Cefoxitin Plus Doxycycline Versus Clindamycin Plus Gentamicin in Hospitalized Pelvic Inflammatory Disease Patients: An Experience from A Tertiary Hospital

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ABSTRACT

Objective: To compare length of hospital stay (LOS) and surgical rate in patients hospitalized with pelvic inflammatory disease (PID) who received either cefoxitin plus doxycycline regimen or clindamycin plus gentamicin regimen.
Methods: Medical records of patients hospitalized with PID from 2004 to 2011 were reviewed. Study population was women aged 14-40 years old who had a first-time, admitted diagnosis and a discharged diagnosis of PID. Patients who had prior hysterectomy, bilateral salpingectomy and were not sexually active were excluded. The patients received either intravenous cefoxitin (2 grams every 6 hours) plus oral doxycycline (100 mg twice a day) regimen or intravenous clindamycin (900 mg every 8 hours) plus gentamicin (240 mg once daily) regimen. Outcomes of interest were LOS and surgical rate.
Results: Of 252 eligible participants, 141 (55.95%) received cefoxitin plus doxycycline and 111 (44.05%) received clindamycin plus gentamicin. The patients receiving cefoxitin plus doxyclycline had statistically significant lower age and less number of cases of tubo-ovarian abscess (TOA) ($P<0.05$). Logistic regression showed the similar LOS and surgical rate in both groups after adjusted with age and TOA. No severe adverse effect was identified in both regimens.
Conclusion: Cefoxitin plus doxycycline regimen appears as effective as clindamycin plus gentamicin regimen for treating hospitalized PID patients in terms of LOS, surgical rate and safety profile.

Keywords: Antibiotics; cefoxitin plus doxycycline; clindamycin plus gentamicin; pelvic inflammatory disease; tubo-ovarian abscess (Siriraj Med J 2018;70: 479-483)

INTRODUCTION

Pelvic inflammatory disease (PID) is a common disease in reproductive-aged women.[1,2] Its prevalence was about 2.2 % of reproductive US population.[1] At Siriraj Hospital, the biggest tertiary hospital in Thailand, PID accounts for 3% of admitted gynaeclogical patients per year.[3] PID is a combination of two of these following clinical manifestations: endometritis, salpingitis, oophoritis, tubo-ovarian abscess and pelvic peritonitis.[4-5] PID was diagnosed by one or more of the minimum criteria: cervical motion tenderness, uterine tenderness or adnexal tenderness plus one or more of the additional criteria: oral temperature

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>38.3°C, cervical mucopurulent discharge, presence of numerous WBC on microscopy of vaginal fluid, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP) and laboratory documentation of cervical infection with N. gonorrhoeae or C. trachomatis.[4] The most common cause of PID is sexually transmitted bacterial infection, especially *Neisseria gonorrhea and Chlamydia trachomatis*.[6,7] These are also the most common pathogens of PID in Thai women.[8] However, a variety of other causative agents have been reported.[9-14] Owing to the frequent co-incidence of anaerobic bacteria, broad-spectrum antibiotics are required.[4] Late commencement as well as incomplete course of antibiotics has shown some association with infertility, chronic pelvic pain and ectopic pregnancy.[15-18]

Intravenous (IV) antibiotic regimen is recommended for patients with tubo-ovarian abscess (TOA), severe clinical signs, PID during pregnancy and poor response to out-patient regimen.[4] Due to higher severity of these conditions, their antibiotic regimens differ from those treated out-patiently.[4] Following the recommendations of the Center for Disease Control and Prevention (CDC)[4], the current first-line regimens are cefoxitin plus doxycycline or clindamycin plus gentamicin. Broad spectrum cephalosporins such as cefoxitin and ceftriaxone effectively cover *Neisseria gonorrhea*, but they fail to treat *Chlamydia trachomatis* and gram-negative anaerobes. Therefore, doxycycline must be added. Clindamycin has a high efficacy for treating anerobic bacteria whereas gentamycin is primarily used against gram-negative bacteria. As a result, clindamycin plus gentamicin regimen is more preferable for treatment of patients with TOA. However, a meta-analysis based on in-patient PID cases showed a similar cure rate between cefoxitin/cefotetan plus doxycycline and clindamycin plus gentamicin, at 92-94%.[19] At the moment, neither of the regimens has shown clear superiority.[20] Thus, the present study aims to demonstrate our experience in using these two regimens in Siriraj Hospital.

MATERIALS AND METHODS

Study design and setting

The cross-sectional study was conducted by reviewing medical charts of consecutive patients being admitted with PID in Siriraj Hospital from 2004 to 2011. Ethical approval was issued by the Siriraj Institutional Review Board (Si 272/2014).

Participants

This study is a part of our published work "Reproductive outcomes of patients being hospitalized with pelvic inflammatory disease"[18] which focused on the long-term sequelae of PID. Inclusion criteria were being 14-40 year-old women with first-time diagnosis with PID and a similar discharge diagnosis (PID or TOA). All patients underwent transvaginal ultrasonography at outpatient department. Indications of hospitalization were in accordance with the CDC guideline, including tubo-ovarian abscess (TOA), severe clinical signs, PID during pregnancy and poor response to out-patient regimen.[21] Women who had undergone hysterectomy, bilateral salpingectomy with or without oophorectomy, and who were not being sexually active were excluded.

Antibiotics regimen

Following CDC 2002 guideline[21], the recommended antibiotic regimens of which were similar to those of the current CDC guideline, either cefoxitin (2 grams every 6 hours) plus doxycycline (100 mg twice daily) regimen or clindamycin (900 mg every 8 hours) plus gentamicin (240 mg once daily) regimen were prescribed for in-patient PID cases in Siriraj Hospital. Re-evaluation of clinical response was routinely done at 48-72 hours after initiating the antibiotics.

Outcome measurement

Outcomes of interest were length of hospital stay (LOS) and need for surgical intervention. LOS >6 days is a poor prognostic indicator of PID.[22,23] Surgical treatment usually resulted from severe conditions including unstable vital signs and worsening of clinical signs.[24]

Statistical analysis

Stata version 12.1 (StataCorp LP, TX) was used to describe participants' characteristics and to demonstrate the comparison between two regimens. Descriptive statistics such as frequency (percentage), mean ± S.D. and median (min, max) were used. Chi- square test and T-test were used for the comparison. Logistic regression was used to explore association between antibiotic regimen and outcomes of interest. P value <0.05 was considered statistically significant.

RESULTS

Of 252 eligible patients, 141 (55.95%) received cefoxitin plus doxycycline and 111 (44.05%) received clindamycin plus gentamicin. Those who received cefoxitin plus doxycycline had the mean age of 24.5±9.3 years, which was significantly less than clindamycin plus gentamicin group (28.0±10.7 years) (p <0.05). Additionally, cefoxtin plus doxycycline group had significantly lower incidence of TOA (12 (8.5%) vs. 64(57.7%), p <0.001).

Other characteristics were comparable between groups, including body mass index (BMI), parity, abortion, high fever and detection of *N. gonorrhea*. Almost all participants had pelvic pain as the presenting symptom. (Table 1)

Patients in cefoxitin plus doxycycline group had lower surgical rate (4.3% vs. 8.1%) and LOS >6 days (6.4% vs. 21.6%) (Table 2). However, after adjusting for age and TOA, there was no significant association between antibiotic regimen and the outcomes of interest (p >0.05). Surgical interventions included three cases of diagnostic laparoscopy and three cases of unilateral salpingo-oophorectomy in cefoxitin plus doxycycline group, and four cases of total abdominal hysterectomy, two cases of unilateral salpingo-oophorectomy and three cases of diagnostic laparoscopy in clindamycin plus gentamicin group. No severe adverse effect of either regimen was noted.

DISCUSSION

The present study re-visits the efficacy of the two intravenous antibiotic regimens recommended by the CDC. Most baseline characteristics were comparable except that cefoxitin plus doxycycline group tended to be initiated in patients with younger age and lower severity of PID. Despite that, when taking age and TOA into consideration, cefoxitin plus doxycycline regimen and clindamycin plus gentamicin regimen resulted in similar outcomes of interest which were surgical rate and LOS >6 days. The findings were compatible with previous studies.[25-28] Moreover, like a recent Cochrane systematic review of RCTs comparing clindamycin plus aminoglycoside versus cephalosporin, the present study demonstrated no difference in adverse effects.[20]

In addition to the findings of the present study, our previous work on the same cohort reported no re-admission owing to persistent PID.[18] This contrasts to

TABLE 1. Baseline characteristics.

	Cefoxitin+Doxycycline (N=141)	Gentamicin+Clindamycin (N=111)	P-value
Age (years)	24.5±9.3	28.0±10.7	0.006
BMI (kg/m^2)	20.6±3.6	21.7±4.2	0.498
Parous women	61 (43.3%)	53 (47.8%)	0.478
Previous abortion	41 (29.1%)	35 (31.5%)	0.674
Body temperature >38.3°C	44 (31.2%)	43 (38.7%)	0.289
Pelvic pain as a chief complaint	135 (95.7%)	107 (96.4%)	0.792
Tubo-ovarian abscess	12 (8.5%)	64 (57.7%)	<0.001
Detection of *N. gonorrhea*	14/48 (29.2%)	11/48 (22.9%)	0.485

TABLE 2. Logistic regression of antibiotic regimen and outcomes.

	Cefoxitin+ Doxycycline (N=141)	Gentamicin+ Clindamycin (N=111)	P-value	cOR (95%CI)	aOR* (95%CI)
Surgical rate	6 (4.3%)	9 (8.1%)	0.199	0.50 (0.17-1.46)	0.87 (0.24-3.19)
LOS >6 days	9 (6.4%)	24 (21.6%)	<0.001	0.25 (0.11-0.56)**	0.44(0.17-1.15)

*Adjusted for age and tubo-ovarian abscess, **p=0.001

Abbreviations: aOR = adjusted odd ratios, cOR crude odd ratios, LOS = length of hospital stay

a previous study which showed a clinical cure rate at around 70 % in TOA cases treated with clindamycin plus gentamicin.[29] Cefoxitin, a third generation cephalosporin is a first-line drug for treating gonorrhea while doxycycline is used to treat chlamydial infection. For uncomplicated PID, this regimen has >90% efficacy.[25-28] Patients with TOA, which is a predictive factor of medical treatment failure[23], tended to receive clindamycin plus gentamicin due to the property of clindamycin against anaerobic bacteria and that of gentamicin for treating gram-negative bacteria. Some evidence showed that gentamicin acts synergistically with clindamycin in the treatment of *C. trachomatis*.[30] The present study supports that cefoxitin plus doxycycline can also be used effectively in patients with TOA.

Parenteral antibiotics for PID which are recommended by the CDC included Cefotetan or cefoxitin plus doxycycline, clindamycin plus gentamicin and ampicillin/sulbactam plus doxycycline.[4] Cephalosporins have been used for a long time and shown supporting evidence in treating PID, although when anaerobic bacteria infection is suspected, cefoxitin appeared more favorable.[31] Ampicillin/sulbactam plus doxycycline is an alternative regimen because of its impressive outcomes in PID patients with inflammatory masses[32] and acceptable safety.[33] Another guideline by the International Union of Sexually Transmitted Infections (IUSTI) has the same recommended first line intravenous antibiotic regimen, but different alternative regimen.[6] Instead of ampicillin/sulbactam, ofloxacin or ciprofloxacin plus metronidazole is classified as the alternative regimen.[6] Previous randomized clinical trials regarding fluoroquinolones and PID, have shown 100% efficacy in eradicating *N. gonorrhea and C. trachomatis*, but lack of anaerobic bacteria coverage. However, *N. gonorrhea* resistant to fluoroquinolone is ubiquitous in Southeast Asia.[34] World Health Organization (WHO) Gonococcal Antimicrobial Surveillance Programme (GASP) has shown that the percentage of gonococcal resistance to ciprofloxacin was 70-100% in Thailand[34], so it is not included in the local guideline.

The strengths of the present study are the homogeneity of participants in terms of ethnicity, severity, their first-time diagnosis of PID and similar discharge diagnosis. Selection bias might be diluted from the fact that all consecutive cases of patients being hospitalized were included. Nonetheless, the primary outcome was not considered from the beginning of the study. Therefore, more severe cases were in clindamycin plus gentamicin group. The well-designed comparative studies between these two regimens are needed as well as novel regimens should be further explored.

In conclusion, clindamycin plus gentamicin regimen is as effective as cefoxitin plus doxycycline regimen in terms of the length of hospital stay and surgical rate among patients hospitalized with PID.

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