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Research Article

Single-Dose Secnidazole Versus 7-Day Metronidazole for Treatment of Bacterial Vaginosis in Non-Pregnant Women – A Non-Inferiority Randomized Controlled Trial

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Abstract

Objective: *This study aims to evaluate the efficacy and safety of single-dose secnidazole in comparison to the standard 7-day course of metronidazole in treatment of BV in non-pregnant women.*

Methods: *The current randomized controlled trial was conducted at Al Zahraa hospital, Jeddah, KSA during the interval between September 2016 and July 2018. The study included non-pregnant women with a diagnosis of BV by presence of at least 3 out of the 4 Amsel's Criteria. Diagnosis was objectively confirmed by Gram staining. A Nugent's score ≥ 7 of Gram staining should be present to diagnose BV in included women. Participating women were randomly allocated into one of the two groups: group I, included women who received oral secnidazole 2 g in a single dose, and group II, included women who received oral metronidazole 500 mg twice per day for 7 days. Recruited women were evaluated on days 7, 14 and 28 after initiation of treatment both clinically and bacteriologically.*

Results: *The results showed that single-dose secnidazole treatment was non-inferior to the 7-day metronidazole treatment course, as the clinical, bacteriological and composite cure rates were all comparable in both groups of women on days 7, 14 and 28 after initiation of treatment. As regards the adverse effects, headache was encountered in a significantly higher proportion of women in group I [Secnidazole] when compared to women of group II [Metronidazole]. Nausea, metallic taste, and abdominal pain were encountered in a significantly higher rates among women of group II [Metronidazole] when compared to those of group I [Secnidazole].*

Conclusion: *Single-dose secnidazole treatment seems to be effective and safer alternative to the standard 7-day course of metronidazole in treatment of BV in non-pregnant women.*

Keywords: Secnidazole – metronidazole – bacterial vaginosis - vaginitis

Introduction

Bacterial vaginosis (BV) is a common condition that is estimated to affect up to 75% of women [1]. The underlying etiology remains highly unclear. Vaginal bacterial flora imbalance, with reduction in Lactobacilli and dominance of anaerobes (e.g. Gardnerella vaginalis) has a key role in pathogenesis of BV [2]. BV is irritant to women due to the unpleasant odor and discharge. In addition, BV was shown to be associated with adverse effects if untreated, including preterm labor and prelabor rupture of the membranes during pregnancy [3], postoperative vault infection in women undergoing hysterectomy [4], and acute pelvic inflammatory disease (PID) [4]. Therefore, treatment of BV is essential for both women's satisfaction and prevention of such adverse sequelae. The treatment of BV relies on anti-microbial agents which both have good activity against anaerobes (particularly Gardnella vaginalis) and have no activity against Lactobacilli, in order to restore the normal balance between those flora. Metronidazole, both orally and vaginally, have been long used effectively for such a target [5,6]. The metronidazole-related side effects are associated, however, with high rates of cessation of medication before completing the course of treatment, posing women to incomplete cure and multiple recurrences [6]. Secnidazole is a second-generation 5-nitroimidazole with a good activity against anaerobes and a longer half-life than metronidazole [7]. Several previous studies have shown the efficacy of secnidazole in treatment of BV [8-10]. This study aims to evaluate the efficacy and safety of single-dose secnidazole in comparison to the standard 7-day course of metronidazole in treatment of BV in non-pregnant women; in order to add to the body of evidence needed to have a US Food and Drug Administration (FDA) approval.

Methods

The current randomized controlled trial was conducted at Al Zahraa hospital, Jeddah, KSA during the interval between September 2016 and July 2018. The study protocol was in agreement to the Helsinki declaration of Ethical Medical Research [last updated in Brazil 2013] and had been

approved by the Ethical Committee of Al Zahraa hospital, Jeddah, KSA. The study included non-pregnant women with a diagnosis of BV by presence of at least 3 out of the 4 Amsel's Criteria [increased homogeneous thin vaginal discharge, pH of vaginal discharge > 4.5, amine odor on application of potassium hydroxide on vaginal discharge, and presence of clue cells on wet mount preparation] [11]. Diagnosis was objectively confirmed by Gram staining. A Nugent's score [12] ≥ 7 of Gram staining should be present to diagnose BV in included women. Women with chronic comorbidities that might affect immunity (e.g. diabetes mellitus, chronic glucocorticoid treatment) and those who had hypersensitivity to either metronidazole or secnidazole were not recruited. Participating women signed informed written consent and were randomly allocated (using computer-generated system) into one of the two groups: group I, included women who received oral secnidazole 2 g in a single dose [Secnid 500mg, Batterjee Pharmaceutical, KSA]; and group II, included women who received oral metronidazole 500 mg twice per day for 7 days [Flagyl® 500 mg, Sanofi France]. Random allocation was concealed to both women and the investigator, and only released after recruitment. Recruited women were evaluated on days 7, 14 and 28 after initiation of treatment. Evaluation included both clinical [enquiring about symptoms of BV and adverse effects, examination and evaluation of Amsel's criteria] and bacteriological [Gram staining and Nugent's scoring]. Clinical cure was defined when no symptoms were reported by the patient, and when there were ≤ 2 of Amsel's criteria. Bacteriological cure was defined when Nugent's score was ≤ 3. Composite cure was defined when both clinical and bacteriological cure was found in the same patient.

Sample Size Justification

Sample size was calculated using the Online Power and Sample Size Calculator, setting the power (1-β) at 0.8 and the type-1 error (α) at 0.05. Data from a previous study [13] showed that the cure rates for secnidazole and metronidazole groups were 58.3% and 57.8% respectively. Calculation according to these values, setting the non-inferiority margin at 0.10, produces a minimal sample size of 273 women in each group. Assuming a drop-out rate of 10%, a total sample size of 602 women was estimated.

Statistical Methods

Statistical analysis was performed using MedCalc® version 7.0. Difference between two independent metric variables was analyzed using independent student's t-test as well as mean difference and its 95% confidence interval. Difference between two categorical variables was analyzed using chi-squared test as well as risk ratio and its 95% confidence interval. Intention-to-treat analysis was adopted in all calculations. Significance level was set at 0.05.

Results

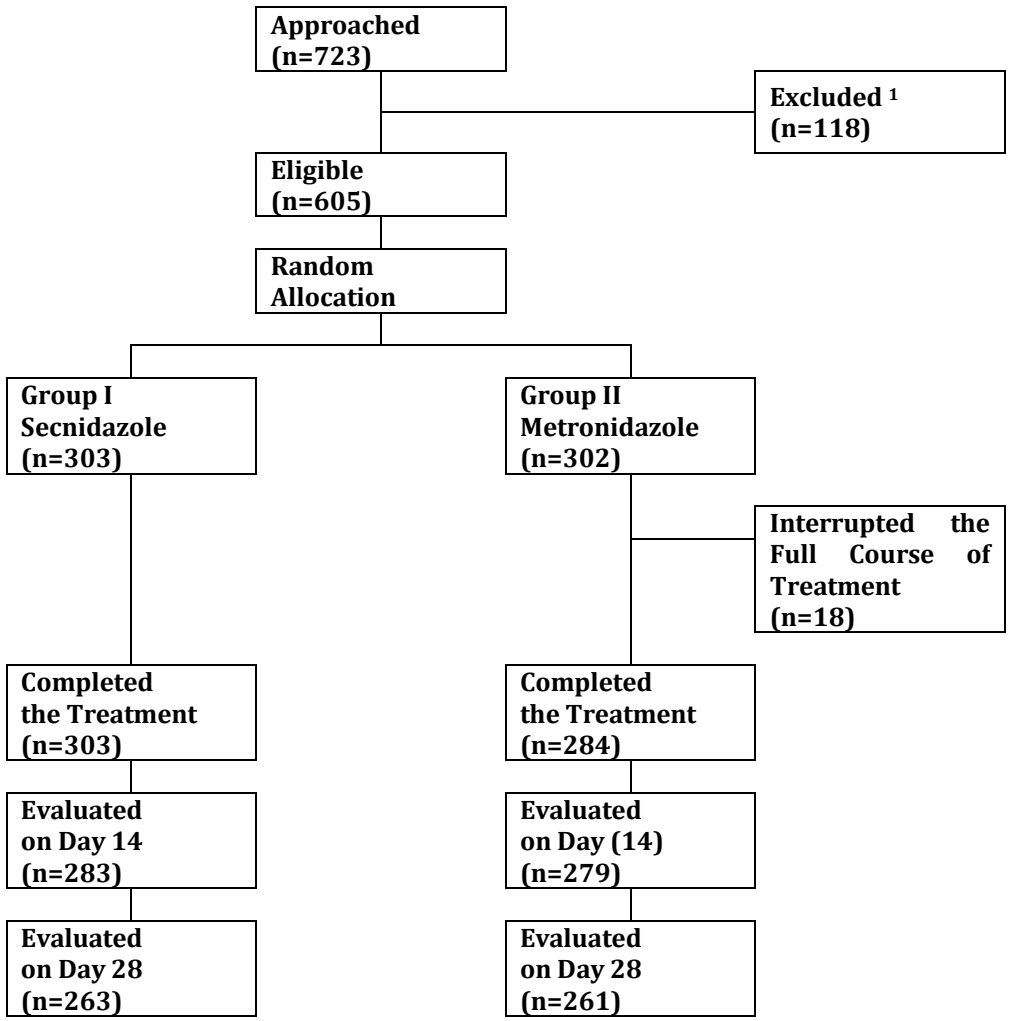
Figure-1 shows a flow-diagram of the study course. A total of 605 women were recruited and randomly allocated into one of the two groups: group I [Secnidazole] (n=303); and group II [Metronidazole] (n=302). There were no significant differences between women of both groups regarding the age, body mass index (BMI), parity and the Amsel's criteria for diagnosis of BV (table 1).

	Group I [Secnidazole] (n=303)	**Group II [Metronidazole] (n=302)**	**MD/RR (95% CI)**	***P***
Age (years)	38.4 ± 8.9	37.8 ± 9.01	-0.6 (-2.1 to 0.41)	0.409 [1]
BMI (kg/m²)	29.6 ± 6.7	29.2 ± 6.3	-0.4 (-1.4 to 0.6)	0.436 [1]
Nulliparity	34 (11.2%)	41 (13.6%)	0.83 (0.54 to 1.27)	0.379 [2]
Initial Amsel's Criteria **3 out of 4** **4 out of 4**	 187 (61.7%) 116 (38.3%)	 168 (55.6%) 134 (44.4%)	1.11 (0.97 to 1.27)	0.128 [2]
Data presented as mean ± standard deviation; or frequency (percentage) BMI body mass index (calculated as weight [kg] divided by squared height [m²]) MD (95% CI) mean difference and its 95% confidence interval RR (95% CI) risk ratio and its 95% confidence interval 1 Analysis using independent student's t-test 2 Analysis using chi-squared test				

Table 1: Difference between Groups regarding Initial Characteristics.

composite cure rates were all comparable in both groups of women on days 7, 14 and 28 after initiation of treatment (table-2, figure-2).

The results showed that single-dose secnidazole treatment was non-inferior to the 7-day metronidazole treatment course, as the clinical, bacteriological and



1 Excluded for not fulfilling the eligibility criteria

Figure 1: Flow-Diagram of Study Course.

	Group I [Secnidazole] (n=303)	Group II [Metronidazole] (n=302)	RR (95% CI)	*P* 1
Day 7				
Clinical Cure	237 (78.2%)	229 (75.8%)	1.03 (0.95 to 1.13)	0.485
Bacteriological Cure	228 (75.2%)	221 (73.2%)	1.03 (0.94 to 1.12)	0.561
Composite Cure	213 (70.3%)	209 (69.2%)	1.02 (0.91 to 1.14)	0.770
Day 14				
Clinical Cure	231 (76.2%)	224 (74.2%)	1.03 (0.94 to 1.13)	0.556
Bacteriological Cure	221 (72.9%)	211 (69.9%)	1.04 (0.94 to 1.15)	0.403
Composite Cure	201 (66.3%)	198 (65.5%)	1.01 (0.9 to 1.13)	0.841
Day 28				
Clinical Cure	224 (73.9%)	217 (71.9%)	1.03 (0.93 to 1.13)	0.566
Bacteriological Cure	207 (68.3%)	201 (66.6%)	1.03 (0.92 to 1.15)	0.644
Composite Cure	197 (65.0%)	191 (63.2%)	1.03 (0.91 to 1.16)	0.650

Data presented as frequency (percentage)
RR (95% CI) mean difference/risk ratio and their 95% confidence interval
1 Analysis using chi-squared test

Table 2: Difference between Groups Clinical and Bacteriological Cure.

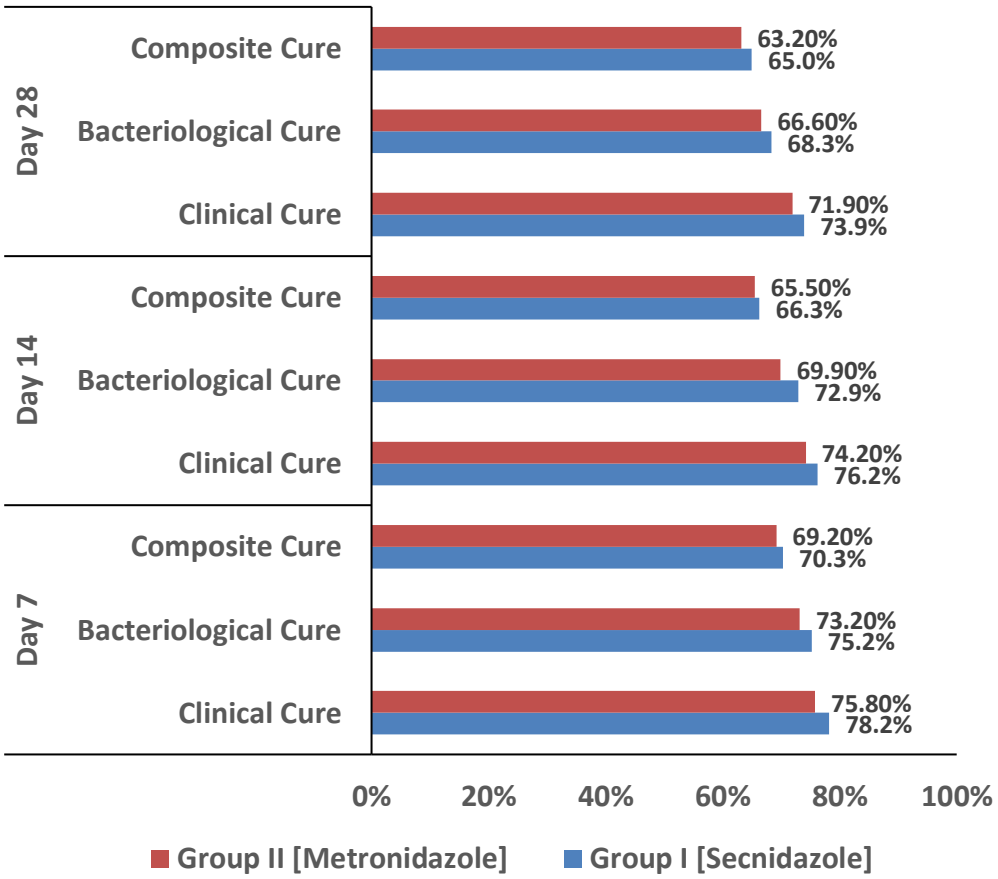


Figure 2: Bar-Chart showing Difference between Groups regarding Cure Rates

abdominal pain were encountered in a significantly higher rates among women of group II [Metronidazole] when compared to those of group I [Secnidazole] (table 3).

As regards the adverse effects, headache was encountered in a significantly higher proportion of women in group I [Secnidazole] when compared to women of group II [Metronidazole] [11 (3.6%) vs. 2 (0.7%), respectively, RR 5.48 95% CI (1.23 to 24.52)]. Nausea, metallic taste, and

	Group I [Secnidazole] (n=303)	Group II [Metronidazole] (n=302)	RR (95% CI)	*P* [1]
Nausea	6 (2.0%)	23 (7.6%)	0.26 (0.11 to 0.63)	0.001
Vomiting	2 (0.7%)	9 (3.0%)	0.22 (0.05 to 1.02)	0.067
Abdominal Pain	3 (1.0%)	14 (4.6%)	0.21 (0.06 to 0.74)	0.007
Metallic Taste	5 (1.7%)	84 (27.8%)	0.06 (0.02 to 0.14)	<0.001
Headache	11 (3.6%)	2 (0.7%)	5.48 (1.23 to 24.5)	0.012
Treatment Interruption	0 (0.0%)	18 (6.0%)	NE	<0.001
Side effects	0 (0.0%)	11 (3.6%)	NE	0.002
Inefficacy	0 (0.0%)	4 (1.3%)	NE	0.131
Other causes	0 (0.0%)	3 (1.0%)	NE	0.246
Data presented as frequency (percentage) RR (95% CI) risk ratio and its 95% confidence interval 1 Analysis using chi-squared test NE not estimable due to nullity in first group				

Table 3: Difference between Groups regarding Adverse Effects.

[in 4 (1.3%) women], and other causes (e.g. non-compliance and cessation of symptoms) [in 3 (1%) women] (table 3).

The rate of women who interrupted the 7-day course of metronidazole treatment was significantly high [18 (6%)]. Reasons for interruption were related to intolerable side effects [in 11 (3.6%) women], inefficacy

Discussion

The current study showed that a single-dose treatment with secnidazole is non-inferior to the 7-day course of metronidazole in treatment of BV in non-pregnant women. Meanwhile secnidazole treatment is featured by absence of non-compliance (just a single-dose treatment), significantly lower side effects (except for the headache). The results of the current study go in agreement with results of previous studies. In a previous randomized trial published in 2005, and conducted on 80 patients, single-dose (1 g) metronidazole was compared to single dose (2 g) secnidazole in treatment of BV. Diagnosis in this trial was based only on Amsel's criteria and cytological finding of Gardnerella vaginalis in Pap smear. Cure rates after 7 days were comparable in both groups, though figures are quite high than those reported in the current study [95% and 97.4%, respectively] [8]. This discrepancy in the cure rates reported in both studies can be explained by the strict criteria for cure adopted in the current study. This has been confirmed in a more recent well-designed trial, published in 2010, and conducted on 577 patients [13]. In this latter trial, single-dose secnidazole (1 g) was compared to 7-day course of metronidazole (500 mg bid). Cure rates were assessed clinically and bacteriologically till 28 days after initiation of treatment. Cure rates were comparable in both groups; and the figures of cure rates were very similar to those of the current trial [13]. In fact, there is a well-observed discrepancy in cure rates following treatment of BV. In the Cochrane systematic review published in 2009 on treatment of BV, the cure rates ranged between 78 and 96% [2]. One of the major points of strength in the current study was the use of both clinical and bacteriological criteria for diagnosis and cure. Another point of strength is adoption of the intention-to-treat analysis. Women who no-show at evaluation on days 14 or 28 and those who interrupted the treatment course in the metronidazole group were considered treatment failures. A third point of strength is the continued evaluation till 4 weeks after treatment; a point that has been stressed upon in the FDA report for management of BV.

Points of weakness included absence of women with comorbidities (e.g. diabetes mellitus), lack of long-term follow-up and assessing the value of treatment in prevention of long-term sequelae of BV, particularly pregnancy-related major adverse sequelae.

In conclusion, Single-dose secnidazole treatment seems to be effective and safer alternative to the standard 7-day course of metronidazole in treatment of BV in non-pregnant women.

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