



Once Daily *In-Situ* Forming Versus Twice-Daily Conventional Metronidazole Vaginal Gels for Treatment of Bacterial Vaginosis: A Randomized Controlled Trial

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Abstract

Background: Bacterial vaginosis (BV) is one of the most common infections in childbearing age.

Aim: To compare the efficacy of metronidazole (once-daily 0.8% MTZ *in situ* gel) versus twice-daily conventional MTZ vaginal gel in the treatment of bacterial vaginosis (BV).

Material and methods: All patients who presented to Assiut Women Health Hospital- Egypt with symptoms suggestive of BV were counseled to participate in the study. One hundred-four eligible participants were randomly assigned to either MTZ *in situ* gel or a conventional vaginal gel. All participants were followed-up twice after one and 4 weeks of the beginning of treatment to ensure cure of infection and any side-effects.

Results: Demographic criteria of the participants were matched in both groups. The cure rate after one week from the treatment was 74.5% in the *in situ* gel group and 63.8% in the conventional vaginal gel group ($P=0.252$), while after 4 weeks, the cure rate showed significant difference in the *in situ* gel group as compared to the conventional vaginal gel group (66.7%) and (40.4%), respectively ($P=0.009$).

Conclusion: Once daily *in situ* MTZ gel (0.8%) is more effective than twice-daily conventional gel after four weeks of treatment with nearly same side effects. These findings confirm the use of this novel and efficient modality of long-term treatment of BV.

Keywords

Bacterial vaginosis; *In situ* gel; Metronidazole

Introduction

Bacterial vaginosis (BV) is one of the most frequent diagnoses in women attending genitourinary clinics. As 50% of cases of BV are asymptomatic, the true prevalence of this condition in the community is uncertain [1]. Metronidazole (MTZ) is considered the

drug of choice for the treatment of BV. It can be given either orally or locally. Formulations for the local administration of the drug include gels and suppositories [2,3]. The acceptance of suppositories is lower than the oral administration of the drug as they might cause irritation and thus affecting the patient's compliance. Moreover, the mode of administration of MTZ does not have a significant difference in the eradication of the pathogenic bacteria [3].

Among the metronidazole gels and lactic acid gels, for local application, lactic acid gels have been found to be more efficient and safer. The recurrence of BV is less common in patients treated with lactic acid gel when compared with patients treated with metronidazole gels [4]. This may be attributed to the inhibition in the growth of the lactobacilli when MTZ is used for the treatment and depends on the concentration of the lactobacilli [5].

Intravaginal deliveries of MTZ for the treatment of BV have shown that there was an improvement in the clinical symptoms of the patients within 21–30 days of the starting of the treatment. Unfortunately, the vagina was not recolonized with lactobacilli within the stated period [2]. The use of formulation consisting polycarbophil-carbopol and lactic acid-chitosan mucoadhesive vaginal gels has also been reported and both of them have been found to be safe [6,7]. Cure rates following intravaginal treatment with MTZ account for 80-90% at the end of treatment and one month after the end of therapy [8]. However, three months after the end of therapy the rate of relapses can overcome 30%. Persistence of an adherent bacterial biofilm, containing mostly *Gardenerlla vaginalis* is the main reason for failure of BV treatment [9].

Suppressive treatment with MTZ gel has been investigated with variable results [10]. Moreover, long-term treatment with MTZ is not recommended because of the high incidence of gastrointestinal adverse reactions, the risk of peripheral neuropathy, and *Candida* super infection [11].

Although the patients are known to tolerate gels better than suppositories or ointments, the direct application of gels into the diseased sites of vagina might be difficult as well as improper. Therefore, vaginal therapy would be significantly improved if an intravaginal administered drug can retain at the site of administration for prolonged time [12].

The *in situ* forming hydro gel is a stimuli sensitive hydrogel that exists as an aqueous solution before administration. When exposed to external physical stimuli like heat, it undergoes reversible volume-phase transition, then immediately turned into standing gels after its contact with the mucosa [13]. Recently, *in situ* gel drug delivery system has been investigated as a more convenient dosage form of topical applications. It's easy to be applied into the vagina with accurate dosing of liquid before turning to gel with even spreading. It had been tried before and proved effectiveness, safety and tolerance [14].

A previous study showed that *in situ* MTZ vaginal gel twice daily is more effective than the conventional vaginal gel product in sustained cure of BV [14]. The current study aims to compare the efficacy of the use of once daily *in situ* MTZ vaginal gel (0.8%) versus twice-daily conventional MTZ vaginal gel in treatment of BV.

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Patients and Methods

The current study was a registered RCT (NCT02365389) conducted in the outpatient Gynecology Clinic of Women's Health Hospital, Faculty of Medicine, Assiut University between May 2014 and October 2014. All women presented with symptoms suggestive of BV to the clinic had been examined and investigated to confirm the diagnosis. The Assiut University Medical Ethical Review Board approved the study.

Study participants

We had included women with proven diagnosis of BV infection by Amsel's criteria. For Amsel's diagnostic criteria to be met, the vaginal pH was measured during the gynecological examination, using a colorimetric tape put in contact with the vaginal wall for 1 min. For the amine-odor (whiff) test to be performed, two drops of 10% potassium hydroxide were added to a fraction of the sample collected from the posterior vaginal fornix. Tests were considered positive when the characteristic fishy odor was detected. A wet-mount specimen was analyzed for the presence of clue cells under 40 X magnification. The clinical diagnosis of BV was considered positive when at least three of the following four criteria were positive: presence of a thin homogeneous discharge, vaginal pH \geq 4.5, positive whiff test, and the presence of clue cells in the wet mount [15]. We had excluded pregnant, lactating women, those who had received any antimicrobial treatment in the last week prior to recruitment and those who refused to participate in the study.

Intervention

All study participants signed a written consent form after reading the patient information sheet or having it read to them. Eligible participants were randomly assigned to one of two groups: Group A (study group) received *in situ* MTZ vaginal gel once daily for 5 days. Treatment in this group was offered in the form of a bottle of an aqueous liquid (100 mL of a preparation composed of 0.8% MTZ, 20% pluronic F-127, 10% pluronic F-68, and 0.01% benzalkonium chloride). Women were asked to put 5 cc of the liquid into the vagina once daily for 5 days using a graded syringe and 10-cm long soft applicator. Women were instructed to insert the application tube while they lay on their back and to stay for 1 min after application. Group B (control group) received conventional MTZ vaginal gel (Tricho gel 0.8%, Sedico, Egypt) twice daily for 5 days, using the supplied nozzle, which applies about 5 gm of gel in the same laying back position.

Sample size

Sample size calculation was based on the primary outcome (the cure rate 4 weeks after treatment). Previous studies reported that women who had treated by conventional gel had only 47.4% cure rate after 4 weeks from the starting of the treatment while those treated by twice daily *in situ* gel had cure rate of 80% [14]. Using two sided chi-square test with α of 0.05, a minimum sample size of at least 84 in the 2 groups (taking a ratio of 1:1 un exposed to exposed), this will give 42 patient in each group, using 80% power to detect 32,6 difference between the 2 groups. (Odds ratio of 1.44)(Epi-info™, CDC, USA,2008)

Randomization

Randomization was done using computer-generated random table. After acceptance of eligible women to participate in the study,

they were assigned randomly to either one of the above groups. Allocation concealment was done using serially-numbered closed opaque envelope. Counseling for participation was done before recruitment. Once allocation had been done, it could not be changed. The study was single-blinded RCT. Patients only were blinded about the nature of the administered drug.

Follow-up schedule

All participants were evaluated two times during the follow-up period; the first after 1 week and the second after 4 weeks from the start of treatment. Evaluation of improvement had been assessed according to Amsel's criteria [15]. Any local vaginal side effects like burning or itching, urinary problem like dysuria or urgency encountered during treatment were recorded. Moreover, any general side effects complained by the patients were also recorded.

Data collection and analysis

The data were collected and entered on Microsoft access database to be analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 18). Comparisons between the groups were done using Student's t-test to compare the mean values between groups in scale variables. However, χ^2 tests were used to compare the dichotomous and ordinal variables in the groups. For analysis P-Value <0.05 was considered significant.

Results

One-hundred twenty five participants with proven BV "having at least 3 out of 4 Amsel's criteria" were approached to participate in this study. Twenty-one women excluded: six women were pregnant, five were lactating and seven had received antibiotic treatments in the prior week. Moreover, three women refused to participate in the study. The remaining 104 patients were randomly assigned to the two groups. Six patients in both groups were lost to follow up (Figure 1).

Table 1 shows the demographic characteristics of the study participants. No significant differences were found between the two study groups with regards patients' age, parity, educational level, current contraceptive use and past history of BV.

Table 2 shows cure rate "based on Amsel's criteria" in the two treatment groups after one week of gel application. There were 38 out of 51 patients (74.5%) in group A in comparison with 30 out of 47 patients (63.8%) in group B with no significant statistical difference.

Table 3 shows the cure rate of BV four weeks after the treatment with cure rate 66.7% (34/51 patients) in the study group in comparison with 40.4% (19/47 patients) in the control group with significant statistical difference (P=0.009).

The only side-effect reported was watery vaginal discharge by 4 patients, three of them in the control group (6.3%) and only one in the study group (2%).

Discussion

The present study was a clinically registered RCT. The current work demonstrated more sustained cure of BV four weeks after treatment with once daily *in situ* MTZ (0.8%) gel for five days as compared with twice daily conventional MTZ vaginal gel for the same period. BV is one of the most common vaginal infections among women of childbearing age. Studies in Europe and the USA have found prevalence between 4.9% and 36.0% [16]. BV is a causative factor of many health hazards including premature rupture of the

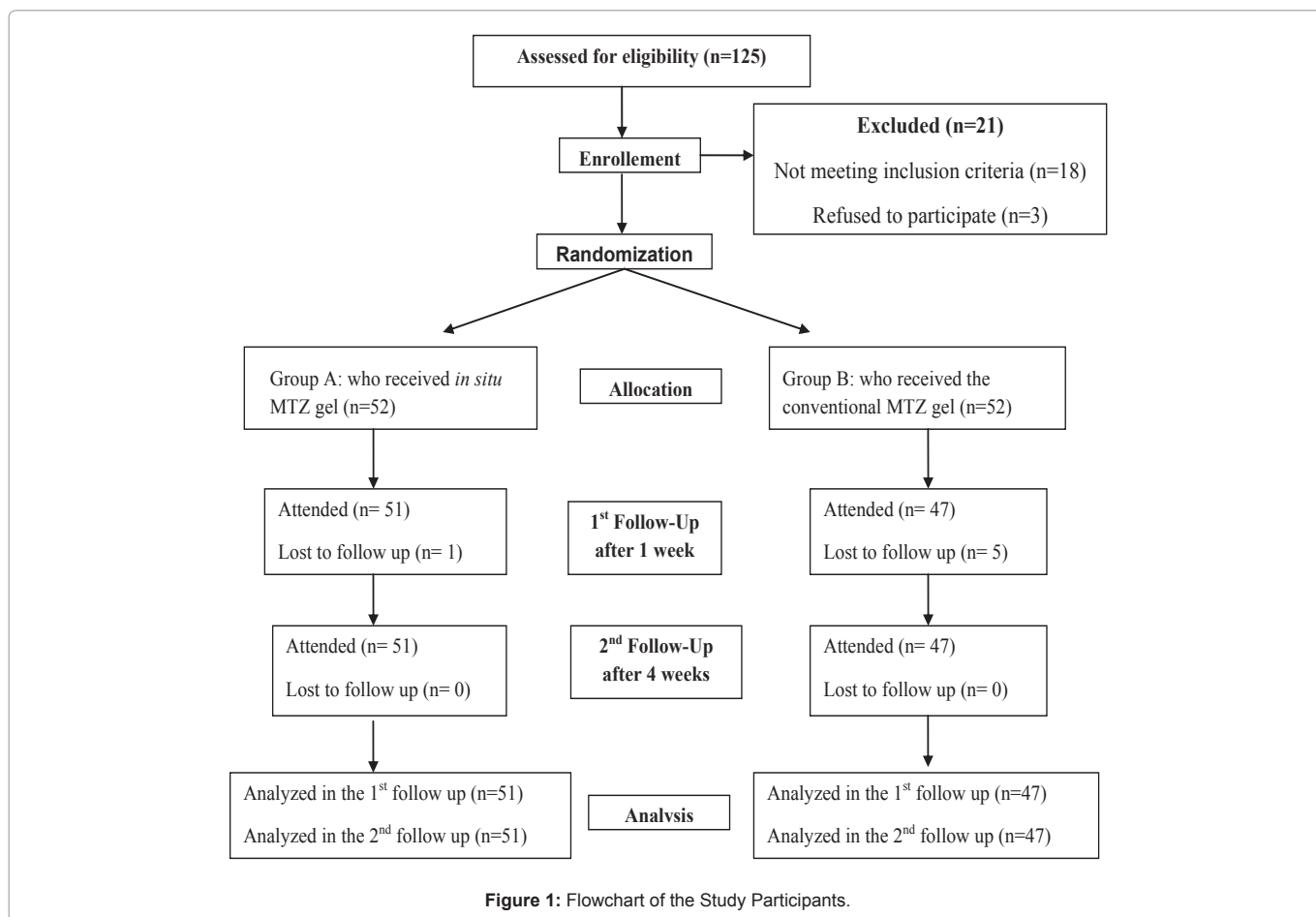


Figure 1: Flowchart of the Study Participants.

	Group A (n= 51)	Group B (n= 47)	P-value
Age (Mean ± SD)	34.22 ± 8.49	33.51 ± 7.61	0.667
Parity (Mean ± SD)	3.69 ± 2.62	3.87 ± 2.06	0.698
Educational level			
≥ 6 years	21 (41.2%)	19 (40.4%)	0.940
< 6 years	30 (58.8%)	28 (59.6%)	
Contraceptive methods			
Hormonal	8 (15.7%)	7 (14.9%)	0.238
Non-hormonal	8 (15.7%)	14 (29.8%)	
None	35 (68.6%)	26 (55.3%)	
History of BV	40 (78.4%)	39 (83.0%)	0.569

Group A: the study group who received *in situ* MTZ gel (0.8%)
Group B: the control group who received the conventional MTZ gels

Table 1: Characteristics of the Study Participants.

amniotic membrane [17], late pregnancy miscarriage [18], chorioamnionitis [19], post-partum endometritis [20], as well as failure of in vitro fertilization and embryo transfer [8]. MTZ is a widely prescribed drug and it is the drug of choice for the treatment of BV. It is a nitroimidazole derivative having activity against anaerobic microbes and protozoa [2,3]. There are different types of drug delivery systems that used for delivery of MTZ that vary significantly in their efficacy, tolerance, compliance and common side effects. Vaginal drug delivery system is better than systemic form regarding common side effects. However, it has two main constrains; the first is the large surface area of the vagina, that usually results inadequate spread of the anti microbial agent over the whole surface, and consequently

	Group A (n= 51)		Group B (n= 47)		P- value
	No.	%	No.	%	
Discharge	16	31.4	29	61.7	0.003
PH > 4.5	21	41.2	22	46.8	0.575
Whiff test +ve	20	39.2	23	48.9	0.333
Clue +ve	9	17.6	13	27.7	0.235
Cure rate	38	74.5	30	63.8	0.252

Group A: the study group who received *in situ* MTZ gel (0.8%).
Group B: the control group who received the conventional MTZ gels

Table 2: Amsel's Criteria for Diagnosis of BV One Week after 5 Days-Treatment.

	Group A (n= 51)		Group B (n= 47)		P-value
	No.	%	No.	%	
Discharge	20	39.2	34	72.3	0.001
PH > 4.5	17	33.3	24	51.1	0.075
Whiff test +ve	20	39.2	23	48.9	0.333
Clue +ve	15	29.4	14	29.8	0.912
Cure rate	34	66.7	19	40.4	0.009

Group A: the study group who received *in situ* MTZ gel (0.8%).
Group B: the control group who received the conventional MTZ gels

Table 3: Amsel's Criteria for Diagnosis of BV 4 Weeks after 5 Days-Treatment.

incomplete cure and recurrence. The second is sustainability of the drug in the vaginal environment. The drug can be exposed to external wash by vaginal douching.

In situ gel is a thermo-sensitive liquid solution, which is rapidly

converted into gel once stimulated by body temperature [13]. Recently, an *in situ* MTZ vaginal gel has been tried for the treatment of BV [14]. *In vitro* characteristics of the institution MTZ gel used had been studied and compared with the marketed conventional vaginal gel product. The comparison included the gelation temperature, *in vitro* release, rheology, and mucoadhesion properties.

The current RCT showed a 74.5% cure rate one week after application of *in situ* MTZ (0.8%) gel once daily in comparison to 63.8 % cure rate after twice-daily conventional MTZ gel treatment. A previous trial held in the same center compared *in situ* gel twice daily versus of conventional gel twice daily revealed that the cure rate was 85 % and 71.4 %, respectively [14].

Our study demonstrated less recurrence rate with *in situ* gel group compared with conventional gel. The 4-week cure rate was significantly higher (66.7%) in women who received *in situ* gel compared with conventional gel (40.4%). Previous work on the *in situ* gel had demonstrated the same higher persistence of cure after 4 weeks of treatment with twice daily *in situ* gel compared with the control of twice daily conventional gel (80 % and 47.4%) respectively [14].

The long-term efficacy could be explained by the ability of the fluid “before gel formation” to spread, dispense through vaginal rugae and to reach almost the entire vaginal surface. Under the body thermal effect the fluid converts by it is physical character in to mucoadhesive gel which ensures sustained contact and effect of MTZ that may persist all over the day.

Pluronic, the main constituent of the delivery vehicle that carried the MTZ in the current study, has strong bioadhesiveness, which is known to improve the intimacy of contact and increase the residence time [21]. The use of this preparation could enable better spreading and coating of the vagina, making the treatment more effective. Additionally, this vehicle is a thermo-sensitive hydro gel that can be applied in an accurate and reproducible quantity, in contrast to the already gelled formulations [22,23].

Oral metronidazole administration is usually followed by many side effects including vaginal discharge, symptomatic candidiasis, and vulvovaginal irritation, which is usually following oral metronidazole therapy. This is beside other gastrointestinal disorders, nausea, and metallic taste [24]. In contrast vaginal application in the current study was accompanied with minor side effects and in few cases including watery vaginal discharge. These side effects were more frequent in the conventional gel group. However, the sample size of the current RCT was not sited to measure this specific point and further studies are needed.

There were some limitations in the present study including the probability of drug reaction to the containing plastic bottle. The drug was only tested in glass bottles; stability of the *in situ* gel deserves further study. Moreover, syringe and novel applicator used for the delivery of *in situ* gel is not easy to be used and may allow leakage. Other applicators available in the market are designed for creams and gel and are not ready to deliver liquid solutions.

In conclusion, once daily *in situ* MTZ gel (0.8%) is as effective as twice-daily conventional gel of same concentration after the end of one week of treatment. Less recurrence rates after four weeks of treatment were encountered with *in situ* gel with nearly the same side effects. Further research is needed to compare the efficacy of once daily versus twice daily administration of the *in situ* MTZ vaginal

gel for treatment of BV. A larger RCT is needed using convenient applicators to confirm safety and efficacy.

Conflict of Interest

The authors declare that they have no conflict of interest.

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