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Original Research Article

A comparative study of moxifloxacin versus combination of doxycycline and metronidazole for treatment of uncomplicated pelvic inflammatory disease

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ABSTRACT

Background: Pelvic inflammatory disease (PID), a common condition among women of reproductive age caused by various aerobic and anaerobic organisms, may sometimes lead to complications like infertility, ectopic pregnancy and chronic pelvic pain. Moxifloxacin is a broad spectrum bactericidal antibiotic acting against many gram positive, gram negative aerobic organisms and anaerobes. Rapid absorption and high bioavailability allow single daily dosing and improves compliance. The present study was done to compare the clinical and microbiological outcomes in PID patients treated with conventional doxycycline- metronidazole and moxifloxacin therapy.

Methods: Women with uncomplicated PID, randomized into two groups either received 400 mg single dose of moxifloxacin daily for 14 days (group A) or doxycycline 100 mg + metronidazole 500 mg twice daily for 14 days (group B). Temperature, TLC count, ESR, CRP, microbiological assessment, Visual analogue score for pain, vaginal discharge, dyspareunia and backache were noted. The bacteriological cure was assessed by high vaginal swab for organism identification by gram stain, 10% KOH and blood sample by ELISA.

Results: Total 60 women were enrolled and randomized into two groups. There was significant reduction of CRP and improved TLC in the moxifloxacin treated group. Visual analogue scores for pain, vaginal discharge and malaise were significantly reduced in the group treated with moxifloxacin. Nausea, vomiting, metallic taste, dyspepsia and diarrhoea were complained by a significant number of patients of doxycycline + metronidazole group, in contrast to the patients receiving moxifloxacin.

Conclusions: Moxifloxacin 400 mg once daily, is effective and safe for treatment of PID.

Keywords: Doxycycline, Metronidazole, Moxifloxacin, Pelvic inflammatory disease

INTRODUCTION

PID (Pelvic Inflammatory Disease) is infection and inflammation of upper genital tract i.e., uterus, fallopian tubes and/or ovaries. It is a common condition among women, usually characterised by presence of abdominal pain and tenderness, dyspareunia, abnormal bleeding, discharge and fever. Infection is often due to bacteria ascending from endocervix to the higher reproductive tract.[1] Diagnosis is mainly from history and clinical

examination, though PID can be confirmed by laparoscopy. *Chlamydia trachomatis* is the predominant sexually transmitted organism associated with PID. Other causative organisms include *Neisseria gonorrhoeae*, Gardenella vaginalis, *H. influenza*, *Mycoplasma hominis*, *Mycoplasma genitalium* and various other aerobic and anaerobic microorganisms.[2-6]

The natural genital flora of females is so varied that determining actual causative agent is difficult. Laparoscopic studies have shown that in 30-40% of cases, PID is polymicrobial. 70% of PID cases may be non-gonococcal and non-chlamydial.

Most cases of PID are presumed to occur in 2 stages. The first stage is acquisition of a vaginal or cervical infection. This infection is often sexually transmitted and may be asymptomatic. The second stage is direct ascent of microorganisms from the vagina or cervix to the upper genital tract, with infection and inflammation of these structures.

Although uncomplicated PID may be asymptomatic, if untreated it can lead to serious complications. Three principal complications of PID are chronic pelvic pain, infertility and ectopic pregnancy.[7] Approximately 25% patients with PID complain of chronic pelvic pain. Delayed diagnosis and treatment result in an incremental increase in the risks associated with PID, particularly for women with chlamydial infections. Repeated infections and inflammations may lead to adhesions and scarring of tubes leading to infertility. Each successive episode of PID has been reported to two fold increased risk of tubal infertility. The risk of ectopic pregnancy is increased 15-50% in women with a history of PID.[8] Another serious complication of chronic PID is formation of tubo-ovarian abscess that may extend to produce pelvic peritonitis and Fitz-Hugh-Curtis syndrome (perihepatitis).[9]

Because of its polymicrobial nature, PID is treated with antibiotics covering a broad spectrum of pathogens .The optimal treatment regimen and long-term outcome of early treatment of women with subclinical PID are unknown. However, antibiotic treatment does not reverse any scarring that has already been caused by the infection. For this reason, it is critical that a woman receive care immediately if she has pelvic pain or other symptoms of PID. Additionally, a woman's sex partner(s) should be treated to decrease the risk of re-infection, even if the partner(s) has no symptoms. Although sex partners may have no symptoms, they may still be infected with the organisms that can cause PID. Prompt antibiotic treatment could prevent severe damage to the reproductive organs. Common antibiotics prescribed for PID include Azithromycin monotherapy 500 mg I.V. daily for 1-2 doses followed by 250 mg orally daily for 12-14 days or in combination with Metronidazole or 1 g orally once a week for 2 weeks in combination with ceftriaxone 250 mg IM single dose.[10,11] If allergy precludes the use of cephalosporin therapy, if the community prevalence and individual risk for gonorrhea are low, and if follow-up is likely, use of fluoroquinolones for 14 days (levofloxacin 500 mg orally once daily, ofloxacin 400 mg twice daily, or moxifloxacin 400 mg orally once daily) with metronidazole for 14 days (500 mg orally twice daily) can be considered.[12-14]

Diagnostic tests for gonorrhea must be obtained before instituting therapy, and persons should be managed as follows.

- If the culture for gonorrhea is positive, treatment should be based on results of antimicrobial susceptibility testing.
- If the isolate is determined to be quinolone-resistant *N. gonorrhoeae* (QRNG) or if antimicrobial susceptibility cannot be assessed (e.g., if only NAAT testing is available), consultation with an infectious-disease specialist is recommended.[15]

Current evidence suggests that adherence to clinical guidelines for PID diagnosis and management is less than optimal. Interventions that make it easier to manage patients and provision of the entire treatment course to the patient at the time of evaluation improved compliance. Although outpatient treatment was described as being as effective as inpatient treatment in mild-to-moderate PID, compliance with antibiotic therapy for PID is poor, particularly in adolescents and in those receiving complex, prolonged treatment regimens.

Moxifloxacin is an 8-methoxy-fluoroquinolone, characterized by a broad spectrum of antibacterial activity and bactericidal action, with good in-vitro activity against gram positive, gram negative aerobic organisms and anaerobes. It also has enhanced potential to minimize the emergence of bacterial resistance.[16-18]

Moxifloxacin also has good tissue penetration and high concentrations in clinically relevant tissues and fluids.[17] Efficacy and safety profile, the pharmacokinetic properties -including rapid absorption and high bioavailability permit once-daily dosing facilitating increased compliance among women.[19] Compared with other fluoroquinolones, moxifloxacin has better in vitro activity against *C. trachomatis*, *Mycoplasma genitalium* and anaerobic bacteria.

Study by Judlin P et al, have shown that Moxifloxacin is an effective option for the treatment of uncomplicated PID, however they have concluded that further studies in broader geographical areas with different and /or variable resistance rates are required to confirm wider applicability.[14]

This study was done to compare the clinical and microbiological outcomes in cases of uncomplicated pelvic inflammatory disease treated with conventional doxycycline- metronidazole regimen and moxifloxacin therapy.

METHODS

This is a prospective randomized parallel group study. Women (aged ≥18 years) presented to the Gynecology outpatient department of a tertiary care hospital with features of uncomplicated pelvic inflammatory disease, between June 2015-May 2016 were recruited for the study. (Uncomplicated PID was defined as PID with no pelvic or tubo-ovarian abscess on pelvic ultrasonography and at laparoscopic examination and not requiring intravenous treatment).

Inclusion criteria

Women fulfilling all three MAJOR criteria -pelvic discomfort, direct lower abdominal tenderness, adnexal and cervical motion tenderness on bimanual vaginal examination and at least one of the following MINOR criteria -pyrexia (rectal or oral temperature >38^{0}C or axillary temperature >37.5^{0}C), elevated C-reactive protein >6 mg/l, white blood cell count (WBC) ≥10 500/mm^3,laparoscopic evidence of PID, cervical infection including mucopurulent cervical discharge or presence of Gram-negative intra- cellular diplococci from the endocervix or untreated recent (<14 days) documented gonococcal or chlamydial cervicitis were included in the study.

Exclusion criteria

- Women who were pregnant or lactating,
- Those who had complicated PID (pelvic or tubo-ovarian abscess, diagnosed by pelvic
- Ultrasonography or by laparoscopic examination within 48 hours before or 24 hours after the start of therapy), those with any condition likely to require surgical intervention within 24 hours of the start of treatment.
- Hypersensitivity to any study drug, related compound or excipient
- History of tendon disorders associated with quinolones,
- History of clinically relevant cardiovascular abnormalities,
- History of epilepsy,
- Defect in glucose-6-phosphate dehydrogenase,
- Patients who had received systemic antibacterial therapy 7 days before enrolment,
- History of uterine, pelvic or abdominal surgery 30 days before treatment,
- Intolerance or inability to follow oral antibiotic regimen,
- Impaired liver function (Child-Pugh C) and/or transaminase levels more than five times
- the upper limit of normal
- Impaired renal function (creatinine clearance 50 ml/minute),
- Neutropenia (<1000/ mm^3)
- Infection with human immunodeficiency virus.
- Women who did not give consent for the study

Using a computer generated number, all women study participants were randomized to one of the two treatment groups initially, and later block randomization was done to equalize the group. Depending upon the randomization prescriptions were given for the regimens

- Group A received 400mg single dose of moxifloxacin daily for 14 days
- Group B received doxycycline 100 mg + metronidazole 500mg twice daily for 14 days.

Assessment period lasted for 6 weeks with the schedule of study visit as follows

- Pre-treatment (48 hours preceding initiation of study drug);
- During therapy (days 4-7)
- test of cure TOC (7-14 days after admission of study drug) and
- Follow up (4-6 weeks after end of therapy).

Microbiological assessments were performed on endocervical , high vaginal swab specimens and blood samples at the laboratory; culture, organism identification was performed 48 hours after start of therapy and at TOC and follow up visits. The clinical cure was assessed by Visual analogue score, Temperature, WBC count, ESR and CRP. The bacteriological cure was assessed by High vaginal swab for Organism identification by gram stain, 10% KOH and blood sample by ELISA.

Statistical analysis

The softwares used were Statistica version 6 (Tulsa, Oklahoma: StatSoft Inc., 2001) and GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007].comparison of numerical variables between the two groups was done by Student's unpaired t test and Mann Whitney U test and categorical variables was done using Fisher's exact test 2-tailed test. A p value of ≤0.05 was considered to be significant.

RESULTS

A total of 60 women were enrolled and randomized over one year, 30 to doxycycline with metronidazole regimen and 30 to moxifloxacin regimen. Compliance in the treatment policy was 100% in both groups without any dropout. Baseline characteristics like age , parity and BMI were comparable between the two groups. Past history of PID, history of IUD use was also similar (Table 1).

Table 2 shows that the baseline disease characteristics were similar in both groups. Their symptoms, sign and investigative findings were similar and indicative of uncomplicated PID. Complain like lower abdominal pain, vaginal discharge, malaise, dyspareunia and low backache were similar in both groups. Presence of disease

characterised by high CRP value, high ESR and total leucocyte count were found in both groups. Presence of infection like clue cell, positive whiff test by KOH, presence of bacteria by gram stain, culture and ELISA were found similar in both groups.

Table 1: Baseline characteristics.

Chracteristics	Group A	Group B	p value
Mean age (±SD) years	27.80 (±3.58)	27.57 (±4.51)	0.825
Mean parity (±SD)	1.93 (±1.11)	2.07 (±1.11)	0.644
BMI (±SD) kg/m^2	23.17 (±4.12)	22.93 (±3.96)	0.824
History of IUD use	7	7	1.000
Past H/O PID	17	19	0.792

Table 2: Baseline disease characteristics.

Disease characteristics	Group A	Group B	p value
VAS pain score	3.80 (±1.827)	3.97 (±1.671)	0.796
VAS vaginal discharge	5.77 (±1.331)	5.70 (±1.264)	0.894
VAS malaise	1.90 (±1.863)	1.90 (±1.863)	1.000
VAS dyspareunia	0.80 (±1.627)	0.90 (±1.539)	0.695
VAS backache	0.87 (±1.224)	0.90 (±1.155)	0.745
CRP value (±SD)	7.13 (±1.74)	6.43 (±1.22)	0.076
ESR (±SD)	15.97 (±9.29)	14.37 (±7.21)	0.459
Mean WBC ±SD (10^9/L)	7.153 (±2.339)	7.471 (±2.091)	0.581
Presence of clue cell n (%)	4 (13.33%)	4 (13.33%)	1.000
Positive Whiff test n (%)	10 (33.33%)	10 (33.33%)	1.000
Pus cell	2. 3(±2.103)	2.27 (±2.033)	0.906
Bacterial infection*			
Gram positive			
Diplococci n (%)	13 (43.33%)	12 (40.00%)	-
Gram negative rods n (%)	18 (60.00%)	20 (66.67%)	-
Gram negative			
Coccobacilli n (%)	17 (56.67%)	19 (63.33%)	-

*Bacterial infection proven by Gram stain, culture or ELISA

Table 3 shows, Visual analogue scores for pain, vaginal discharge, malaise were significantly reduced in the group treated with moxifloxacin compared to the comparator group (p 0.000). There was no statistically significant reduction between the groups when dyspareunia (p= 0.506) and backache (p= 0.079) were considered.

Efficacy analysis

As seen from Table 3, the mean CRP (post treatment) values between the two groups were significant with p value of 0.000, showing significant reduction of CRP after treatment with moxifloxacin compared to doxycycline + metronidazole. There was no statistically significant reduction of ESR after treatment with moxifloxacin compared to doxycycline + metronidazole. The mean TLC (post treatment) values between the two groups were significant with p value of 0.017 showing significant reduction of TLC occurs after treatment with moxifloxacin compared to the comparator.

Table 3: Therapeutic response between the two groups.

Disease characteristics	Group A	Group B	p value
VAS pain score	1.10 (±0.960)	2.63 (±1.426)	0.000
VAS vaginal discharge	1.40 (±1.276)	3.00 (±1.619)	0.000
VAS malaise	0.27 (±0.521)	1.67 (±1.561)	0.000
VAS dyspareunia	0.30 (±0.988)	0.43 (±0.898)	0.506
VAS backache	0.20 (±0.484)	0.57 (±0.858)	0.079
CRP value (±SD)	4.13(±0.973)	5.07 (±0.980)	0.076
ESR (±SD)	11.50(±4.47)	11.83 (±4.29)	0.459
Mean WBC ±SD (10^9/L)	6.147 (±1.814)	7.405 (±2.139)	0.581
Presence of clue cell n (%)	0	1 (3.33%)	1.000
Positive Whiff test n (%)	0	1 (3.33%)	1.00
Pus cell	0.40 (±0.675)	0.87 (±1.008)	0.121
Bacterial infection*			
Gram positive			
Diplococci n (%)	5 (16.67%)	9 (30.00%)	0.360
Gram negative rods n (%)	5 (16.67%)	10 (33.33%)	0.233
Gram negative			
Coccobacilli n (%)	6 (20.00%)	13 (43.33%)	0.094

*Bacterial infection proven by Gram stain, culture or ELISA

The p values obtained by fisher's exact 2 test for pus cells, clue cells seen in gram stain and Whiff test positivity result by KOH, after treatment showed adequate treatment efficacy with no significant difference between the two groups. Though there was reduction in bacterial load after

treatment in both groups but there was no significant difference between them with all the p values being >0.05.ELISA for IgM chlamydial antigen was carried out in both the groups. Neither of the groups showed any positivity before and after treatment.

Safety analysis

As seen from Table 4, statistically significant number of patients complained of nausea in the doxycycline and metronidazole group (73.33%) versus 16.67% in the moxifloxacin group. Though none of the subjects in Group A complained of vomiting, metallic taste or dyspepsia, 6 (20%), 17 (56%), 3 (10%) subjects from group B complained of vomiting, metallic taste and dyspepsia respectively. Incidence of diarrhoea and metallic taste were significantly more in the doxycycline and metronidazole group. Diarrhoea was complained by 2 (6.67%) group A subjects and 14 (46.67%) group B subjects. Though there is increased incidence of vomiting, flatulence, dyspepsia and headache in the group B subjects, but they are not statistically significant.

Table 4: Comparison of drug related side effects between the groups.

Drug side effects	Group A	Group B	p value
Nausea	5 (16.67)	22 (73.33)	<0.001
Vomiting	0	6 (20.00)	0.024
Flatulence	0	3 (10.00)	0.237
Dyspepsia	0	3 (10.00)	0.237
Metallic taste	0	17 (56.67)	<0.001
Diarrhoea	2 (6.67)	14 (46.67)	<0.001
Pain abdomen	5 (16.67)	7 (23.33)	0.748
Headache	3 (10.00)	10 (33.33)	0.057

DISCUSSION

The aim of this study was to compare the efficacy and safety of moxifloxacin, a new fluoroquinolone, used as monotherapy, with a first line dual combination of doxycycline plus metronidazole. This is one of the few studies in women with PID to compare these two regimens. Only women with uncomplicated PID were recruited into this study. Diagnosis was based on clinical and laboratory criteria. There were no significant differences between treatment groups in demographic characteristics. The baseline disease characteristics including history of previous PID were similar between groups and indicated a population with signs and symptoms of relatively mild to moderate PID. The incidence of IUD usage between the two groups was also not significant between the groups.

Although pathogens were isolated from a relatively low number of women, the absence of infection from the endocervix does not exclude a diagnosis of PID.[19] Diagnosis is based on clinical findings and all women included in the study met minimal criteria of the United States Centres for Disease Control for the diagnosis of PID (lower abdominal tenderness, bilateral adnexal tenderness and cervical motion tenderness.[20] Hence, while the microbiological data did not confirm the presence of a causative organism, clinical signs were strongly suggestive of a diagnosis of PID.

Efficacy analysis

An established scoring system (VAS- visual analogue score) for assessing clinical symptoms permitted an objective evaluation of severity and clinical response to treatment. Diagnosing women using accepted clinical criteria for PID, knowing that not all women have microbiological evidence of PID, enabled the results to be extrapolated to typical clinical practice. From this study it was evident that the clinical efficacy of moxifloxacin is better than the comparator regimen. Ross JD et al, in his MAIDEN study showed that clinical resolution rates with moxifloxacin (90.2%) and ofloxacin (90.7%) metronidazole group were comparable.[21] Heysteck et al, reported a clinical cure rate of 81.5% in women treated with moxifloxacin versus 83.2% in those treated with the comparator regimen.[12] Present study showed that there was reduction in bacteria after treatment with both moxifloxacin and doxycycline + metronidazole but there was no significant difference between the two groups. Present study confirmed both the drugs to be effective equally in bacterial vaginosis.

From a descriptive standpoint, the bacteriological response was slightly better in the moxifloxacin group, giving no indication of inferior efficacy for moxifloxacin compared with the combination of doxycycline plus metronidazole. Judlin et al, in MONALISA study showed similar response.[14] Present study data are in agreement with Ross et al, who reported that moxifloxacin appeared to provide at least comparable efficacy to regimens in current use.[22] Monotherapy is often associated with greater compliance than combination therapy; however, such a difference was not seen in the current study.[23] This may be due to potentially greater understanding of the importance of treatment compliance.

Safety analysis

Present study conclusions also align with Heystek et al, who found that moxifloxacin was well tolerated and associated with fewer gastrointestinal events than ciprofloxacin plus doxycycline plus metronidazole.[12] Side effect profile with single daily dose moxifloxacin was found to be better compared to doxycycline with metronidazole combination. This was supported by Dunbar-Jacob et al, (part of the PEACH study) who found low adherence to a twice daily regimen of oral doxycycline in an outpatient setting, suggesting the need to determine the effectiveness of antibiotic regimens involving longer dosing intervals.[24,25] Ball P et al, in their study showed that the type and incidence of adverse events in women treated with moxifloxacin in this study were consistent with the drug's safety profile obtained cumulatively from clinical

and post marketing studies.[26] From a safety perspective, both treatments were well tolerated and there were no major safety issues with either treatment regimen.

CONCLUSION

The management of uncomplicated PID requires broad-spectrum antibiotic regimens to cover all potential pathogens. The combination of Doxycycline and metronidazole is often used as first line therapy. However, the clinical response rate is not always satisfactory. There is always scope of more effective drug. This study confirmed that fluoroquinolones, specifically moxifloxacin, are effective and well tolerated in the treatment of uncomplicated PID.

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