A Comparison of the Efficacy of Single Dose Cefazolin versus Single Dose Cefazolin plus 7-day Mupirocin Ointment Wound Application in Preventing Surgical Site Infection Among Patients Undergoing Major Obstetric and Gynecologic Procedures at a Tertiary University Hospital: A Two-year Single Blinded Randomized Controlled Trial*

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ABSTRACT

Objective: Surgical Site Infection is a common complication among all surgical cases. It is the most common nosocomial infection identified in the developing world with pooled incidence of 11.8 per 100 surgical procedures. In this institution, the SSI rate in major obstetric and gynecologic cases in years 2000 to 2013 is 12.68%.

Objective: To compare the efficacy of a single dose Cefazolin versus a single dose Cefazolin plus 7-day Mupirocin ointment wound application in preventing surgical site infection among women undergoing major obstetric and gynecologic abdominal surgical procedures.

Methodology: Included in this study were 164 female participants, 18 to 65 years of age and who underwent major obstetric and gynecologic surgical procedures. Participants were randomly assigned to group A and B, wherein all participants were given single dose of 2-grams Cefazolin, intravenous, 30 minutes prior to skin incision. For the participants in group B, an additional 7- day application of mupirocin ointment on incisional wound during the post- operative period was done. Assessment for occurrence of SSI and healing time using a standardized collection tool and Southampton wound scoring system, respectively was done on the 8th, 15th and 30th post-operative days.

Results: Incidence of surgical site infection was 2.45% (4 out of 164 participants). It was slightly higher in the Cefazolin only with three cases, and only one case in the Cefazolin plus mupirocin group. However the difference of SSI occurrence between the two groups is not statistically significant. Wound healing time was also evaluated and found comparable between treatment groups.

Conclusion: Single dose Cefazolin plus 7-day once daily Mupirocin ointment is comparable to single dose of Cefazolin in preventing Surgical Site Infection in patients undergoing major low-risk obstetric and gynecologic surgeries. Therefore, addition of mupirocin in uncomplicated major obstetric and gynecologic surgical cases is not cost-beneficial.

Key words: Cefazolin, mupirocin, surgical site infection, obstetric surgery, gynecologic surgery

Surgical Site Infection (SSI) is defined as an infection occurring within 30 days after procedure.[1] It is a type of Healthcare Associated Infection (HAI) that occurs after an invasive surgical procedure. It is the most common nosocomial infection identified in the developing world with pooled incidence of 11.8 per 100 surgical procedures and remains the second most common in high income countries such as America and Europe.[2]

Surgical Site Infection is preventable, yet it remains to be one of the most common and costly

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causes of health care associated infection leading to substantial morbidity and mortality. Furthermore, it requires longer hospital stay, increases cost of treatment and affects patient's productivity.[3] Newly delivered mothers who acquire SSI experience added burden in terms of inconvenience in nursing their child and maintaining their household.

Generally, there is a perception that presence of SSI reflects poor quality of care. For this reason, various infection control protocols were developed and are being constantly updated to lower its incidence. Most institutions comply to the advancements in operating room practices, sterilization methods, barriers, surgical technique, and use of antibiotic prophylaxis. Yet, surgical site infection remains to be the most common nosocomial infection in surgical obstetric patients.[4,5,6] Gynecologic surgeries on the other hand, have similar SSI rates to other procedures in high-income countries.[7] In this institution, the prevalence rate of SSI in a 4-year study among obstetric and gynecologic patients was 12.68%.[8]

One of the major variables in the prevention of SSI is administration of surgical antibiotic prophylaxis. It is one of the tenets in the basic guideline for surgical infection control. The antibiotic recommended to prevent surgical site infections is a single dose first generation Cephalosporin administered intravenously 30 minutes to 1 hour prior to the surgical procedure.[9]

Additional treatment modality on top of the standard surgical practice may lead to a further reduction of SSI occurrence. Mupirocin ointment demonstrated potential as an adjunct to the basic surgical recommendations.[10] Topical mupirocin has excellent coverage on major skin pathogens. It increases patient compliance and has a relatively safe profile.[11] In this regard, aside from a single dose of antibiotic, about 10% of obstetrician and gynecologist prescribe application of mupirocin during each dressing.[8,12] Hence, this study would like to address this query: Is the combination of single dose Cefazolin with Mupirocin better than single dose Cefazolin alone in reducing the incidence of SSI among women undergoing elective obstetric and gynecologic procedures?

Review of Related Literature

Surgical Site Infection is classified as superficial, deep, and in organ or space. Superficial SSI involves the skin or subcutaneous tissue around the incision plus presence of either purulent drainage from the incision, organisms isolated from an aseptically obtained culture of fluid or tissue from the incision, presence of pain, swelling, and redness at the incision site. Deep SSI's involve deep soft tissues such as the fascia and muscles and presence of either purulent drainage from the incision but not from the organ or space of the surgical site. The last type is the Organ or Space SSI which is documented as presence of purulent discharge from a drain placed through the organ or space. The last two types of SSI may present with fever, localized pain, an abscess or any evidence of infection that is present either by direct examination, histopathologic or radiologic examination.[1]

The fundamental precursor for SSI emanated from microbiologic contamination from endogenous skin and vaginal flora. Microbial contamination of the wound during the procedure may be endogenous or exogenous in origin. The most frequently isolated pathogens in cases of SSI's are *Staphyloccocus aureus*, Coagulase-negative staphylococci, *Escherichia coli*, *Enterobacteraciae faecalis*, *Pseudomonas aeruginosa*, Enterobacter spp., and Klebsiella spp. These pathogens are part of the normal flora of the skin and the gastronintestinal tract.[13]

There are several factors that influence surgical wound healing and potential for infection. These include patient-related variables that are modifiable and non-modifiable. Modifiable patient-related factors include nutritional status, presence of diabetes mellitus, tobacco use, anemia and corticosteroid use. Non-modifiable factors include age and gender. Procedural-related variables include decontamination of medical devices and surgical instruments, adequate pre-operative antisepsis, choice and timing of antibiotic prophylaxis as well as length of hospital stay.[2]

Antibiotic prophylaxis is one of the strategies to prevent infectious complications associated with surgical procedures. This involves administration of an effective antimicrobial agent prior to exposure or contamination during surgery. Prophylactic antibiotic can reduce the incidence of post cesarean section infectious morbidity by as much as 75%. The risk reduction is observed in both planned and emergency cesarean delivery.[2]

The American College of Obstetrician and Gynecologists (ACOG) has issued a practice bulletin on antibiotic prophylaxis for gynecologic and obstetric procedures. The choice of an appropriate

agent for prophylaxis should take into account the following characteristics: 1) low toxicity; 2) established safety record; 3) not used routinely to treat serious infections; 4) wide spectrum of activity including the microorganisms most likely to cause infection; 5) achieves therapeutic concentration in tissues during the procedure; 6) administered for a short time; and 6) administered in a manner that will ensure its presence in the surgical sites at the time of incision.[14]

For most procedures, a first generation cephalosphorin such as Cefazolin is the drug of choice for prophylaxis. It has been most widely studied with proven antimicrobial efficacy as it has spectrum of activity against organisms commonly encountered in surgery. Aside from this, it has a desirable duration of action, reasonable safety, and of low cost. Administration of prophylactic Cefazolin prior to skin incision resulted in a decrease in both endometritis and total post cesarean infectious morbidity, compared with administration at the site of cord clamping.[9]

In a double blind, randomized trial in 2007, involving 357 women who underwent cesarean section, the administration of a single dose two grams Cefazolin intravenously 30 minutes prior to skin incision was able to prevent post-operative infectious morbidity including SSI.[9] Supporting this study, the World Health Organization (WHO) released a guideline for the prevention of SSI stating that the optimal timing for antibiotic prophylaxis administration is within 120 minutes before incision with consideration of the half-life of the antibiotic.[2] The half-life of Cefazolin is 90 to 150 minutes. Low quality evidence showed the administration of antibiotic prophylaxis at 120 minutes or 30 minutes prior skin incision has either benefit or harm to reduction of SSI rate.[9] However, the duration time of the procedure should be considered. For both obstetrical and gynecologic cases, procedures usually last 2 to 3 hours. Hence, administration of Cefazolin 30 minutes prior to incision site is recommended by numerous literature to ensure that adequate blood and tissue concentrations are present prior to start and end of the surgery wherein the body is most susceptible to bacterial contamination. Post-surgical antibiotic administration is unnecessary.[9]

According to Su Hy, et al, the use of single dose preoperative Cefazolin prophylaxis was as effective as four doses of Cefazolin for preventing serious infectious morbidity among patients who underwent hysterectomy. In this 3-year study, there were 548 patients randomized to receive either single-dose of 2 grams Cefazolin or 1-day 4- doses of 500 mg Cefazolin prophylaxis. A total of 531 completed the study. Only one of 267 patients in the single-dose group developed a trocar wound infection and one of 264 patients in the 1-day group developed vaginal cuff infection. Had a single dose of prophylactic antibiotics been administered to all patients, the antibiotic cost would have been reduced by 75 to 80%. Shortening of the duration of antibiotic prophylaxis also reduced medical costs and microorganism resistance.[15]

The same study compared the efficacy of Cefazolin and Vancomycin in preventing SSI in high-risk area for methicillin-resistant *S. aureus* (MRSA), suggested that Vancomycin is less effective than Cefazolin. Cefazolin was able to decrease SSI rate (6%) compared to Vancomycin (1.4%). For this reason, Vancomycin is often used in combination with Cefazolin at some institution with both methicillin-susceptible *S. aureus* (MSSA) and MRSA SSI's.[15]

According to the survey conducted by Reyes, obstetricians affiliated in the Philippine Obstetrical and Gynecological Society (POGS) accredited hospitals in Metro Manila resort to administering multiple antibiotics and multiple doses during and post cesarean section because of non-confidence on single course administration in terms of preventing infection. Most of the residents in all year levels from both private and government institutions prefer giving 3 to 4 courses of antibiotic intravenously, then shifted to oral and administered for 7 days. In low-risk cases, obstetricians give multiple intravenous courses and discontinue administration after 24 hours. For high-risk cases antibiotic administration was extended, shifted to oral and completed for 7 days. The obstetrician reiterated that the use of prescribing a 7-day antibiotic use was a form of defensive practice. With this treatment scheme, they are confident that surgical site infection will be prevented more effectively.[12]

In FEU-NRMF, obstetric and gynecologic consultants and residents prefer giving 3 to 4 courses of the antibiotic intravenously, after which the antibiotic is shifted to oral, and is administered for 7 days. Some obstetricians apply a topical antibiotic, like Mupirocin, to the incision site for one week, starting on third post-operative day when the initial dressing is done.

Topical antibiotics such as mupirocin, applied to surgical wounds healing by primary intention probably reduce the risk of SSI relative to no

antibiotic and no topical antiseptic use. Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. It inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transferyl-RNA (tRNA) synthethase. Due to its unique mode of action, mupirocin does not demonstrate cross-resistance with other classes of antimicrobial agents. It has a bacteriostatic property at minimum inhibitory concentrations (MIC) and bactericidal property at the higher concentrations reached when applied locally. Mupirocin is highly protein-bound and the effect of wound secretions of the MIC's of mupirocin has not yet been determined. Mupirocin has been shown to be active against susceptible strains of *S. aureus* and *Streptococcus pyogenes*. It is active against most isolates of *Staphylococcus epidermidis*. These isolates are commonly found in the skin. Eradicating these organisms from the wound site may prevent them from invading and colonizing the incision site.[16]

Hood, et al. compared Mupirocin and Neomycin citing that there was no clear evidence of a difference between Mupirocin and Neomycin in reducing risk of SSI in 99 studied participants. The quality of evidence for this outcome was rated as very low, downgraded twice for this single trial being at a high risk of attrition bias, and once for imprecision. There was no information available for the outcomes of allergic contact dermatitis, anaphylaxis and patterns of antibiotic resistance, or the secondary outcome measures of wound healing, patient satisfaction, quality of life or financial cost for either study.[17]

Hence, there is a greater potential to eradicate organisms causing SSI with the addition of Mupirocin to the recommended single dose Cefazolin. A greater reduction in the incidence of such infection can be expected. This will result to reduced physical and mental stress to the patient as well as lower cost of medical expenses.

FEU-NRMF Medical Center is a tertiary hospital in the north of the National Capital Region in Luzon. In 2018 alone, there were 535 major operations done in the Department of Obstetrics and Gynecology. Four hundred one cases were under Pay while 134 cases were under Service. Out of the total 535 cases, only 33 cases met the exclusion criteria for this study which included BMI greater than 30, operative time more than 3 hours and blood loss greater than 1.5 liters.

Significance of the Study

Administration of prophylactic antibiotic during major operations is recommended by the World Health Organization to prevent surgical site infection. A single dose prophylactic Cefazolin has been widely used. Studies showed that the efficacy is comparable to multiple doses of other recommended empiric antibiotics.

However, despite administration of prophylactic antibiotic like Cefazolin and Cefuroxime, the 4-year prevalence of surgical site infection in this institution was 12.68%. The authors would like to further reduce the incidence of SSI to 5%, similar to the worldwide incidence, or even lesser.

A topical antibiotic can aid in reducing the incidence of SSI without the systemic adverse effects that are associated with oral and intravenous antibiotic preparation. Mupirocin, a topical antibiotic has coverage against the common organisms that may contaminate surgical wounds. It may also aid in the promotion of wound healing.[10,11]

With these valuable effects, the authors would like to find out if the addition of mupirocin to single dose Cefazolin will be more efficacious in preventing the incidence of surgical site infection. Subsequently, this would lower the burden of the cost of treatment that will entail the use of broader spectrum antibiotics in treating SSI. In turn, this would also lessen the anxiety that the patient may experience due to presence of complications.

The objective of this study was to compare the efficacy of a single dose Cefazolin versus a single dose Cefazolin plus 7-day Mupirocin ointment wound application in preventing surgical site infection among women undergoing major obstetric and gynecologic abdominal surgical procedures.

MATERIALS AND METHODS

Study Design

This is a single-blinded randomized controlled trial on the efficacy of single dose Cefazolin versus single dose Cefazolin plus Mupirocin in reducing the incidence of surgical site infection among patients who underwent major obstetric and gynecologic abdominal surgical procedures.

Setting and Population

This study was conducted among private and service patients of FEU-NRMF Medical Center who were scheduled for major Obstetric and Gynecologic procedures.

Inclusion Criteria

This study included women with the following:

1. Ages between 18 to 65 years old
2. Underwent uncomplicated elective cesarean section for term pregnancy
3. Cesarean section with internal examination of $\leq$ 6 cm, intact bag of water, and exploratory laparotomy: salpingectomy, salpingostomy, oophorocystectomy, salpingoophorectomy and myomectomy and total abdominal hysterectomy with bilateral salpingoophorectomy, as well as hysterectomy.

Exclusion Criteria

Those participants with following profile were excluded.

1. Antibiotic use in the past two weeks
2. Known medical comorbities such as obesity, malignancy, diabetes mellitus, hypertension, connective tissues and immunosuppresive disease
3. For pregnant women, ruptured bag of water for $\geq$ 6 hours, thickly meconium stained amniotic fluid and multifetal pregnancy
4. History of substance abuse with tobacco, alcohol or illicit drug use
5. Has known allergy to any of the study drug

Withdrawal Criteria

Participants who after recruitment developed the following were withdrawn from study.

1. Elective operative procedure duration extended to more than 3 hours
2. Intraoperative blood loss reached more than 1.5 liters for hysterectomy and greater than 1 liter for cesarean section
3. Intraoperative bowel perforation
4. First case allergic reaction to any of the study drug
5. Expressed desire to and or voluntarily withdraws at any time during the study proper

Methodology Proper

This is a two-year prospective, randomized controlled study. Patients who underwent major obstetrical and gynecologic procedure and eligible to participate were recruited for the study. Recruitment for this study began on October 2019 and ended on July 2020. Prior to inclusion, the purpose and procedure of the study were discussed with the participants who were later asked to sign an informed consent. The participants were then randomized to their respective treatment group. Randomization was carried out using computer-generated random numbers. Participants were also stratified based on the type of surgical procedure such as obstetrical and gynecologic. Those assigned to group A were given single dose intravenous Cefazolin. For those in group B, aside from single dose intravenous Cefazolin, Mupirocin ointment was applied on their incision wound immediately post operation. All the participants were given single dose of 2 grams Cefazolin administered intravenously 30 minutes prior to surgery. For those who were assigned to the group B, 2% Mupirocin ointment was generously applied on the whole length of the incision site wound once a day after application of Povidone iodine from days 3 to 9 postoperatively which was also designated as day 1 to 7 of Mupirocin application.

Aside from private patients, those who were admitted at the service ward were included. For the participants admitted in the service ward, the primary surgeon of the operation for major gynecologic procedures was a fourth year resident, assisted by either fourth year or a third year residents. For obstetric procedures, the primary surgeon was a fourth year or third year resident. Closing of the subcutaneous tissue up to the skin was done by a second year resident for both gynecologic and obstetric procedures. The repair was done in a standardized fashion. The peritoneum was closed using Chromic 2-0 sutures with simple continuous suturing technique. The fascia was closed using Vicryl 0 suture with simple interlocking suturing technique. The subcutaneous layer was closed using Vicryl 2-0 suture using simple continuous suturing technique and the skin was closed using Vicryl 4-0 suture with subcuticular suturing technique.

All the participants were instructed on proper wound care. The wound was cleaned and dressed once a day by application of povidone iodine using cotton balls in one swipe repeated 3 times and was dressed with Tegaderm. Wound cleaning was started on the 3rd day post-operation and every day until the wound has healed. To assess for wound healing, the Southampton wound scoring system was used. The end point for wound healing was achieved once a score of 1 was obtained. The wound healing was recorded on the post-operative day follow-up with which a score of 1 was obtained. For all participants, Tegaderm with pad was applied every day after each wound cleaning.

The wound of all participants was inspected and evaluated for signs of infection from 3rd day post operation, and on subsequent days, which was on 8th, 15th, and 30th post-operative days. The evaluation included inspection for occurrence of SSI and healing. With regards to inquiry on adverse effects associated with Mupirocin, the inquiry was made on the 3rd and 8th post operation day. The expected adverse effects of Mupirocin are skin rashes, pain and pruritus on the application site. All of these are classified as acute inflammatory reactions that occur 48 to 72 hours after exposure. Those admitted in the charity ward were instructed to follow up at the out-patient department (OPD) and private patients had their follow up with their attending Physician's clinic. The residents who evaluated the wound on the follow-up days were from the second year level. Evaluation of the wound was conducted prior to application of Mupirocin ointment. Thus, ensured that the resident who assessed the wound was blinded to treatment received by the participant.

The primary endpoint of this study was gross disruption or purulent discharge at site of incision, which was closely monitored up to the 30th post-operative day. Once diagnosed with SSI, specimen from the wound discharge was sent for gram stain and culture and sensitivity and were managed with administration of the appropriate antibiotic.

A standardized data collection tool was used to gather the necessary data. The data gathered included the participants' age, BMI, type of surgical procedure, designation of the surgeon (Consultant, 4th year resident, 3rd year resident), duration of the surgery, estimated blood loss, adverse effects and time of healing.

Sample Size Calculation

The basis for the sample size computation is the formula on proportion comparing independent samples. The computation was based on the proportion 1 (P1) which is 63%, the incidence of SSI among patients given single dose Cefazolin alone as reported from the study of Reyes.[13] While proportion 2 (P2) is based on the possible absolute reduction in SSI incidence of 20%. Thereby, a decrease in SSI by possibly 83% can be expected if single dose Cefazolin will be followed up by a 7-day daily mupirocin ointment wound application. With an alpha error 5%, power of 80%, and a one-tailed alternative hypothesis, the sample size required for this study is 76 per group or a total of 152 for the two groups. However, to account for possible 20% dropout during the study, the sample size was increased to 92 per group or a total of 184 for the two groups.

Data Analysis

Results were entered and encoded using Microsoft. Data analysis was done using Stata 9.0.

Univariate analysis such mean and range were used to describe age, duration of the surgery, blood loss and time of healing.

Frequency distribution was used to describe the proportion of participants having the type of elective major Obstetric or Gynecologic abdominal surgical procedure, subjects with and without surgical site infection and proportion of subjects who experienced adverse effects.

For the comparison of the proportion of participants with SSI and occurrence of adverse effects between the 2 treatment arms, Chi-square or Fischer exact test was used. For the comparison of the mean healing time between the 2 treatment arms, the t test was used. The analysis was separately conducted for obstetric and gynecologic procedures.

Ethical Consideration

The proposal of the study underwent institutional technical and ethical review. The conduct of the study was only initiated after technical and ethical approval was obtained.

Prior to inclusion in the study, the admitting resident asked each participant to sign an informed consent. During this process, the investigator discussed the purpose and details of the study with

the participant. This ensured that the participant fully understood the methods as to how the study was conducted. Thereby, giving the participant the prerogative to refuse inclusion in the study. The participant was also allowed to withdraw at any time during the study period without incurring penalty.

The information of the participants were kept confidential. To maintain anonymity of the participants, each was assigned a number code which appeared at the right upper hand corner of their corresponding data collection form. Their names were only written on a master list with their corresponding number code. This master list was kept sealed in an envelope. The collected information was kept securely so that no unauthorized access can occur. Electronic data were stored in a password protected computer. Patient's information was not displayed where third parties can inadvertently see it. The research data were stored in a locked cabinet and password protected computer for 3 years after the study has been completed after which, all data will be destroyed and deleted.

The participants were informed that there was no monetary compensation involved. However, Mupirocin was given to the patient free of charge during the 7-day treatment. With regards to Cefazolin, this is a standard prophylactic antibiotic given to prevent SSI based on several practice guideline recommendation. It was given as part of the preoperative standard care.

In this study, there were 4 participants who developed SSI during the post- operative period. They were referred to the consultant in charge and appropriate antibiotic was prescribed. These participants were instructed to complete the antibiotic for 7 days. On follow up, after completion of the antibiotic, the infection on the incisional wound was noted to resolve. Since Surgical Site Infection is a complication of any surgical procedure, therefore the patient shouldered the expense that arose from such complication.

Development of adverse acute allergic reaction to mupirocin during the 3rd and 8th post-operative days would mean immediate discontinuation of the ointment and withdrawal of the participant from the study. Regular follow-up should be continued to ensure the patient's recovery. None of the participants developed such adverse effects.

Mupirocin ointment given to Group B was shouldered by the primary investigator. Hence, no conflict of interest exists in this study.

The contact number of the primary investigator was made available to the participants. If side effects occur, they were advised to immediately seek medical consultation with the principal investigator for the service patients or the attending Obstetrician-Gynecologist for the private patients.

RESULTS

In this study, a total 164 participants were recruited. There were 82 participants who were randomized to Cefazolin with Mupirocin group and 82 participants were assigned to the Cefazolin treatment arm. The overall age range of the participants is 19 to 68 years old, with mean age of 31.53 years. The gravidity (G) of the participants ranged from 0 to 6 with a mean of 1.90, while parity (P) ranged from 0 to 6 and a mean of 1.71. The age of gestation (AOG) has a mean of 27.81 weeks, which ranged from 0 to 41 weeks. The mean length of surgery time is 117.05 minutes, ranging from 45 to 210 minutes. The mean estimated blood loss (EBL) is 501.22 ml which ranged from 200 to 1500 ml. Healing time of abdominal incision site ranged from 8 to 30 days, with a mean of 13.59 days. With regards to the type of surgery, there were 119 (72.56 %) participants who underwent obstetric surgery while 45 (27.44%) had gynecologic surgery. (Table 1)

Stratified sampling was done wherein the stratification variable is the type of surgery which are obstetric and gynecologic. Among the obstetric cases, there were 69 (57.98%) who underwent primary Cesarean Section (CS), about 44 (36.97%) underwent repeat CS and 6 (5.04%) had CS with bilateral tubal ligation (BTL). There was no significant difference in terms of the type of obstetrical procedures that the participants had between the two treatment arms. (Table 2)

The participants' who underwent obstetrical surgical procedures were aged 19 to 40 years old, with mean age of 29 years. Their gravidity ranged from 1 to 5, with mean of 1.8. While the parity ranged from 1 to 4, with mean of 1.7. The age of gestation ranged from 34 to 41 weeks with the mean of 38.32 weeks. The mean length of surgery time is 119 minutes with range of 45 to 175 minutes. For the estimated blood loss, it ranged from 300 to 900 ml with a mean of 473.53 ml. There was no significant difference in the baseline characteristics of the participants who underwent obstetrical cases between the 2 arms. (Table 3)

Healing time of abdominal incision site ranged from 8 to 30 days with a mean of 12.87 days. Out of all obstetrics cases, only two developed SSI. While none had side effects. With regards to the comparison of outcome between the two treatment arms among patients who underwent cesarean section, there was no statistically significant difference in the mean healing time and proportion of the SSI. (Table 4). There was no adverse effect noted among all obstetric participants.

Table 1. Comparison of the means of the baseline characteristics between cefazolin with mupirocin and cefazolin among obstetric and gynecologic cases

Baseline Characteristics	Cefazolin with Mupirocin Mean (SD)	Cefazolin Mean (SD)	p-value
Age in years	32.46 (± 9.68)	30.60 (± 8.17)	0.18
Gravidity (G)	2.01 (± 1.33)	1.79 (± 1.09)	0.25
Parity (P)	1.82 (± 1.24)	1.61 (± 1.03)	0.25
Age of Gestation (AOG) in weeks	28.89 (± 16.53)	26.73 (± 17.18)	0.42
Surgery Time in minutes	118.99 (± 36.20)	115.12 (± 31.98)	0.47
Estimated Blood Loss (EBL) in ml	496.95 (± 210.28)	505.49 (± 266.09)	0.82
Statistical test done: t-test		statistically significant p-value <0.05	

Table 2. Comparison of the proportion of participants according to type of cesarean section (CS) between cefazolin with mupirocin and cefazolin among obstetric cases

Type of CS	Cefazolin with Mupirocin n (%)	Cefazolin n (%)	p-value
Primary CS	35 (56.45%)	34 (59.65%)	0.29
Repeat CS	22 (35.48%)	22 (38.60%)	
CS with BTL	5 (8.06%)	1 (1.75%)	
Statistical test done: t-test		statistically significant p-value <0.05	

Table 3. Comparison of the means of the baseline characteristics between cefazolin with mupirocin and cefazolin among obstetric cases

Baseline Characteristics	Cefazolin with Mupirocin Mean (SD)	Cefazolin Mean (SD)	p-value
Age in years	29.89 (± 4.96)	28.54 (± 3.70)	0.10
Gravidity (G)	1.97 (± 1.12)	1.65 (± 0.80)	0.08
Parity (P)	1.79 (± 0.96)	1.61 (± 0.77)	0.28
Age of Gestation (AOG) in weeks	38.2 (± 1.04)	38.4 (± 1.18)	0.23
Surgery Time in minutes	110.65 (± 35.05)	106.61 (± 29.12)	0.50
Estimated Blood Loss (EBL) in ml	478.23 (± 175.70)	468.42 (± 185.0.8)	0.77
Statistical test done: t-test		statistically significant p-value <0.05	

Table 4. Comparison of outcomes between cefazolin with mupirocin and cefazolin among obstetric cases

Outcome	Cefazolin with Mupirocin N=62	Cefazolin N=57	p-value
Surgical Site Infection n (%)	0	2 (3.51)	0.14
Healing Time $\bar{x}$ in days (SD)	13.03 (+ 5.6)	12.70 (+ 4.8%)	0.36

For the gynecologic cases, there were 16 (35.56%) who underwent Total Abdominal Hysterectomy with Bilateral Salpingooophorectomy (TAHBSO) and 29 (64.44%) underwent adnexal surgery. (Table 5). Adnexal surgery done to the participants in this study included salpingectomy, oophorocystectomy, oophorectomy and salpingo-oophorectomy.

The age of the participants who underwent gynecologic surgery ranged from 19 to 68 years old, with mean age of 37 years. The gravidity ranged from 0 to 6, with mean of 2.13. The parity ranged from 0 to 6 with mean 1.75. The mean length of surgery time is 139.11 minutes with range of 60 to 210 minutes. For the estimated blood loss, it ranged from 200 to 1,500 ml with a mean of 574.44 ml. There was no significant difference between the baseline characteristics of the participants in the two treatment arms. (Table 6).

Similar to those who underwent obstetrical surgery, the healing time of the abdominal incision site for those who had gynecologic surgery ranged from 8 to 30 days with a mean of 15.48 days. Even the number of gynecologic cases with SSI (2) was similar to those who had obstetric surgery. There was no significant difference in the mean healing time and proportion of SSI between the two treatment groups (Table 7). Among all the gynecologic cases, there were also no side effects noted to occur in both treatment arms.

The overall rate of SSI in this study is 2.45%. The surgical site infection rate was noted to be eight times higher in gynecologic procedures with 2 (4.44%) cases compared to obstetrical procedures having 2 (1.70%). There were 3 out of 82 (3.66%) cases in the Cefazolin only group as compared to only 1 out of 82 (1.22%) in the Cefazolin plus Mupirocin arm. But the difference in SSI rates between the 2 arms is

Table 5. Comparison of the proportion of participants according to type of gynecologic procedure between cefazolin with mupirocin and cefazolin

Type of Gynecologic Surgery	Cefazolin with Mupirocin n (%)	Cefazolin n (%)	p-value
TAHBSO	9 (47.37%)	10 (52.63%)	0.74
Adnexal Surgery	11 (42.31%)	15 (57.69%)	
Statistical test done: t-test		statistically significant p-value <0.05	

Table 6. Comparison of the means of the baseline characteristics between cefazolin with mupirocin and cefazolin among gynecologic cases

Baseline Characteristics	Cefazolin with Mupirocin Mean (SD)	Cefazolin Mean (SD)	p-value
Age in years	40.45 (± 15.21)	35.28 (± 12.66)	0.22
Gravidity (G)	2.15 (± 1.87)	2.12 (± 1.53)	0.95
Parity (P)	1.95 (± 1.90)	1.6 (± 1.47)	0.49
Surgery Time in minutes	144.85 (± 26.84)	134.52 (± 30.15)	0.24
Estimated Blood Loss (EBL) in ml	555 (± 291.05)	590 (± 385.14)	0.74
Statistical test done: t-test		statistically significant p-value <0.05	

Table 7. Comparison of outcomes between cefazolin with mupirocin and cefazolin among gynecologic cases

Outcome	Cefazolin with Mupirocin N=20	Cefazolin N=25	p-value
Surgical Site Infection n (%)	1 (5%)	1 (4%)	0.87
Healing Time in days (SD)	16.25 (+ 7.66)	14.88 (+ 7.47)	0.27

not statistically significant. The difference in healing time between the two treatment groups was also found to be not statistically significant. (Table 8)

There were no dropouts in this study. All the participants recruited completed the treatment allocated to them and the required 30 day follow up period. The original sample size of 76 per arm was achieved in this study since it had 82 participants per treatment group. The computed 92 participants per treatment arm was made to adjust for possible dropouts. But since there were no dropouts, the 82 participants included per treatment group in this study sufficed.

DISCUSSION

Surgical Site Infection is a common complication of all surgical cases. The overall SSI rate is 11% in low to middle income countries (LMIC). In Cesarean Section procedures, the incidence of SSI is 11.7% in the LMIC while a much lower rate was observed in Europe at 2.9%.[1] With regards to the incidence of SSI in the United States, it was reported to occur in 1.70% of hysterectomy surgeries.[7]

In this study, the surgical site infection rate for Cefazolin only group is 3.66% and 1.22% in the Cefazolin plus mupirocin group. As per procedure, the SSI rate for obstetric group is 0.84% while rate in gynecologic surgeries is significantly higher at 6.66%. Further analysis on the SSI occurrence in this study showed: 1) only 1 (1.66%) obstetric case in Cefazolin only group developed SSI, 2) about two (8.70%) gynecologic cases in Cefazolin only group had SSI occurrence, and 3) only 1 (4.55%) gynecologic case in Cefazolin plus mupirocin group had SSI. These 4 cases had similar profile in terms of surgical time ranging from 110 to 180 minutes and estimated blood loss ranging from 500 to 1000 ml. Adequate preparation of the procedure is also taken into consideration in the development of SSI as 2 of the aforestated cases were emergency procedures.

Higher incidence of SSI in emergency cases was also noted in a study by Pabitha Devi and Saravanakumar, the possible explanation why the risk of developing SSI is higher among surgery cases wherein the overall SSI rate in elective clean and clean-contaminated cases was 4.34% whereas emergency cases had 12.41%. Furthermore, this study concluded that the most common isolated microorganism from elective surgeries was *Escherichia coli* and *Proteus mirabilis* was the common isolate for those who underwent emergency cases. Therefore, first or second generation cephalosporins as surgical antimicrobial prophylaxis may not be the optimal choice of drug is emergency surgical cases.[19]

In the study of Promentilla, et al., prevalence of SSI was two times higher in the emergency obstetrical and gynecologic surgical cases compared to the elective cases. The reason for this is because the standard preoperative preparation normally done within the facility is inadequately met in emergency cases in contrast to an elective procedure. Preoperative preparations such as timed antibiotic prophylaxis, adequate antiseptic skin preparation, bowel preparation, correction of anemia or other medical problem are among the recommended practices that are usually not met in an emergency procedure. Hence, predisposition for SSI development is expected.[8]

In the present study, the incidence of SSI is 2.45% which is lower than the pooled global rate. Likewise, it is lower compared to the prevalence of SSI in this institution from 2009 to 2013 which was 12.68%.[8] The possible reason why the SSI rate in this study is lower is that the authors/investigators only included uncomplicated and low-risk cases with surgical time of less than 3 hours and estimated blood loss of less than 1000 ml for obstetric and 1500 ml for gynecologic surgical cases.

In terms of SSI occurrence, the present study showed that there is a tendency to have lesser SSI when mupirocin was added, although the difference is not statistically significant. This means that adding mupirocin in the wound care of participants

Table 8. Comparison of outcomes between cefazolin with mupirocin and cefazolin among overall obstetric and gynecologic surgical cases

Outcome	Cefazolin with Mupirocin N=82	Cefazolin N=82	p-value
Surgical Site Infection n (%)	1 (1.21)	3 (3.66)	0.32
Healing Time x in days (SD)	13.45 (± 5.74)	13.80 (± 6.33)	0.64

who underwent obstetric and gynecologic surgery did not produce any significant benefit in reducing SSI rate in low-risk cases. Similar observation was noted in a randomized clinical trial which evaluated the effect of the application of ointment including mupirocin to clean surgical wounds. Likewise, the authors of the present study also noted no difference in the overall patient satisfaction compared to the control group.[10]

The tendency to lower SSI rate with the addition of mupirocin is due to the occlusive nature of the ointment that drives the active ingredient into the skin more rapidly, as well as the bactericidal properties of mupirocin. Mupirocin's mode of action is inhibition of tRNA synthethase. This property is unique on its own as it differs from that of any available antibiotic. It has high level of activity against gram-positive cocci which are the most common pathogens isolated in SSI, while it has little effect on the normal skin microflora that contributes to the skin's natural defenses.[11,20] Heal, et al., concluded that use of a topical antibiotic such as mupirocin decreased the rate of SSI whether it is used with an antiseptic or used alone.[18]

Mupirocin used in the present study is formulated as 2% mupirocin ointment in a polyethylene glycol vehicle. An ointment base contains 80% oil and 20% water.[18] These components contribute to the occlusive nature of mupirocin. Occlusive dressing increases reepithelization by 30 to 50% compared to those who had non-occlusive dressings. An increase in collagen synthesis by 20 to 60% was also reported. Occlusive dressings increase wound healing through promotion of epithelial cell migration. Presence of a moist wound environment prevents air exposure that causes tissue desiccation leading to enhanced wound healing.[21] A Cochrane systematic review concluded that the use of antibiotic ointment such as mupirocin may have a role in accelerating wound healing in both acute and chronic conditions.[11,18]

In the present study, wound healing was a little faster in the Cefazolin only arm compared with the Cefazolin plus Mupirocin group. However, the difference is not statistically significant. This was similar to the study conducted by Dixon, et al. wherein the addition of Mupirocin ointment has no beneficial effect in terms of wound healing probably due to the increased occurrence of scar formation. The increase in scar formation observed was attributed to the increased risk of skin necrosis in the Mupirocin group, which is hypothesized to impede skin perfusion.[10] With decreased blood flow to the area of the wound, healing may not be expected to hasten. This is probably the reason why the addition of mupirocin in the present study did not significantly shorten the healing time. Although based on available literatures, there is still a limited number of studies regarding the occurrence or non-occurrence of tissue necrosis with mupirocin use.

Documented adverse effects include allergic contact dermatitis, pruritus, burning pain, dry skin and adverse scar outcomes.[10] However, these adverse effects were not observed in the present study. There are reports of increasing incidence of mupirocin resistant *Staphylococcus aureus* (MRSA) isolates.[22,23] Although, in the present study wound culture was not done.

The cost of 2 grams Cefazolin ranges from PhP904 to 1,262.00. While a 15- gram tube of mupirocin costs PhP198 to 840. Based on the participants usage, a 15- gram tube was enough to be generously applied on the incision site once a day for 7 days with an incision length of 10 cm or lesser, while additional 15-gram tube was added to those having an incision of 11 cm to 18 cm. The difference in price range of the products depended on the brand. As for the participants' total cost per treatment arm, for those participants with the Cefazolin group alone, the cost was around PhP1,262.00, and for those with additional Mupirocin on top of the 2 grams Cefazolin used with 10 cm or lesser skin incision consumed PhP 2,102.00. The cost was even higher among those with 11 to 18 cm skin incision since they spent around PhP2,942.00 for 2 grams Cefazolin plus 7-day Mupirocin ointment application. Therefore, adding Mupirocin to patients with 10 cm or lesser skin incision would mean an additional PhP840.00. While for those with skin incision of 11 to 18 cm, an additional expense of PHP 1,680.00 may be incurred. Hence, for low-risk obstetric and gynecologic surgical cases, the addition of mupirocin is not cost beneficial.

The present study was limited to uncomplicated cases. Thereby, the results of this study took into account the effect of Mupirocin as an additional modality on the incidence of SSI for low-risk cases only.

CONCLUSION

Single dose Cefazolin plus 7-day once daily application of Mupirocin ointment is comparable

to single dose of Cefazolin in preventing Surgical Site Infection in patients undergoing major low-risk Obstetric and Gynecologic surgeries. Based on present results, addition of mupirocin does not significantly lower the incidence of SSI nor improve wound healing as compared to Cefazolin alone. Hence, mupirocin as an adjunct to the Cefazolin may not be beneficial as it may contribute to additional cost and increase risk of antibiotic resistance. Therefore, addition of mupirocin in clean, uncomplicated major obstetric and gynecologic cases is not recommended.

RECOMMENDATION

Mupirocin is therefore not necessary as part of post-operative wound care among low risk surgical cases. Hence, the authors would like to recommend that single dose of Cefazolin with Mupirocin be investigated among patients undergoing major obstetric and gynecologic procedures at high risk for infection. To further investigate on the effects of mupirocin, the authors suggest inclusion of the following parameters: 1) pain on the incision site, 2) wound scar appearance, 3) ease of use, 4) overall patient satisfaction.

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