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# Randomized, double-blind, comparative study of oral metronidazole and tinidazole in treatment of bacterial vaginosis

Indu M. Raja, Asha Basavareddy<sup>1</sup>, Deepali Mukherjee, Bikash Ranjan Meher<sup>2</sup>

## Abstract:

**Objective:** To compare the efficacy and tolerability of oral metronidazole and tinidazole in patients with bacterial vaginosis (BV) using Amsel's criteria.

**Patients and Methods:** This was a randomized double-blind study, conducted by the Departments of Pharmacology and Gynecology of a tertiary care teaching hospital. Patients diagnosed with BV received either tablet metronidazole 500 mg twice daily for 5 days or tablet tinidazole 500 mg once daily + one placebo for 5 days and instructed to come for follow-up at the 1<sup>st</sup> week and 4<sup>th</sup> week. They were categorized as cured, partially cured, and not cured based on Amsel's criteria at the end of the study and compared between two groups using Chi-square test.

**Results:** A total 120 women were enrolled in the study, of which 114 completed the study. The treatment arms were comparable. The cure rate with low-dose tinidazole was significantly more compared to metronidazole at 4<sup>th</sup> week ( $P = 0.0013$ ), but not at 1<sup>st</sup> week ( $P = 0.242$ ). The adverse drug reactions were less with tinidazole compared to metronidazole.

**Conclusion:** Tinidazole at lower dose offers a better efficacy than metronidazole in long-term cure rates and in preventing relapses with better side effect profile.

## Key words:

Bacterial vaginosis, cure rate, metronidazole, tinidazole, tolerability

Bacterial vaginosis (BV) represents a synergistic polymicrobial syndrome, in which the normal protective lactobacilli are replaced with large quantities of commensal anaerobes (100–1000-fold above normal value) resulting in symptomatic vaginitis in many women.<sup>[1]</sup> The normal vaginal ecosystem is disrupted resulting in an overgrowth of harmful anaerobic bacteria at the expense of protective bacteria. Common anaerobic pathogens associated with BV are *Gardnerella vaginalis*, *Prevotella* species, *Mobiluncus* species, *Mycoplasma hominis*, and *Atopobium vaginalis*.<sup>[2]</sup> Women in their reproductive age group are most commonly affected by BV and present clinically as abnormal foul-smelling vaginal discharge.<sup>[3]</sup> BV has an increased susceptibility to herpes simplex virus infection, human papilloma virus infection, human immunodeficiency virus (HIV), and other sexually transmitted diseases.<sup>[4,5]</sup> It is associated with serious sequelae such as increased risk of

preterm deliveries, first trimester miscarriages, chorioamnionitis, postpartum and postabortal endometritis, and pelvic inflammatory disease affecting the quality of life in these women.<sup>[6,7]</sup>

BV treated with nitroimidazoles carries significant positive outcome. Metronidazole, a nitroimidazole antimicrobial agent, has been used in clinical medicine for more than 45 years and currently is the drug of choice for all anaerobic infections.<sup>[8]</sup> Metronidazole administered either orally or topically according to multiple dose regimen has long been established as a standard treatment of BV, with 77.9% cure rate.<sup>[9-11]</sup> However, necessity to administer the drug for longer duration potentially reduces compliance, thus increasing the risk of incomplete cure and recurrence of BV.<sup>[12]</sup>

Tinidazole is a relatively newer nitroimidazole derivative with greater antimicrobial activity than metronidazole which was used for the treatment

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Department of  
Pharmacology,  
Sri Venkateshwara  
Medical College,  
Puducherry,  
<sup>1</sup>Department of  
Pharmacology, Sri  
Devaraj Urs Medical  
College, Tamaka, Kolar,  
Karnataka, <sup>2</sup>Department  
of Pharmacology,  
All India Institute of  
Medical Sciences,  
Bhubaneswar,  
Odisha, India

## Address for correspondence:

Dr. Asha Basavareddy,  
E-mail: [dr.ashareddy@gmail.com](mailto:dr.ashareddy@gmail.com)

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of *Trichomonas vaginalis* infection.<sup>[13,14]</sup> Favorable pharmacokinetic profile and lesser side effects seen with this drug have evolved it as an alternative to metronidazole for BV.<sup>[15]</sup> Available data suggest that tinidazole is more beneficial in refractory or relapsing BV cases.<sup>[16]</sup> Tinidazole has been tried in 2 g single dose with outcome comparable with metronidazole but not well tolerated due to high dose. The standard dosage regimen for metronidazole is 500 mg twice daily for 7 days for BV. Considering that tinidazole has the potential of being more efficacious drug for BV based on its larger half-life and superior side effect profile as compared to oral metronidazole, we intended to compare the efficacy and tolerability of metronidazole 500 mg twice daily dose with 500 mg single dose of tinidazole for 5 days, as there is no comparison between these two regimens.<sup>[17]</sup>

## Patients and Methods

This was a randomized double-blind study, conducted by the Departments of Pharmacology and Gynecology of a tertiary care teaching hospital from April 2013 to May 2014. The study protocol was approved by the Institutional Ethics Committee (SVMCH/IEC/STS2012/27) and registered in clinical trial registry of India (CTRI/2014/04/004557).

After obtaining written informed consent, women with abnormal vaginal discharge and diagnosed with BV were recruited into the study. We excluded women with history of active bleeding, genital malignancies, intake of antimicrobials within 14 days, alcohol intake, and smoking. Before recruitment, pregnant and lactating women were excluded. The recruited women were subjected to detailed history taking, pelvic and vaginal examinations by a gynecologist. The patients were explained about the study and procedures involved. A case record form was maintained to collect the demographic data and to assess the clinical progress of the patients. The patients were requested to give their details regarding education, occupation of the family head, and family income per month and were scored according to modified Kuppuswamy's socioeconomic status scale which had maximum score of 29.<sup>[18]</sup> Based on the scores, they were divided as upper (26–29), upper middle (16–25), lower middle (11–15), upper lower (5–10), and lower (<5). Under strict aseptic precaution with cuscus speculum, a high vaginal swab was taken using a sterile swab (sterile swab obtained from the Department of Microbiology).

The diagnosis of BV was made using Amsel's criteria which included 4 factors: (a) Homogenous milky or creamy white vaginal discharge, (b) pH of vaginal secretion above 4.5, (c) fishy odor with or without addition of 10% KOH solution, and (d) presence of clue cells on microscopic examination.<sup>[19]</sup>

### Vaginal pH

Vaginal secretions or discharge was collected from the lateral vaginal wall with a cotton swab, and they were then transferred onto strips of pH paper (Qualigens fine chemicals, India). This was compared with the standardized colorimetric reference chart to estimate the actual pH.

### Whiff Test

A drop of vaginal discharge was mixed with 2–3 drops of 10% potassium hydroxide taken on a glass slide to look for the "fishy smell."

### Gram Stain

The vaginal discharge was smeared on a clean glass slide which was air-dried and heat fixed. It was stained by Gram's method using an acetone-alcohol (1:1) mixture as decolorizing agent, and dilute carbol fuchsin was added as the counter stain and was examined for the presence of clue cells.

If 3 of the 4 criteria were positive, the patient was taken as BV-positive.

Patients diagnosed with BV were randomly divided into two groups using random number table. Patients received either tablet metronidazole 500 mg twice daily for 5 days or tablet tinidazole 500 mg once daily + one placebo for 5 days. Both test drugs were powdered and filled into empty capsules, which were sealed in separate packets and assigned specific code number. These packets were dispensed to the patients by a nurse who was unaware of the study protocol. The principal investigator and patients were blinded in the study. Decoding of the numbers was done after the study was completed. Placebo tablets were acquired from Goodman Pharmaceuticals, Puducherry, and test drugs were purchased from similar brand to ensure the uniformity (tinidazole 500 mg from Healthy Life Pharma Pvt., Ltd., metronidazole 500 mg, JB chemical and pharmaceutical limited, Mumbai, India).

Patients were instructed about the personal hygiene and abstinence from sexual intercourse during the study period. They were also advised not to take any other medications during this period. Patients were instructed to come for follow-up at the 1<sup>st</sup> week and 4<sup>th</sup> week. Detailed vaginal examination was done to look for any vaginal discharge. The patients were examined by the gynecologist and their diagnosis was noted down. Vaginal pH, Whiff test, and Gram stain were done during the follow-up visits.

Patients were categorized as follows:

- Cured - If there was no factor positive in Amsel's criteria
- Partially cured - If any two of the factors in Amsel's criteria present
- Not cured - If 3 or more factors present.<sup>[11]</sup>

The primary endpoint of the study was to assess the number of females having complete cure with these regimens and our secondary endpoint was to evaluate the side effects with these drugs. Patients with persistent symptoms at their 1<sup>st</sup> follow-up visit were considered as relapse cases and were prescribed other antibiotics/vaginal creams such as tablet clindamycin 300 mg twice daily for 7 days or clindamycin cream 2% 5 g single applicator, and tablet secnidazole 2 g. They were excluded for the final analysis at 4<sup>th</sup> week. Adverse drug reactions were noted in both groups of patients at their 1<sup>st</sup> and 4<sup>th</sup> week follow-up visits.

### Statistical Analysis

#### Sample size

The sample size of 110 was calculated considering the cure rate of metronidazole as 70% and tinidazole as 95% using nMaster software version 1 developed by department of Biostatistics, Christian Medical College, Vellore.<sup>[11]</sup> Considering 10% lost to follow-up cases, a total sample size was 120. Data were analyzed by Chi-square test and Student's *t*-test using SPSS statistics for windows, version 17.0. SPSS Inc., Chicago; *P* < 0.05 was considered statistically significant.

### Results

The study participant allotment and follow-up are illustrated in Figure 1. The baseline characteristics of the study cases in both groups were comparable [Table 1].

Efficacy was assessed based on the clinical cure rate (by Amsel's criteria)<sup>[19]</sup> at 1<sup>st</sup> week and 4<sup>th</sup> week after the treatment [Table 2]. *P* value of overall cure rate of BV was not significant between both groups at 1<sup>st</sup> week. The cure rate with metronidazole was 91.2% and with tinidazole was 96.5%. At 4<sup>th</sup> week, the tinidazole group had significantly higher cure rates compared to metronidazole group. Thirteen patients in metronidazole group presented with either relapse or reinfection. At 4<sup>th</sup> week, the cure rate of metronidazole was 75% and tinidazole was 94.54%. The secondary aim of the study was to compare the side effects of both drugs in patients treated for BV and compared using Chi-square test [Figure 2].

### Discussion

The most common cause for vaginitis is BV which is empirically treated with metronidazole or clindamycin. Unfortunately, it is associated with only 50%–80% cure rates and high recurrence. Tinidazole, which is similar to metronidazole but with a longer half-life and more favorable side effect profile, has been used in BV in the dose of 2 g single dose with better cure rates. In this study, we have used tinidazole in low dose 5 days regimen and compared it with usual regimen of metronidazole. We screened 286 patients for BV, of which 120 were recruited. We observed that most of the patients were from lower socioeconomic class as our tertiary care hospital is situated in rural area. The first follow-up (after 1 week) was to assess the immediate cure and the second (after 4 weeks) to find out the relapse of the disease. The cure rate between metronidazole (91.2%) and tinidazole (96.5%) at the end of 1<sup>st</sup> week was not statistically significant. At 4<sup>th</sup> week, the overall

**Table 1: Comparison of metronidazole and tinidazole in bacterial vaginosis: Demographic and baseline characteristics of the study participants**

Parameter	Metronidazole (n=57)	Tinidazole (n=57)	<i>P</i>
Age group (mean±SD), years			
18-34	29.03±4.29	29.23±4.21	0.855
35-51	40.47±4.29	41.72±5.07	0.452
>51	56.71±3.45	60.5±8.52	0.293
Socioeconomic status (%)			
Upper middle	9 (15.8)	5 (8.8)	0.228
Lower middle	8 (14)	15 (26.3)	
Upper lower	29 (50.9)	23 (40.3)	
Lower class	11 (19.3)	14 (24.6)	
Number of patients with first episode of white discharge, <i>n</i> (%)	28 (49.12)	30 (52.7)	0.707
Previous history of white discharge present, <i>n</i> (%)	29 (50.9)	27 (52.7)	0.78
Patients without history of white discharge, <i>n</i> (%)	5 (8.77)	5 (8.77)	
History of use of IUD, <i>n</i> (%)	9 (15.79)	12 (21.05)	0.468
Mean pH of vagina (mean±SD)	5.9±0.62	5.6±0.59	0.36

The baseline demographic data are comparable between two groups. SD=Standard deviation, IUD=Intrauterine device

**Table 2: Comparison of metronidazole and tinidazole in bacterial vaginosis: Comparison of cure rates among the groups using Amsel's criteria**

Parameter	Metronidazole (n=57)	Tinidazole (n=57)	<i>P</i>
Follow-up at 1 <sup>st</sup> week			
Cure	52	55	0.242
Partially cured	5	2	
Not cured	0	0	
Percentage of cure rate	91.2	96.5	
Follow-up at 4 <sup>th</sup> weeks			
Cure	39	52	0.0013*
Partially cured	10	3	
Not cured	3	0	
Percentage of cure rate	75	94.54	
Mean pH at 4 <sup>th</sup> weeks	4.4±1.16	3.84±0.61	

The difference between treatment groups was not significant in the 1<sup>st</sup> week follow-up but was significant at 4<sup>th</sup> weeks follow-up. \*Chi-square test. *n*=Number of patients

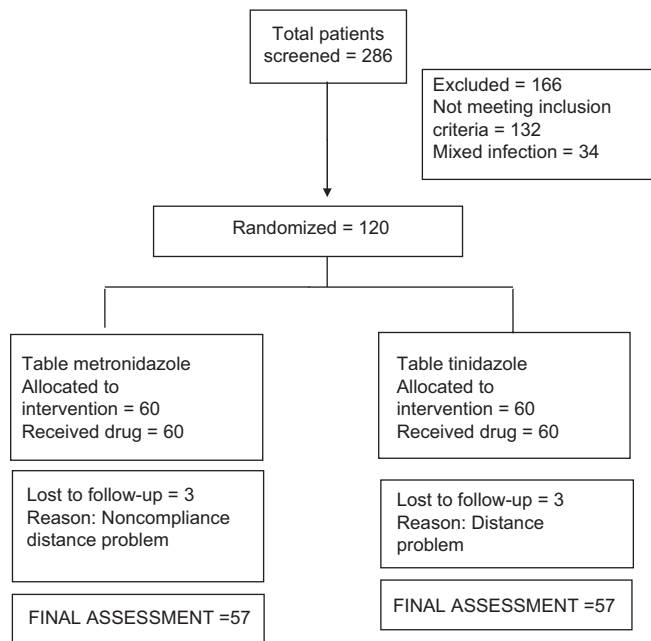


Figure 1: Consort diagram

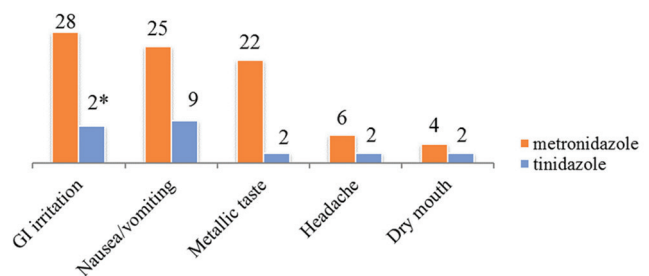


Figure 2: Adverse drug reaction profile in both groups. \*Significant difference between metronidazole and tinidazole using Chi-square test, *P* = 0.03

cure rate with metronidazole (75%) was significantly less compared to tinidazole (94.54%). This finding was comparable with some studies which showed cure rate of 95%–97% with tinidazole,<sup>[11,20]</sup> and with few other studies, the findings were contrast as they did not find any difference in the cure rates between metronidazole and tinidazole.<sup>[15]</sup> This difference could be due to varied hygienic practices followed by the patients. In our study, most of the patients were from upper lower or lower socioeconomic class. Although instruction was given to maintain personal hygiene, there could be deviation particularly for long-term follow-up (4 weeks).

We observed a lower recurrence rate with tinidazole compared to metronidazole which is comparable with other studies.<sup>[21]</sup> This could be due to tinidazole's wider spectrum of activity and better pharmacokinetic profile. Tinidazole has greater and longer antimicrobial activity compared to metronidazole, which is important in preventing recurrence of BV. The BV is associated with reduction in number of vaginal lactobacilli leading to increase in vaginal pH. After treatment, there was reduction in vaginal pH in both groups but to a greater extent with tinidazole. The vaginal pH being the key factor for increased incidence of BV in reproductive age group is better reduced with tinidazole. Many adjuvant drugs such as ascorbic acid lactobacillus strain and probiotics have been tried to decrease vaginal pH, thereby decreasing the recurrence of BV.<sup>[2,22,23]</sup> Among the study population, most of the patients had adverse drug reactions, of which majority belonged to metronidazole group and few in tinidazole group. The adverse effects were tolerable in both groups. Tinidazole is known for its better side effect profile compared to metronidazole. Many studies have shown similar finding with very few having contradictory findings where they have reported no difference between the drugs in cure rates and tolerability.<sup>[24]</sup>

Despite considerable research effort and recent advances, BV remains an enigmatic condition. Molecular tools have revealed the complex microbiology of BV but again have not found a credible single causal pathogen.<sup>[1]</sup> Until the pathogenesis of anaerobic vaginosis is completely understood, treatment will remain unsatisfactory. The clinicians use various regimens for treating BV; we have compared the two most commonly used regimens in our setup as the clarity regarding these regimens did not exist. Our study had certain constraints such as inability to do antibiotic culture sensitivity to identify the different species of organisms involved in the pathogenesis of BV in our patients. The number of lactobacilli per colony forming unit and strains was not counted. We did not find the association of BV with hormonal contraceptive use and its association with HIV and other sexually transmitted disease. Nonetheless, this randomized trial showed superiority of tinidazole in efficacy and tolerability with compared to metronidazole.

### Conclusion

Tinidazole 500 mg once daily orally offers a better efficacy than metronidazole 500 mg twice daily dose in long-term cure rates and in preventing relapses with better side effect profile.

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### Conflicts of Interest

There are no conflicts of interest.

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