Comparison of Ceftriaxone Plus Weekly Azithromycin or Daily Ofloxacin for Outpatient Treatment of Pelvic Inflammatory Disease: a randomized clinical trial

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Abstract

Objective: To compare the efficacy of ceftriaxone plus Ofloxacin or Azithromycin for cases of pelvic inflammatory disease (PID).

Materials and Methods: This clinical terial was performed on 180 women with PID from March 2005 to March 2007 in Parastarane-Shahed Hospital. Patients with PID were randomly divided to receive injection of Ceftriaxone 250 mg plus Ofloxacin 200 mg per day or Azithromycin 1 g per week for two weeks (90 cases in each group). The degree of pain was assessed on days 7, 14, 30 and clinical cure was assessed on days 14 and 30. Statistical analysis was done based on Fisher exact test, Mann-Whitny and student t-test.

Results: From 180 patients eligible for the study, 138 cases were enrolled for protocol analysis. Significant differences were observed regarding the degree of pain between two groups. Clinical cure was 90% (70 of 78) for Azithromycin and 83.3% (50 of 60) for Ofloxacin.

Conclusion: Combination of Ceftriaxone plus weekly Azithromycin for two weeks is not only equivalent to Ceftriaxone plus daily Ofloxacin for two weeks but also seems to be better for the treatment of mild PID.

Key words: Pelvic Inflammatory Disease, Azithromycin, Ofloxacin

Introduction

Pelvic Inflammatory Disease (PID) is one of the most serious infections facing women today. Untreated or incompletely treated women may suffer from life-threatening consequences, and even adequately treated women are at much higher risk for potentially serious sequels like infertility, chronic pelvic pain, and ectopic pregnancy (1).

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One million women are treated for acute PID and about 250000 to 300000 women are hospitalized with the diagnosis of PID each year. The majority of clinically recognized cases occur in sexually active women under the age of 25 (1). Chlamidya Trachomatis, Neisseria Gonorrhoea, faculative and anaerobic microorganisms associated with Bacterial Vaginosis have all been implicated in the pathogenesis of PID (1, 2).

Many combined regimens for outpatient cases are recommended by the Center for Disease Control and Prevention (3). These are inconvenient, requiring twice per day dosing for 14 days. Azithromycin, an azalide antibiotic with a long (68 hours) half - life (4), has a spectrum of activity against Chlamydia. In recent

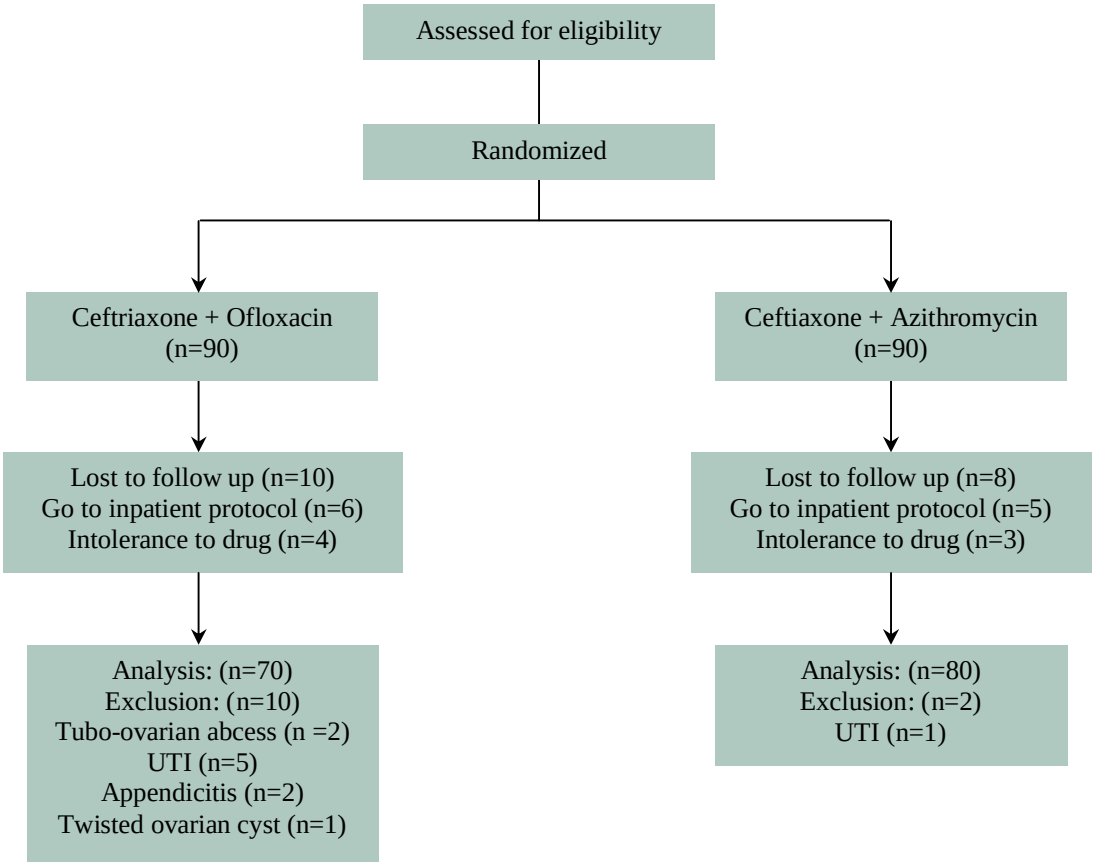

Figure1: Diagram of participating patients

investigations, Azithromycin has been very useful in many inpatient regimens (5, 6). We decided to examine the effectiveness of combination therapy with Ceftriaxone (250 mg intramuscular, single dose) plus Azithromycin (1 g per week for two weeks), versus Ceftriaxone (250 mg intramuscular, single dose) plus Ofloxacin (200 mg per day for two weeks).

Materials and methods

Women with complaint of pelvic pain were evaluated for the presence of PID from March 2005 to March 2007 in Parastarane-Shahed Hospital, Tehran. One hundred and eighty patients were enrolled in this randomized clinical trial. The study was approved by the ethical committee of the hospital according to Helsinki declaration. After being informed about the aim of the study, a written consent was taken for each patient.

Inclusion criteria for mild PID were as below:

1. pelvic pain < 30 days.
2. pelvic organ tenderness on bimanual examination.
3. leukorrhea defined as >10 WBC per hpf as viewed microscopically in secretion mixed with normal saline solution or cervicitis defined as mucopurulant, yellow or green exudates observed on the cervix.
4. normal ultrasonographic scan.

Exclusion criteria included:urinary tract infection, abscess, endometriosis, fever above 38 ^{o}C, pelvic pain more than 30 days, allergy to mentioned drugs, history of antibiotic therapy within the last week, other abdominopelvic pain causes like appendicitis, diverticulitis, ovarian cyst, oral intolerance defined as one episode of vomiting after first oral medication, and delivery, abortion and surgery within the last week.

Initial physical examination and follow up visits were performed by the same researcher. In the case of presence IUD was removed before the initial treat-

Table 1: Intervention given to each groups

Day	Intervention
0	Standard interview
	Assessment of the degree of pain (VAS & McPS)
	First endometrial biopsy
	250 mg Ceftriaxone intramuscular
	200 mg Ofloxacin per day or Azithromycin 1 gr per week
7	Second dosage treatment 200mg Ofloxacin per day or 1 gr Azithromycin per week for new week
	Standard interview
	Assessment of pain (VAS & McPS)
14	Assessment of pain (VAS & McPS)
	Standard interview
30	Assessment of pain (VAS & McPS)
	Standard interview
	Endometrial biopsy

VAS: Visual Analog Scale
McPS: McCormack Pain Scale

ment. Sexual intercourse had to be avoided during the study. A visual analog scale (VAS) (7) of pain, and the modified McCormack (8, 9) scale were used to assess the degree of pain at all visits.

So the diagnosis for mild PID was mainly clinical and the treatment was started before laboratory test reports. Patients were randomly divided in two groups. We prepared at least 200 cards written on the back of them A or B. All the patients were asked to select randomly a card from the box.

Trial in group A was: Ceftriaxone (Exir & Tehran Darou co, Iran) (250 mg intramuscular, single dose) plus Ofloxacin (Exir & Tehran Darou co, Iran) (200 mg per day for two weeks) and the trial in group B was: Ceftriaxone (250 mg intramuscular, single dose) plus Azithromycin (Exir & Tehran Darou co, Iran) (1 g per week for two weeks). For maintaining patient compliance, drugs were given to patients only for 7 days, forcing them to return and receive the reminder of the treatment (Table 1). In order to not to postpone PID treatment, we ignored the double-blind design. As a result, just the patients did not know the drug they used.

At the first visit, an endometrial biopsy was performed using Endorret plastic currete (Tasnim Gostar product Inc.) and was repeated after 30 days. Histopathologic endometritis was defined as presence of a plasma cell or more per x 120 field in the endometrial stroma plus 5 neutrophils or more per x 400 field in the endomethrial surface (10). N. gonorrhea was recognized with Thayer-Martin culture and Chlamidya antigen testing with Polymerase Chain Reaction (PCR) method was performed in all samples (11). Nugent criteria were used for detection of bacterial vaginosis on gram stain of cervical secretions (11, 12).

Primary outcome measure of this study was defined as: 60% or more reduction in the total pain score at day 7 compared with baseline (12). Secondary outcome measure was defined as: absence of pelvic discomfort and tenderness on days 14 and 30, temperature <37 and WBC <10000/ mm^3 (7).

Statistical analysis was performed with student t-test, Mann-Whitney test and Fisher exact test through SSPS 13 (SPSS Inc. Chicago IL). P <0.01 was considered as the significant level (7, 13, 14).

Results

From March 2005 to March 2007, 180 patients with mild PID were enrolled in this investigation. They were eligible for the study and were assigned to one of the treatment regimens (Table 1). Ten patients lost on follow up in the group A and eight patients in group B. Total compliance was achieved in 150 pat-

Table 2: Demographic and clinical characteristics of the study groups

	Azithromycin (n=80)	Ofloxacin (n=70)	P-Value
Mean age	30.1 ± 1.5	28.5 ± 2.1	0.42
Previous PID diagnosis	38 (47.5%)	35 (50%)	0.71
Contraceptive usage	42 (52.5%)	31 (44.2%)	0.45
Barrier usage (condom)	20 (25%)	28 (40%)	0.25
Mean McPS at day 0	10.6 ± 0.5	10.3 ± 0.42	0.45
Mean VAS at day 0	4.5 ± 0.29	4.8 ± 0.27	0.58
Median McPS at day 14	4 (2-8)	6 (1-10)	0.92
Median VAS at day 14	0.5 (0-3)	1.73 (1-5)	0.51
Median McPS at day 30	0.8 (0-4)	1.2 (1-3)	0.20
Median VAS at day 30	0	0.73 (0-5)	0.21

PID , pelvic inflammatory disease , McPS , McCormack pain scale , VAS , visual analog scale

Table 3: Cure according to different criteria

	Reduction of 60% or more		
Treatment	Per protocol	VAS	McCormack
Ofloxacin	50/60 (83.3%)	27/50 (54%)	17/50 (34%)
Azithromycin	70/80 (90%)	58/70 (82%)	35/70 (50%)
P	0.2	0.001	0.09

VAS , visual analog scale
McCormack , McCormack pain scale

ients (70 cases in group A and 80 cases in group B) (Figure 1). The mean and standard deviation of age was 30.1± 1.5 years in group A and 28.5± 2.1 years in group B with no statistical differences. But significant difference was found in pain score on day 0, 14, 30 between two groups (Table 2). Four cases of N. gonorrhea were detected in group B and twenty cases of Chlamydia were diagnosed in both groups (12 cases in group B and 8 cases in group A). All of them were cured on day 30. According to VAS the cure rate for Ofloxacin group was 54% (25/50) and for Azithromycin group was 82% (58/70) (P=0.001) (Table 3). All cases with endometritis in the first biopsy had complete cure in the second biopsy on day 30. Something interesting, four cases in group B and 3 cases in group A were diagnosed without endometritis in the first biopsy however; histological endometritis was seen in the second biopsy (Table 4). The major side effects in Ofloxacin group were malaise and gastrointestinal disturbance like intestinal distention and nausea. No adverse reaction was observed with Azithromycin.

Discussion

The initial hypothesis in this study was that Azithromycin and Ofloxacin were equivalent drugs for treating mild PID. It was mirrored the original work of *Savaris* et al as closely as possible (7, 14, 15). Despite the challenges facing the study of PID due to anaerobic organisms as a result of fact that only one-third to one-half of PID cases are attributed to N.gonorrhoea and or C.trachomatis and the fact that bacterial vaginosis, anaerobic gram-negative rods, and mycoplasma have been identified among women with PID, the microbiological efficacy of treatment regimens should be determined (16, 17, 18, 20, 21). Due to the concern of lacking anaerobic coverage with Ofloxacin, emphasized by the high rate of treatment failure among patients with nongonococal, nonclamydial PID, the Center for Disease Control and prevention suggests the optimal addition of Metronidazole (3, 19). A recent meta-analysis of 12 randomized clinical trials of Azithromycin versus Doxycyclin for treatment of PID demonstrated that the treatment regimens were equally efficacious, with

Table 4: Histologic findings in the first and second endometrial biopsies

Treatment group	First	Second	
Azithromycin			
With endometritis	68	Absence of endometritis	54
		Presence of endometritis	4
		No material available	10
Without endometritis	14	Absence of endometritis	8
		Presence of endometritis	4
		No material available	2
No material available	8	Absence of endometritis	4
		Presence of endometritis	1
		No material available	3
Ofloxacin			
With endometritis	45	Absence of endometriris	22
		Presence of endometritis	2
		No material available	21
Without endometritis	35	Absence of endometritis	18
		Presence of endometritis	3
		No material available	14
No material available	10	Absence of endometritis	3
		Presence of endometritis	0
		No material available	7

Data are number.

cure rates of 97% and 98% respectively (3). In populations that have erratic health-care seeking behavior, poor treatment compliance, or unprecictable follow-up, Azithromycin might be more costeffective because it enables the provision of a single dose of directly observed therapy (22, 23). Ofloxacin and Levofloxacin are effective treatment alternatives but are more expensive and offer no advantage in the dosage regimen. Other quinolones are not reliably effective against PID or have not been evaluated adequately. Not surprising, compliance with single dose Azithromycin therapy has been reported to be 100%. Azithromycin was found to have a high rate of clinical success, similar to that of other regimens [97% for Azithromycin monotherapy, compared with 96% for Azithromycin-Metronidazole and in our study 90% (70/78) for Azithromycin] (15). Moreover, Azithromycin provided excellent rates of eradication of C.trachomatis, N.gonorrhoea, M.hominis, and anaerobes.

Although outpatient management of mild to moderate PID is used increasingly, we have little information whether reproductive outcomes are similar to those with inpatient management using intravenous antibiotics, particularly in young, nulliparous women. We think that endometrial biopsy before and after starting treatment may be useful for describing the competence of outpatient treatment. When histological findings are considered, the rate of cure was 48.5% (15 of 35) for Ofloxacin, compared with 57.1% (24 of 42) for Azithromycin. New data show that endometritis is present in asymptomatic women. Furthermore half of patients from the PEACH Trial and five cases of 43 patients from *Savaris* trial had endometritis after end of treatment (7, 12, 16-18). In this study, the same findings were observed (Table 4).

This fact underscores the need for researches on agents to eradicate anaerobes for PID treatment. Regimens with shorter duration and monotherapy regimens are promising and may increase compliance. However, there exists limited evidence for the recommendation of alternative therapies for the treatment of anaerobic infections in PID.

Although Azithromycin provides coverage against a wide range of anaerobic and aerobic pathogens, fluoroquinolones including Ofloxacin have generally been found to have limited activity against anaerobes (24, 25). In the most recent randomized clinical trial about fluoroquinolones by Ross et al., Moxifloxacin was found to have high rates of clinical resolution (90%) and microbial cure for N. gonorrhea and other gram negative anaerobes (26).

It is believed that ideal therapeutic option would be used is single agent with proven clinical efficacy like Azithromycin (19). However known, Ofloxacin has limited activity against anaerobic microorganisms and may not be effective in all cases of PID (20, 21). In addition, there has been increasing number of reports due to clinically relevant resistance of N. gonorrhea isolates to fluoroquinolones, as well as in vitro evidence of resistance in Chlamydia isolates (21).

It is important to remember that the use of short course treatment is related to the better patient compliance. This trial like *Savaris* study (7) showed that 1 gr Azithromycin per week for two weeks is effective for mild PID and suggested that, this regimen should be considered for replacing the Ofloxacin or Doxycyclin.

Animal models may provide better insights to choose regimens for the treatment of non gonococal PID. Rapid single dose oral Azithromycin therapy has been found to prevent infertility in a mouse model of Chlamydial salpingitis. Similarly, Azithromycin was found to be more effective than Doxycyclin and Ofloxacin in the microbiological cure of C. trachomatis infection and the prevention of immunopathological upper reproductive tract damage in a macaque model of PID (27). Studies of reproductive sequelae following various PID treatment regimens in humans are needed.

In summary, focus on reproductive and gynecology morbidity, rather than on short term clinical and microbiological cure is greatly recommended. Whether currently prescribed PID antibiotic regimens are effective in prevention of subsequent reproductive morbidity is largely unknown. Arguably, long term PID complications represent the most important outcomes. Ultimately, microbe specific and optimized treatment needs to preserve fertility following PID and also recurrent and persistent infection, improving long term prognosis for women with PID.

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