Comparison of Azithromycin and Doxycycline in Treatment of Acute Uncomplicated Pelvic Inflammatory Disease

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ABSTRACT

Introduction: Pelvic inflammatory disease (PID) refers to an infectious and inflammatory disorder of the female upper genital tract. It is common among young sexually active individuals and is a major health problem both in the developed and developing countries. It is usually a polymicrobial infection, however, *Chlamydia trachomatis* (serovars D-K) is the commonest causative agent transmitted sexually. PID is diagnosed basically by history and clinical examination and the treatment is initially empiric. Doxycycline is a good old drug in use for PID and Azithromycin is a new macrolide with promising effects for same. This comparative study aimed to measure efficiency and compliance of once daily for five days Azithromycin with twice a day for 14 days Doxycycline in the treatment of mild, uncomplicated acute PID.

Methods: A descriptive cross-sectional study was conducted in randomly selected 100 consecutive outpatients with mild uncomplicated acute PID. Comparative outcome of Azithromycin and Doxycycline in correlation with reduction of amount, consistency and malodor of vaginal discharge along with reduction in fornical tenderness, compliance and frequency of adverse drug reactions was done. Comparison of categorical variables was done by chi-square test with p-value <0.05 as statistically significant.

Results: Among 100 cases 50 (50%) were treated with tablet Azithromycin and 50 (50%) with tablet Doxycycline. Comparative analysis on reduction of amount, consistency, malodor of vaginal discharge and reduction of fornical tenderness were statistically significant ($p < 0.05$), showing Azithromycin more effective than Doxycycline. Besides, compliance was better and there were less adverse drug reactions with Azithromycin.

Conclusion: Azithromycin has better efficiency and compliance over Doxycycline in the treatment of mild, uncomplicated, acute PID.

Keywords: azithromycin, chlamydia trachomatis, doxycycline, pelvic inflammatory disease, efficiency

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INTRODUCTION

Pelvic inflammatory disease (PID) refers to an infectious and inflammatory disorder of the female upper genital tract, that comprises the uterus, fallopian tubes, adjacent parametrium and the overlying peritoneum.[1] Dissemination of infection and inflammation may occur to the abdomen and perihepatic structures.[2] During the last decade, there is increasing incidence of PID among sexually active young couples especially commercial sex workers and has become a major health problem both in the developed and in developing countries.[3]

Exact incidence and prevalence of PID is still not known in Nepal and such comparative study has not been done yet. WHO in 2005, estimated around 448 million curable new cases of sexually transmitted infections (STIs) in age group 15-49 years occur annually.[4] Women of Sub-Saharan Africa and Southeast Asia, who are in resource limited regions are at increased risk of sequelae and complications. In developed countries, annual incidence of PID is around 10-20 per 1000 reproductive age group women.[5]

Pelvic inflammatory disease starts with the infection of vagina and cervix that ascends up. Commonest sexually transmitted causative agent associated with PID is *Chlamydia trachomatis* (serovars D-K). Other organisms include *Neisseria gonorrhoeae, Gardnerella vaginalis, Hemophilus influenza,* and *Anaerobes* such as *Peptococcus and Bacteroides species*.[6] PID is primarily a polymicrobial infection in almost 30-40% of cases which usually starts with an isolated infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.[7] PID may occur from a granulomatous salpingitis caused by *Mycobacterium tuberculosis* or *Schistosoma species* in some regions, and it may be commonly associated with HIV infection.[8,9]

Multiple sexual contacts, a prior history of STIs and sexual abuse are some of the risk factors for PID.[10] Surgical interventions such as curettage, endometrial biopsy and hysteroscopy breach the barrier of cervix and thereby predispose ascending infections.[11,12] Besides, broad spectrum and frequent use of antibiotics, diabetes mellitus and long term steroid treatment may predispose to PID. Infertility, ectopic pregnancy and tubo-ovarian abscess are some of the common complications of PID.[13,14]

Acute PID is basically diagnosed by history and clinical examination. Young woman with multiple sexual contacts, not using any contraception, and residing in STIs prevalent area is a classical high risk patient for PID. Around 75% patients present with abnormal vaginal discharge and around 40% present with unexpected vaginal bleeding, often post sexual intercourse. Some common physical findings are tenderness of uterus, adnexa and cervical motion. In fact there is no single conclusive test for PID however, various imaging, laboratory analysis and procedures can be performed to have the definitive diagnosis.[15-17]

In any suspected case of PID it is recommended to use broad spectrum antibiotics empirically. Chosen antibiotics need to be effective against *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, Gram-negative facultative organisms, Anaerobes, and Streptococci. Treatment also depends on the clinical presentation, complications or sequelae and culture growth whenever possible. Both oral and parenteral formulations are available for acute symptoms and for microbiologic cure. Doxycycline is the time tested oral therapy and Azithromycin is also available in recent days. After 72 hours of therapy all patients need to be reassessed to see clinical progress and compliance. Several studies have shown poor compliance with Doxycycline therapy and around 20 - 25% patients of PID remain unrecorded. Centers for disease control and prevention (CDC) recommends Azithromycin or Doxycycline as a first-line drug for the treatment of Chlamydia infection. Medical treatment with these agents is 95% effective.[18,19] In this comparative study treatment regimen considered is either tablet Azithromycin-500mg once daily for five days or tablet Doxycycline-100mg twice a day for 14 days.

The hypothesis of this study is Azithromycin better over Doxycycline in the treatment of mild, uncomplicated acute PID and the aim is to test the hypothesis and to measure the outcome in terms of efficacy and compliance.

METHODS

This study was conducted after ethical approval from a subject committee of Western Regional Hospital-Pokhara and Department of Obstetrics and Gynecology, Tribhuvan University Teaching

Table 1: Reduction of amount of vaginal discharge on examination

Drug	90-100%	80-90%	70-80%	Total	p-value
Doxycycline	17 (34%)	21 (42%)	12 (24%)	50 (100%)	0.04
Azithromycin	18 (36%)	22 (44%)	10 (20%)	50 (100%)	
Total	35 (35%)	43 (43%)	22 (22%)	100 (100%)	

Table 2: Reduction of consistency of vaginal discharge on examination

Drug	90-100%	80-90%	70-80%	Total	p-value
Doxycycline	7 (14%)	25 (50%)	18 (36%)	50 (100%)	0.021
Azithromycin	12 (24%)	22 (44%)	16 (32%)	50 (100%)	
Total	19 (19%)	47 (47%)	34 (34%)	100 (100%)	

Table 3: Reduction of malodor of vaginal discharge on examination

Drug	90-100%	80-90%	70-80%	Total	p-value
Doxycycline	17 (34%)	22 (44%)	11 (22%)	50 (100%)	0.042
Azithromycin	19 (38%)	24 (48%)	7 (14%)	50 (100%)	
Total	36 (36%)	46 (46%)	18 (18%)	100 (100%)	

Table 4: Reduction of fornical tenderness on examination

Drug	90-100%	80-90%	70-80%	Total	p-value
Doxycycline	4 (8%)	43 (86%)	3 (6%)	50 (100%)	0.012
Azithromycin	9 (18%)	30 (60%)	11 (22%)	50 (100%)	
Total	13 (13%)	73 (73%)	14 (14%)	100 (100%)	

Hospital (TUTH). Patients enrolled after written informed consent. A descriptive cross-sectional study in 100 consecutive patients in tertiary care hospital with a working hypothesis of Azithromycin is efficacious than Doxycycline in the treatment of acute uncomplicated PID.

Women of reproductive age group (15-49 years) attending Gynecology outpatient department having lower abdominal pain and abnormal per vaginal discharge with abdominal and/or pelvic organ tenderness on examination were included for the study. Anyone having pregnancy, utero-vaginal prolapse, recent history of any antibiotic use or any known allergy to study medication, temperature 38^0C/100.4^0F or higher, rebound tenderness, no clinical improvement after 72 hours of treatment were excluded. Detailed general and specific history of the patient were taken before subjected to clinical examination.

Pregnancy test with a 'test kit' was done for all enrolled patients and they were asked to micturate before clinical examination. For gynecological examination, women were kept relaxed in dorsal position with the knees flexed. Perineum inspected for any rashes, excoriation, tears or any signs of

Table 5: Compliance

Drug	Non-Compliant	Compliant
Doxycycline	5 (10%)	45 (90%)
Azithromycin	0 (0%)	50 (100%)
Total	5 (5%)	95 (95%)

Table 6: Adverse Drug Reactions

Drug	Yes	No
Doxycycline	33 (66%)	17 (34%)
Azithromycin	10 (20%)	40 (80%)
Total	43 (43%)	57 (57%)

inflammation. Per speculum (Cusco's) examination performed in a good source of light. Any abnormality in the vagina and cervix along with amount, color, consistency and odor of vaginal discharge were also noted. Per vaginal and bimanual examination was done for the assessment of uterine size, position, mobility and adnexal condition. Any suspected mass or tenderness felt in the fornices and pouch of Douglas were noted. Pain measured as per *numeric pain rating scale* who could quantify their pain in given numbers (0 to 10 for no pain, moderate pain to worst possible pain) and *verbal pain intensity scale* for those who could express but could not quantify in numbers (no pain, mild, moderate, severe, very severe and worst possible pain). Patients were randomly selected for treatment with either Doxycycline or Azithromycin and individually instructed to take the medication properly. Tablet Azithromycin 500 mg to be taken once daily with or without food for total 5 days and tablet Doxycycline 100mg to be taken twice daily for 14 days with adequate amount of water (at least 1-2 glass) remaining propped up/seated for at least 30 to 60 minutes to avoid esophageal irritation.

Both treatment group patients were followed after 72 hours and then after 14 days. As an outcome measure they were asked about any reduction of vaginal discharge (amount, consistency and malodor), reduction of fornical tenderness, compliance and adverse drug reactions of the given medication.

All data collected in a printed questionnaire and analyzed using Statistical Package for Social Sciences (SPSS) version 19. The frequency and descriptive statistics were evaluated. Comparison of categorical variables was done by Chi-square test. P value less than 0.05 was considered statistically significant.

RESULTS

Out of 100 cases 50 (50%) were treated with tablet Azithromycin and 50 (50%) with tablet Doxycycline. Comparative analysis on reduction of amount of vaginal discharge (Table 1), consistency of vaginal discharge (table 2), malodor of vaginal discharge (table 3) and fornical tenderness (Table 4) were statistically significant ($p < 0.05$), showing Azithromycin to be more effective than Doxycycline. Additionally, compliance (Table 5) was better and there were less adverse drug reactions (Table 6) with Azithromycin.

DISCUSSION

In this study reduction of amount, consistency and malodor of vaginal discharge along with reduction of fornical tenderness were statistically significant ($p < 0.05$) for Azithromycin supported by Gerbase AC et al,[20] Johora M[21] and Eckert Lo et al.[22] Comparing the five days single daily dose of Azithromycin with 14 days twice daily dose of Doxycycline, this study showed better compliance and less adverse drug reactions for Azithromycin over Doxycycline supported by Thapa S[23] and Crossby R et al.[9] Besides, Azithromycin appeared more efficacious as explained by a randomized case study done by Savaris RF et al.[19]

Our study has some limitations. Firstly, small sample size which may only be a tip of the iceberg makes it difficult to draw any conclusion. Secondly, women of reproductive age group only were taken into consideration hence, it is difficult to generalize the result. Thirdly, pain scales being subjective can have individual bias.

CONCLUSION

A Macrolide, Azithromycin has better compliance and efficiency than Doxycycline for acute uncomplicated PID. Hence, it can be concluded that Azithromycin is a better option in the treatment of mild, uncomplicated form of acute PID.

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