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Triple Therapies Versus Clindamycin Plus Gentamicin in The Treatment of Acute Pelvic Inflammatory Disease, A Randomized Controlled Trial

Porntip Sirayapiwat MD,*
Surasith Chaithongwongwatthana MD,*
Suranan Tirawatnapong MSc.**

* *Department of Obstetrics and Gynecology,*
** *Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand*

ABSTRACT

Objective To compare the effectiveness of antibiotic regimens between triple therapies and clindamycin plus gentamicin for the treatment of women hospitalized for acute pelvic inflammatory disease (PID).

Design Prospective randomized clinical trial.

Setting Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital.

Subjects 44 non-pregnant women who were hospitalized for inpatient treatment of acute PID from April 2001 to July 2002.

Intervention Subjects were randomly assigned into two groups. Patients in group A (n=22) were given intravenous ampicillin plus gentamicin plus metronidazole (triple therapies) while the patients in the other group (group B, n=22) were given intravenous clindamycin plus gentamicin.

Main outcome measures Response rate of antibiotic regimens (triple therapies and clindamycin plus gentamicin) at 72 hours after treatment by using clinical and laboratory results which composed of severity of pain, body temperature, leukocyte counts and serum C-reactive protein (CRP) level.

Results The response rate of patients in group A was lower than in group B (54.5% versus 81.8%), but no statistical significance (p=0.10). The severity of pain and serum CRP level of patients in the group B were significant lower (p<0.01 and p=0.04, respectively), but the length of hospital stay in the both groups were not different. The need for surgical intervention in group A (27.3%) was significantly higher than in group B (0%) (p=0.02)

Conclusions For the treatment of acute PID, triple therapies and clindamycin plus gentamicin were not significantly different in the response rate at 72 hours, but the need for surgical intervention was higher in the triple therapies group.

Key Words : Pelvic inflammatory disease, antibiotics, serum CRP, randomized controlled trial

Pelvic inflammatory disease (PID) is a polymicrobial infection that may produces long term reproductive sequelae including re-infection, tubal factor infertility, ectopic pregnancy and chronic pelvic pain.

Neisseria gonorrhoeae, Chlamydia trachomatis, a variety of gram positive and gram negative anaerobic and aerobic microorganisms are the common pathogens, therefore the treatment of PID requires broad spectrum antibiotics which cover such polymicrobial pathogens. Currently, in King Chulalongkorn Memorial Hospital, the hospitalized acute PID women have been treated with triple therapies which composed of ampicillin plus gentamicin and metronidazole for many years, but there were no study about the effectiveness or response rate of this regimen. In 1993, the Center for Disease Control and Prevention (CDC) recommended the two antibiotic regimens for the treatment of hospitalized acute PID patients[1] which documented rates of clinical efficacy range from 90 to 95%.[2-4] The regimen A of CDC recommendations is the combination of intravenous cefoxitin or cefotetan plus intravenous or oral doxycycline while the regimen B is the combination of clindamycin and gentamicin given intravenously.

The purpose of this randomized clinical trial is to compare the effectiveness and the side effects between the triple therapies (ampicillin plus gentamicin plus metronidazole) and the regimen B of CDC recommendation (clindamycin plus gentamicin) for the treatment of acute pelvic inflammatory disease. We chose regimen B of CDC recommendation because the regimen A composed of intravenous or oral doxycycline, which had limitation for using in our setting. There is no intravenous form of doxycycline available in our hospital. The oral form of doxycycline is not suitable for using in hospitalized patients because most patients need to be observed in abdominal sign and prohibited oral ingestion. Moreover, its common side effect is nausea and vomiting which often already present in these patients.

Materials and Methods

Approval for the study was obtained from the Ethical Committee of the Faculty of Medicine, Chulalongkorn University before we started this trial. From 1st April 2001 to 31st July 2002, 44 patients with acute PID who were hospitalized in King Chulalongkorn Memorial Hospital were enrolled in this study. To be considered for inclusion, the patients must be more than 16 years old and give the written consent prior to enter into this study. A clinical diagnosis of acute PID was made when the patient demonstrated all of the following:[5] lower abdominal tenderness, adnexal tenderness and cervical motion tenderness. In addition, one or more of the following had to be present: oral temperature ≥ 38.3°C, abnormal cervical discharge, elevated ESR or C-reactive protein (CRP) and endocervical specimen positive for Neisseria gonorrhoeae or Chlamydia trachomatis. The patients were excluded if they had one of the following criteria: pregnant or lactation, history of hypersensitivity to penicillin, aminoglycosides, clindamycin or metronidazole, severe hepatic disease, renal impairment (serum creatinine level more than 2 mg/dl) or evidence of ruptured tubo-ovarian abscess.

After admission, a complete history was taken, included type of contraception, history of previous PID, sexually transmitted disease (STD), ectopic pregnancy, or infertility.

The severity of pelvic or lower abdominal pain was self-evaluated recorded by the patients after admission and repeated once daily, using “visual analog scale” (VAS) ranged from 0 cm. (absent) to 10 cm. (most severe pain), until the patient was discharged from the hospital.

Followed the full clinical and pelvic examination, pre-treatment investigations were obtained; included a complete blood count with differential; studies of renal and hepatic function; serological tests for syphilis; hepatitis B virus and HIV; endocervical specimens, blood and urine culture and sensitivity test; serum C-reactive protein (CRP) level. A pelvic ultrasonography was performed in each patient within 24 hours of enrollment to determine whether tubo-ovarian abscess was present.

Randomization codes were computer-generated and sealed in the envelope, then the patients were randomly assigned to treated with one of the two regimens depended on their codes (A or B). The

patients in group A (triple therapies) received intravenous therapy of 1 gm of ampicillin every 6 hours plus 5 mg. per kg. (not exceed 240 mg.) of gentamicin once daily and 500 mg of Metronidazole every 8 hours. The patients in group B were given intravenous clindamycin 600 mg.[1,6-8] every 8 hours and 5 mg. per kg. (not exceed 240 mg.) of gentamicin once daily. In both groups, the parenteral therapies were continued until the patients were afebrile for a minimum of 48 hours then all patients were given a regimen of oral doxycycline 100 mg orally every 12 hours to complete a-14-day course of therapy.

All patients were clinically evaluated by physical examination and visual analog scale daily. Any adverse drug reactions were observed and recorded and if they were severe, the given antibiotics would be stopped and changed to the other regimens.

On the third day after admission, the clinical therapeutic response was evaluated by determining all of the followings: the severity of pain (VAS), oral body temperature (BT), leukocyte counts, and serum CRP level. Serum CRP level was measured with particle enhanced immunonephelometry by BM100 (Behring Nephelometer 100 Analyzer, Frankfurt, Germany). The normal value was less than 5 mg/L.

The outcome was defined as "response" if the patient had all of the following criteria : improvement of severity of pain (reduction of VAS), defervescence (BT below 37.5°C or decrease 1°C from the admission day), leukocyte count less than 10,000 cells/mm^3, and reduction of serum CRP level more than 50% from the initial level on the admission day. [9,10] The outcome was defined as "failure" in the patients who did not meet all criteria for "response" or in whom required a therapeutic surgical procedure.

Criteria for discharge from the hospital included the absence of or minimal adnexal tenderness, afebrile for at least 48 hours and the ability to take oral therapy. The duration of hospital stay was recorded.

SPSS for Windows version 10.0 was used for data analysis. Chi square or Fisher exact test was used to evaluate the difference of proportions. The Student *t* test was performed to compare the mean values between groups. Statistical significance was defined as a *p* value of less than 0.05.

Results

Between 1st April 2001 and 31st July 2002, 44 women were enrolled in this study. 22 women were randomly allocated to ampicillin plus gentamicin plus metronidazole treatment group (group A) and the other 22 women were in clindamycin plus gentamicin group (group B). The demographic data of both groups were demonstrated in table 1.

Table 1. Demographic data

	Group A (n = 22)	**Group B (n = 22)**
Age (year) *	31.2±9.1	24.9±7.6
Nulliparous **	8 (36.4%)	12 (54.6%)
Contraception **	10 (45.5%)	12 (54.6%)
Infertility **	7 (31.8%)	4 (18.2%)
History of PID/STD **	7 (31.8%)	8 (36.4%)

* presented as mean ± SD, ** presented as number (percent)

Table 2. Microorganisms isolated from endocervical specimen

	Group A (n=22)	Group B (n=22)
E.coli	3	1
Klebsiella sp.	1	1
Beta streptococcus group B	1	1
Staphylococcus aureus	1	0
Neisseria gonorrhoeae	1	0
E.coli + Klebsiella sp.	0	1

No patient in this study used intrauterine device as a contraceptive method. The blood culture was positive in one patient and the microorganisms recovered was E. coli. There was also only one positive urine culture, group B beta streptococcus was isolated. The most common microorganism isolated from the endocervical specimen was E. coli as shown in table 2. Neisseria gonorrhoeae was recovered in one specimen.

Prior to treatment, body temperature, leukocyte counts and serum CRP level were not significantly different between the groups (table3). But the severity of pain was significant lower in group B (p=.01). The number of tubo-ovarian abscess (TOA) in group A (31.8%) was more than group B (18.2%), but no statistical significance (p=0.48). The serum CRP level was increased in 93.2% of all patients.

The clinical response were evaluated at day 3 after admission and were also shown in table 3. The body temperature and the leukocyte counts were not different between the groups. But the severity of pain assessed by VAS and serum CRP level in group B was significantly lower than in group A (p<0.01 and p=0.04, respectively). However if we calculated the improvement of VAS by subtracting the VAS of day 3 from day 0 ,the result was not different between two groups (p=0.65).

Table 3. Clinical and laboratory indices of disease severity

		Group A (n=22)	Group B (n=22)	
BT (°C) *	Day 0	38.5±0.7	38.1±0.8	p=0.31
	Day 3	37.3±0.8	36.9+0.6	p=0.17
VAS (cm.) *	Day 0	8.7±1.7	7.2±2.1	p=0.01
	Day 3	2.7±2.7	0.9±0.9	p<0.01
	Day 0 –Day 3	5.9±2.7	6.3±2.5	p=0.65
Leukocyte counts (cell/mm^3) *				
	Day 0	14017±5228	15869±6002	p=0.21
	Day 3	8249+2589	7894±1895	p=0.61
Serum CRP level (mg/L) *				
	Day 0	129.9±73.7	99.8±68.9	p=0.18
	Day 3	99.8±93.9	52.9±39.2	p=0.04
TOA **		7 (31.8%)	4 (18.2%)	p=0.48

* presented as mean ± SD, ** presented as number (percent)

Table 4. Overall outcome of patients hospitalized for PID

	Group A (n=22)	Group B (n=22)	
Outcome : response **			
All cases	12 (54.6%)	18 (81.8%)	p=0.14
Excluded TOA	9/15 (60.0%)	15/18 (83.3%)	p=0.24
Surgical intervention **			
All cases	6 (27.3%)	0	p=0.02
Excluded TOA	3/15 (20%)	0/18	p=0.08
Duration of inpatient therapy (days) *			
All cases	6.0±2.5	5.0±2.4	p=0.24
Excluded TOA	5.1±1.3	4.7±1.7	p=0.41

* presented as mean ± SD, ** presented as number (percent)

The "response" rate in group B (81.8%) was more than group A (54.6%), but no statistical significance (p=0.14) (table 4). When excluded cases which had TOA, the response rate in group A and in group B were 60.0% and 83.3% respectively. The number of patients required surgical intervention in group A was significant higher than group B (27.3% versus 0%, p=0.02). However, when excluded cases which had TOA, the less number of subjects could not detect statistical difference (20.0% in group A versus 0% in group B, p=0.08). The duration of inpatient therapy between the groups was not different. No serious side effect was noted in both groups, only one patient in group B reported watery diarrhea during treatment.

Discussion

This randomized clinical trial was conducted to compare the effectiveness of antibiotic regimen in the treatment of acute pelvic inflammatory disease. We compared the regimens between the triple therapies, which currently used in King Chulalongkorn Memorial Hospital and the clindamycin plus gentamicin regimen, which recommended by CDC. One of the limitations of this study is that we just use "Amie" media to transport the endocervical specimens for culture that may cause low positive culture. Only 25% of endocervical cultures in our study were positive for microorganisms. One specimen was positive for Neisseria gonorrhoeae and no anaerobe pathogens nor Chlamydia trachomatis was recovered. The lack of microbiological data, especially in cases that not respond to the treatment, could make the clinicians unknown whether they gave appropriate antibiotics. Hemsell DL and colleague collected both the endocervical specimens and endometrial specimens from the acute PID patients and found that mean six bacterial species were recovered from each women and N. gonorrhoeae was the most frequently recovered bacteria (47% of patients).[3]

Serum CRP is an acute-phase protein synthesized by hepatocytes, produced in response to inflammation. Its short half life (6-8 hours) allows the rapid detection of changes in inflammation. Serial measurement can be used to assess the efficacy of treatment because it rises in direct proportion to the extent of inflammation and falls rapidly in response to therapy.[9] We chose serum CRP level as one indicator of the clinical outcome because its had shown as a sensitive test in the previous studies.[9-11] Reljic M and Gorisek B[11] reported that the serum CRP level increased in 96% of the acute PID patient prior to treatment and was the more reliable indicator than leukocyte counts, BT or ESR in assessing the clinical response. Teisala K[10] found that the mean CRP levels decreased by the third day of treatment and reflecting

the clinical response to therapy faster than the serial ESR determination did. Mercer LJ, et al.[9] studied the outcome of medical treatment of TOA and reported that the serum CRP level decreased at least 20% per day below the previous day's value until return to normal level in the responders. In our study, the serum CRP level prior to treatment increased in 93.2% of the patients. On the third day of treatment, its level decreased in more than 50% from the initial level of the admission day in the response group. From our results, the serum CRP determinations might be a useful predictor of the short-term response to antibiotic therapy in cases with acute PID.

Short term clinical evaluation in our study showed a higher percentage of the response rate in the patients received clindamycin plus gentamicin (81.8%) compared with whom received triple therapies (54.6%), but not statistically significant. The overall response rate in both groups (68.2%) was lower than in the previous studies. Hemsell DL, et al.[3] reported the similar effectiveness among the three regimens of antibiotics recommended by the CDC at about 94% of response rate. The lower percentage of response rate in this study might be due to the use of different criteria. If we use the need of surgical intervention as a failure of the treatment, the response rate in the patients received clindamycin plus gentamicin regimen would be significantly higher than in the triple therapies (100% versus 72.7%, p=0.02).

The presence of abscess had impact on the rate of failure of antibiotic regimen.[3,12] Ciraru-Vignenon N and colleague[12] compared amoxycillin and clavulinic acid with ampicillin plus aminoglycoside plus metronidazole in the treatment of acute PID. They reported the similar results in both groups but the surgery for failed medical treatment in advanced stages of PID (TOA) was practiced more often in the triple therapies group. In our study, even randomization, there was a higher proportion of TOA in triple therapies group than in the other group that may cause bias. When cases with TOA were excluded from analysis, the third day response rate in the patients received clindamycin plus gentamicin and triple therapies were 83.3% and 60.0% respectively. Considering the number of patients required surgical intervention when excluded TOA cases, the percentage in the patients received triple therapies was higher than in the patients received clindamycin plus gentamicin, but no statistical difference shown (20% versus 0%, p=0.08). To test the difference, it needs more subjects in further studies.

In conclusion from our findings, for the treatment of acute PID, the short term response in both regimens were not difference, but the number of surgical intervention was higher in ampicillin plus gentamicin plus metronidazole treatment group.

To determine the appropriate antibiotic regimen for the treatment of acute PID patients in King Chulalongkorn Memorial Hospital, it requires further studies about the long-term outcome and the cost-effectiveness among the antibiotic regimens.

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