CH/2013/RR-20.

Primary outcome

To compare the effectiveness of single dose of 2 g cefazolin versus single dose of 2 g cefazolin and 1.6 g tinidazole as anti-microbial prophylaxis in gynecological surgeries in terms of postoperative infectious morbidity. The infectious morbidity was measured for 1 month postoperatively by febrile morbidity, SSI, and UTI.

Secondary outcome

The secondary outcome is to evaluate the need for additional postoperative antibiotics for fever, UTIs, vaginal discharge, and SSIs. This was assessed during the duration of hospital stay and up to 1 month postoperatively.

Eligibility criteria

All patients who were admitted to gynecology ward for an elective benign gynecological surgery within the study period of 1 year were screened for eligibility. The elective gynecological surgeries included were abdominal surgeries, laparoscopic hysterectomy, vaginal hysterectomy, and surgeries for pelvic organ prolapse/stress urinary incontinence. The abdominal surgeries that were included were abdominal hysterectomy, exploratory laparotomy, myomectomy, surgeries on ovaries, and fallopian tubes. The patients who had diabetes, anemia, jaundice, retrovirus positive, renal disease on immune-suppressive therapy, autoimmune disorders, localized skin infection, any known allergy to either cefazolin or tinidazole, and any history of fever or intake of any antibiotic within last 7 days before surgery were excluded.

A total of 200 eligible patients were enrolled and were randomized into two groups of 100 each after taking an informed written consent. Simple randomization was done by computer generated random number tables preoperatively. No restriction was used in the study. Allocation concealment was achieved by using sequentially numbered, opaque, and sealed envelopes. The opaque envelopes were kept with the other research investigator other than the principal investigator. The operating team opened the opaque envelopes and handed over to the principal investigator who then administered the mentioned intervention. The participants were blinded to the intervention and the principle investigator was blinded till the assignment of intervention.

Group A received single dose of 2 g cefazolin 30–60 min before the incision and Group B received single dose of 2 g cefazolin 30–60 min and 1.6 g tinidazole 60–120 min prior to incision [7]. In Group A, 2 vials of injection cefazolin 1 g/vial were each reconstituted with 2.5 mL sterile water to make a total dose of 2 g in 5 mL sterile water. The same was administered slow I/V after sensitivity testing. In Group B, 2 bottles each of 400 mL tinidazole infusion with dose 2 mg/mL (making a total dose of 1.6 g) were administered within 60–120 min before incision [7]. The patients who encountered some unexpected intraoperative complications such as gastrointestinal or urinary tract injury were excluded postoperatively as they required multiple doses of antibiotics.

All the surgical aseptic precautions were carried out as per the department protocol. The patients were catheterized on the surgery table after induction of anesthesia. Vaginal cleansing was done with betadine preoperatively. The abdomen was cleaned with betadine before incision. Intraoperative and postoperative complications were noted. Postoperative care was provided as per the protocol.

In the postoperative period, a follow-up of the patients was done for febrile morbidity, SSI, UTI, and vaginal discharge till 30 days.

- Postoperative care was provided and the patients were monitored for any signs and symptoms of sepsis-local or systemic while admitted and were followed up telephonically till 30 days postoperative after discharge from the hospital
- On day 2, the dressing was changed and the stitch line was examined for local erythema, induration, local rise of temperature, wound discharge, or wound gaping. Stitch line was examined every day thereafter
- On day 2 hemogram, urine routine and microscopy, urine culture and sensitivity was sent. The patients were treated

according to the results obtained from these laboratory parameters as per the department protocol, and the antibiotics were changed as per the sensitivity reports.

Statistical analysis

Data were summarized separately for the quantitative variables using the measures of central tendency (mean, median, and dispersion [standard deviation]) and for qualitative variables/ categorical variables using frequencies and proportions. Normality of quantitative data was checked by the measures of Kolmogorov–Smirnov tests of normality. Discrete categorical data were presented as *n* (%). Mann–Whitney test and *t*-test was applied for skewed and normal data, respectively. For categorical data, comparisons were made by Pearson Chi-square test or Fisher's exact test as appropriate. McNemar Test was applied for the comparison between the categorical values of different timings. All statistical tests were two-sided and were performed at a significance level of $P = 0.05$. The analysis was conducted using SPSS for IBM (version 23.0) (SPSS is Statistical product and service solutions, IBM company, USA).

Results

In our study, a total of 350 patients who were admitted to gynecology department for elective benign surgeries were screened and 200 patients matched the inclusion criteria and were enrolled for the study [Figure 1].

The patients in two groups were comparable for age and BMI. The mean age for Group A was 41.52 years ± 10.13 and for Group B was 40.69 years ± 9.76 ($P = 0.55$). The mean BMI for Group A was 25.46 ± 2.72 and for Group B was 24.79 ± 2.66 ($P = 0.08$).

The most common indication was abnormal uterine bleeding due to Leiomyoma in 64% followed by pelvic organ prolapse and benign adnexal mass (~13% each). Other indications were abnormal uterine bleeding due to polyp, adenomyosis, and those patients who were admitted for tubal recanalization. The data were analyzed separately for abdominal surgeries, laparoscopic surgeries, and vaginal surgeries. Fifty percent of each group underwent abdominal surgeries, 37.5% of Group A patients and 62.5% of Group B patients underwent laparoscopic surgery and 60.7% of Group A patients and 39.2% of Group B patients underwent vaginal surgeries. The difference in the distribution of cases was comparable.

The results were analyzed for various outcomes that could affect postoperative infectious morbidity and those were compared for each type of surgery between both the groups. The factors affecting postoperative infectious morbidity were duration of surgery, average blood loss, need for blood transfusions, duration of hospital stay, and need for additional antibiotics. The difference for each factor between the two groups was found to be statistically nonsignificant for each type of surgery [Table 1].

Postoperative infectious morbidity was analyzed in terms of fever, SSI, and UTI. No patient in vaginal and laparoscopic groups suffered from infectious morbidity. However, among the patients who underwent abdominal surgeries, postoperative fever occurred in 6 patients (35.3%) in Group A and 11 patients (64.7%) in Group B ($P = 0.38$). Only one patient (33.3%) in Group A and two patients (66.7%) in Group B had SSI ($P = 1.0$). Five patients (71.4%) in Group A and two patients (28.5%) in Group B had UTI ($P = 0.44$). Overall, 10 patients (45.4%) in Group A and 12 patients (54.5%) in Group B had infectious morbidity ($P = 0.81$). Infectious morbidity is not the total of number of patients who suffered from febrile morbidity, UTI and SSI but consists of either one or two or all three of these factors [Table 2 and Figure 2].

The data were also analyzed for infectious morbidity among two groups for both categories of wound, i.e., clean and clean-contaminated surgeries. It was seen that for clean surgeries postoperative fever occurred in 11.7% in Group A and 21.8% in Group B ($P = 0.32$). 6.2% in Group B and no patient in Group A had SSI ($P = 0.23$). 5.8% in Group A and 3.1% in Group B had UTI ($P = 1.0$).

For, clean-contaminated surgeries, postoperative fever occurred to 3% in Group A and 5.8% in Group B ($P = 0.68$). 1.5% in Group A and none in Group B had SSI ($P = 0.49$). UTI occurred in 4.5% in Group A and 1.4% in Group B ($P = 0.36$).

Thus, there was no statistically significant difference between the two groups [Table 3 and Figure 3].

Discussion

The major morbidity after gynecological surgeries is due to postoperative infections as they increase the duration of hospital stay, need for additional antibiotics, resources, and number of re-admissions. It has been established in various randomized controlled trials and meta-analysis, that administration of any prophylactic antibiotic decreases postoperative infectious morbidity when compared with placebo. However, evidence is not considered sufficient to elaborate which antibiotic either individually or in combination is safest and most effective [8]. There is no doubt that Cefazolin is agreed upon as a standard AP agent but it is ineffective against anaerobes. And, most of the postoperative infections following gynecological surgeries are because of anaerobes, thus there is a need to search for more efficacious and safe single or a combination of antibiotics for prophylaxis in gynecological surgeries.

The importance of adding anti-anaerobic agent as AP is underlined by the fact that bacterial vaginosis (BV) is a crucial risk factor for postoperative infections [9,10]. BV is the alteration of vaginal flora when there is an abundance of anaerobic bacteria. However, BV being majorly asymptomatic is generally not suspected before a gynecological surgery [11]. If BV is treated preoperatively with an anti-anaerobic agent then the risk for postoperative infections can be reduced [12]. Thus, either anti-anaerobic agent can be given preoperatively to all patients undergoing gynecological surgeries or it can be given to those who test positive for BV on universal preoperative testing. But, it has been seen that this second option is costlier than the first in lowering the rate of postoperative infections [13].

In our study, the groups were comparable for the mean age and BMI. 74% of the patients underwent abdominal surgeries whereas

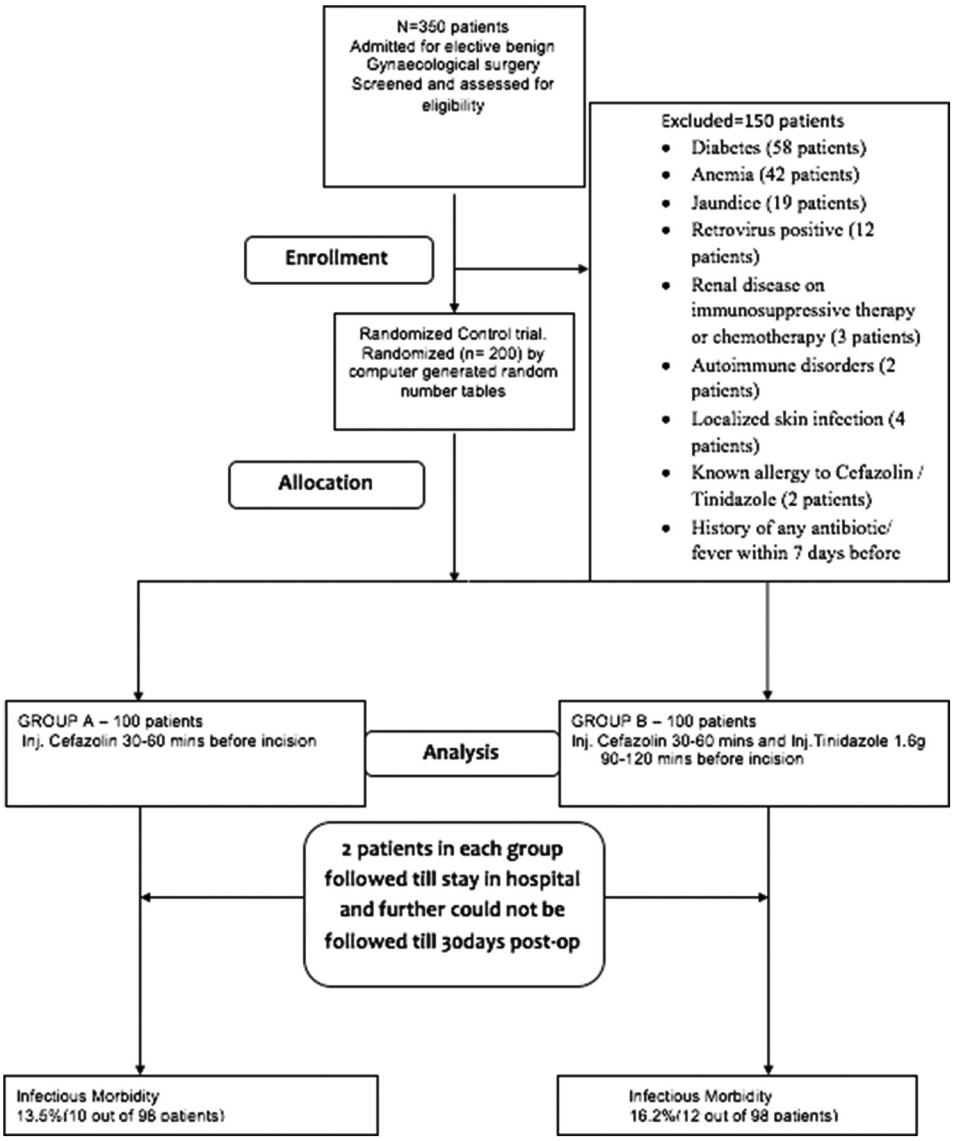

Figure 1: Consort flowchart to depict the study design

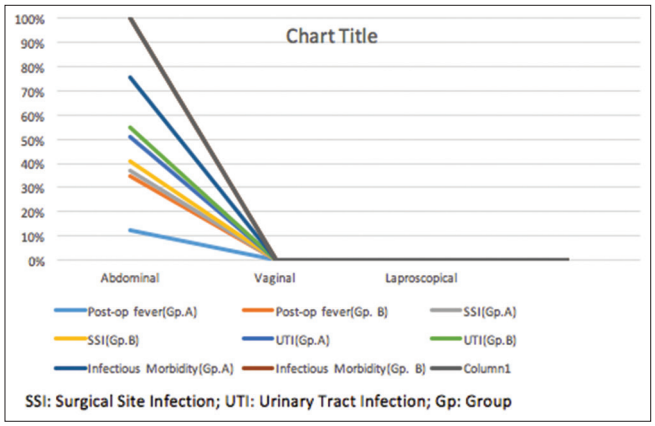

Figure 2: Postoperative morbidity. SSI: Surgical site infection, UTI: Urinary tract infection, Gp: Group

12% and 14% of the patients underwent laparoscopic and vaginal surgeries respectively for benign gynecological procedures.

AP was given as per protocol of the study. In the study performed by Simões *et al*. [14] out of a total of 75 patients, 25 each received as AP-2 g cefazolin; 2 g per oral tinidazole 12 h before surgery; Cefazolin plus Tinidazole respectively. In the double blind study performed by Evaldson *et al*., [7], out of total 98 patients, 49 patients received single dose of I.V. 1600 mg tinidazole within 2 h preoperatively whereas 49 patients received a placebo. In three separate randomized double-blind trials conducted by Janssens *et al*. [15], 175 patients were included. In Study 1, out of 53 patients, 26 patients received placebo and 27 patients received tinidazole as AP. Tinidazole was given as 2 g orally 18 h preoperatively, and 1 g tinidazole each 6 h later, on day 3, 4 and 5. In Study 2, out of 92 patients, 46 in each group received 2 g tinidazole 6–8 h preoperatively versus placebo. In Study 3, 30 patients undergoing vaginal hysterectomy were randomized into two groups of tinidazole versus placebo of 15 each. The patients in tinidazole group received 1600 mg infusion within 1 h preoperatively. In meta-analysis by Brummer *et al*. [16], 38.5% women received cefuroxime, 9.9%

Table 1: Comparison of factors affecting postoperative infectious morbidity

Routes of surgery Total Group A=100 Group B=100	Surgery duration		Blood loss (mL)		Blood transfusion		Duration of hospital stay		Additional antibiotics	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
Abdominal Group A (*n*)=74 Group B (*n*)=74	2.03 h (0.67 h-4.83 h)	2.00 h (1 h-4 h)	450.68 (100-2500)	348.98 (100-2500)	3	4	4.81 days±0.805	4.99 days±0.884	2	3
Vaginal Group A (*n*)=17 Group B (*n*)=11	2.49 (1 h-4.83 h)	2.59 (1.5 h-5 h)	241.18 (100-600)	218.18 (100-500)	1	0	4.94 days±0.827	4.91 days±0.831	0	2
Laparoscopy Group A (*n*)=9 Group B (*n*)=15	3.14 (1.5 h-7 h)	2.83 (2 h-4 h)	344.44 (100-1000)	240.00 (100-500)	1	0	4.56 days±0.726	5.33 days±0.816	1	0
P value for each factor between 2 groups for different routes of surgeries										
Abdominal	0.8		0.71		1.0		0.21		0.89	
Vaginal	0.758		0.651		1.0		0.92		0.08	
Laparoscopic	0.51		0.23		0.37		0.21		0.37	

Table 2: Postoperative morbidity

Routes of surgery	Febrile morbidity, *n* (%)		SSI, *n* (%)		UTI, *n* (%)		Infectious morbidity, *n* (%)		Infectious morbidity (Group B)	Column1
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B		
Abdominal	6/74 (8.10)	11/74 (14.8)	1/74 (1.3)	2/74 (2.7)	5/74 (6.7)	2/74 (2.7)	10/74 (13.5)	12/74 (16.2)	16.20%	
Vaginal	0	0	0	0	0	0	0	0	0	
Laparoscopic	0	0	0	0	0	0	0	0	0	
P value for each group for abdominal surgery	0.38		1.0		0.44		0.81			

SSI: Surgical site infection, UTI: Urinary tract infection

Table 3: Infectious morbidity among two groups for clean and clean-contaminated surgeries

Type of surgery	Postoperative fever (%)		SSI (%)		UTI (%)	
	Group A	Group B	Group A	Group B	Group A	Group B
Clean N (Group A)=34 N (Group B)=32	4 (11.7)	7 (21.8)	0	2 (6.2)	2 (5.8)	1 (3.1)
Clean-contaminated N (Group A)=66 N (Group B)=68	2 (3)	4 (5.8)	1 (1.5)	0	3 (4.5)	1 (1.4)

SSI: Surgical site infection, UTI: Urinary tract infection

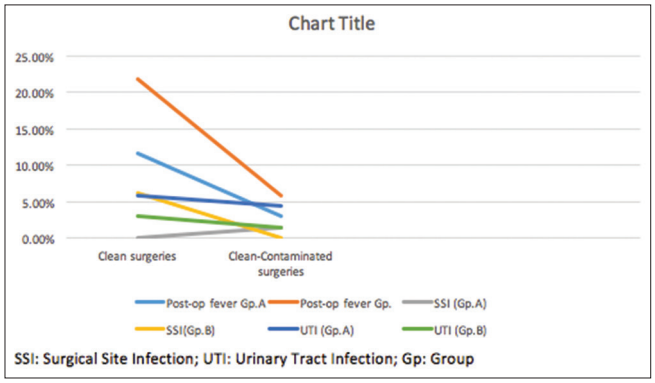

Figure 3: To compare infectious morbidity among two groups for clean and clean-contaminated surgeries. SSI: Surgical site infection, UTI: Urinary tract infection, Gp: Group

received metronidazole and 43.0% received metronidazole plus cefuroxime. The dosage of intravenous cefuroxime was 1.5 g and of metronidazole was 0.5 g at the time of induction.

Abdominal surgeries

In our study, 8.1% in Group A and 14.8% in Group B had febrile morbidity. 1.3% in Group A and 2.7% in Group B had SSI. 6.7% in Group A and 2.7% in Group B had UTI. The difference between both groups for febrile morbidity, SSI and UTI was statistically nonsignificant. These findings were in-keeping with similar studies performed by Brummer *et al*. [16] and Evaldson *et al*. [7]

Infectious morbidity in our study was seen in 13.5% in Group A and 16.2% in Group B, the difference being statistically non-significant. This result was similar to studies

conducted by Brummer *et al*. [16] and Evaldson *et al*. [7]. As per a study performed by Simões *et al*. [14], 5 out of 75 patients had infectious morbidity out of which 4 patients belonged to tinidazole group and one belonged to combined cefazolin and tinidazole group. However, the power of this study was low to establish this difference as statistically significant. In the 55 abdominal hysterectomy patients present in study 1 and 2 combined, conducted by Janssens *et al*. [15], the total wound infection morbidity (WIM) was 50% in the placebo group as compared to 37.5% in study 1 and 47.4% in Study 2 in tinidazole groups. The clinically relevant morbidity that consisted of Grades 2 and 3 was lower in the tinidazole group, however this difference was statistically nonsignificant.

In the meta-analysis performed by Mittendorf *et al*. [17] serious postoperative morbidity was seen in 11.4%, 6.3%, and 5.0% who received cefazolin, metronidazole, or tinidazole respectively, the difference was statistically nonsignificant. However, they did not compare the effects of combined AP. They concluded that "at least three drugs-cefazolin, metronidazole, and tinidazole-are efficacious for prevention of infectious morbidity associated with abdominal hysterectomy but more randomized controlled trials are required to find other efficacious prophylactic antibiotics and the trials should consist of one of these three drugs as a control."

Vaginal surgeries

In our study, amongst the patients undergoing vaginal surgeries, no patient developed any infectious morbidity. In a similar study conducted by Brummer *et al*. [16], statistically nonsignificant difference was found between the groups undergoing vaginal hysterectomy for febrile morbidity, SSI, UTI and infectious morbidity.

There was no infectious morbidity in any patient who underwent vaginal hysterectomy in any of the three groups in study conducted by Simões *et al*. [14]. As per Janssens *et al*. [15] amongst the 90 patients who underwent vaginal hysterectomy and received oral Tinidazole prophylaxis, there was a statistically significant difference in WIM from 69.2% in the placebo group as compared to 27.3% in tinidazole group of Study 1, 25.9% in tinidazole group of Study 2, and 26.3% in the combined tinidazole group of Study 1 and 2. There was a highly statistically significant difference between placebo versus tinidazole group with regards to Grade 3 of WIM i.e. there were 5 patients out of 52 in placebo group as compared to zero patient out of 38 in the tinidazole group. Thus, they concluded that "Tinidazole antibiotic significantly reduced postoperative infectious morbidity as compared to a placebo." They also concluded that, 2 g oral tinidazole dose was equally effective and more convenient than the 6 g multidose regimen of oral tinidazole and also that better results are produced by one single preoperative dose of 1600 mg iv tinidazole when compared with oral regimen.

In the Cochrane Database of Systematic Reviews on "Antibiotic Prophylaxis for elective hysterectomy" [18], it was seen in one of the randomized controlled trial that fewer patients who underwent benign vaginal hysterectomies and received cephalosporin plus antiprotozoal were diagnosed with SSI, UTI, or postoperative fever compared with women who received antiprotozoal alone. According to this review it was still unclear whether combined antibiotics are more effective and safer as compared to single antibiotics as the quality of the evidence was low for these comparisons.

Laparoscopic surgeries

In our study, amongst the patients undergoing laparoscopic hysterectomy, no patient developed infectious morbidity in either group. Similarly, Brummer *et al*. [16] concluded that the difference amongst the groups for febrile morbidity, SSI, UTI and infectious morbidity was statistically nonsignificant.

A retrospective cohort study was conducted on patients in the Michigan Surgical Quality Collaborative from July 2012 through February 2015. There were a total of 18,255 abdominal, vaginal, laparoscopic, or robotic hysterectomies for benign or malignant indications. The patients received either cefazolin; second-generation cephalosporin, or cefazolin plus metronidazole. The overall rate of SSI was 1.8%. On comparison with cefazolin plus metronidazole, it was found that risk of SSI was significantly higher for patients who received cefazolin (odds ratio, 2.30) or second-generation Cephalosporin (odds ratio, 2.31). Thus, concluding that "prophylactic cefazolin plus metronidazole resulted in lower SSI rates compared with cefazolin or second-generation cephalosporin."

As regards the need of additional antibiotics in our study, a total of 5 patients who underwent abdominal hysterectomy were given postoperative antibiotics such as amoxicillin/clavulanate, piperacillin-tazobactam, metronidazole for reasons like dense adhesions, bowel handling, placing an intra-abdominal drain, gut injury.

Only 1 patient who underwent laparoscopic hysterectomy received cefixime and metronidazole for dense adhesions intra-operative. 2 patients who underwent vaginal hysterectomy received postoperative antibiotics like cefixime plus metronidazole and cefazolin plus tinidazole because vaginal pack was placed for 48 h. However, these reasons for giving antibiotics are not established indications for administering postoperative antibiotics according to the present literature and guidelines.

Strength

Our study was a randomized control trial where the factors which affect the rate of infectious morbidity such as age, BMI, duration of surgery, ABL, intraoperative blood transfusion, postoperative antibiotics, and duration of hospital stay were matched, and thus, the rates of infectious morbidity derived from our study are a true reflection of the effect of prophylactic antibiotic. Furthermore, unlike our study, there are fewer studies in the literature comparing cephalosporin with a combination of cephalosporin and anti-anaerobic agent.

Limitation

The outcome of our study, i.e., there is no statistically significant advantage of adding an anti-anaerobic agent to cefazolin as AP cannot be established with certainty because of a small sample size. Only a small proportion of patients was suffering from infectious morbidity to conclude the results from.

Conclusion

There are a number of studies which compare one single anti-microbial agent for AP against another or placebo, but there is a paucity of such studies which compare an anti-anaerobic agent with the standard anti-microbial agent, i.e., cefazolin. Thus, we recommend the need of a large sample sized study which compares cefazolin and an anti-anaerobic agent with cefazolin alone to establish the advantage, if any, of addition of an anaerobic cover as AP for gynecological surgeries.

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Conflicts of interest

There are no conflicts of interest.

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