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Research Article

# Efficacy and tolerability of two intravaginal formulations containing clindamycin plus clotrimazole in women with vaginal infections: A pilot study

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ABSTRACT

Aims: To compare the effectiveness and tolerability of soft gelatine capsule versus Extended-release tablet containing clindamycin with clotrimazole in vaginal infections. Subjects and Methods: Following baseline vaginal examination, 66 women having clinical diagnosis of vaginal infection were randomized to receive three doses [once daily] of an immediate release (SG-group) or an extended release combination of clindamycin with clotrimazole (ER-group) and followed up for assessing resolution of clinical and microbiological evidence of vaginal infection by 8th day; maintenance of clinical and microbiological cure at 29th day; and occurrence of side effects. Results were presented using descriptive statistics. Qualitative data was analyzed by Fischer's Exact test Unpaired t-test was used for quantitative data. Results: 27 women from SG-group and 30 women from ER-group completed the study. In SG-group, 69.23% had complete cure and 7.69% had partial remission at 8th day of which 88.89% maintained remission, while in ER-group 73.68% women had a complete cure of which 85.71% maintained remission on 29th day. Delayed remission was observed in 25% women from SG-group and 60% women from ER-group, while none of the women experienced intolerable adverse effects. Conclusion: Both formulations containing clindamycin plus clotrimazole were effective, as empiric therapy, in inducing and maintaining microbiological as well as clinical remission in women with clinical diagnosis of vaginal infection to a similar extent but should not to be recommended for cases specifically identified to have trichomoniasis. An adequately powered study using a larger population should be conducted to further explore differences between these two formulations.

**Key words:** Clindamycin, Clotrimazole, Vaginal formulation, Vaginal infections.

## INTRODUCTION

Vaginal discharge, being the most common reason for non-pregnancy, non-routine gynaecologist visits, is often due to infections that may lead to gynecologic and obstetric complications, huge health care costs, low success and frequent recurrences.[1,2] Hence, a timely diagnosis and appropriate treatment is essential. Prompting the clinician to make a presumptive diagnosis based on symptoms, nature of discharge and signs. Therefore, WHO introduced the concept of 'Syndromic management' of reproductive tract infections[3,4] whereby diagnosis and treatment is not directed to specific disease based on testing, but rather towards syndromes and treatment is generally given for most of the diseases that could cause that syndrome. Furthermore, microbiological diagnosis barely correlates with clinical diagnosis[5,6] and 30% cases have infections of polymicrobial nature[7] giving rise to need for treatment that covers all common vaginal pathogens. Since, most commonly encountered aetiologies of vaginal discharge are trichomoniasis, moniliasis, bacterial vaginosis, chlamydial infection and gonorrhoea, according to the principles of syndromic management, treatment in clinical set-up should be directed against all these diseases. Current syndromic management for vaginal discharge in patients without evidence of cervical discharge or abdominal pain consists of Secnidazole/ Metronidazole: 2 g single oral dose STAT (or Tab. Tinidazole 500 mg orally, twice daily for 5 days) and Fluconazole 150 mg single oral dose STAT (or topical Clotrimazole 500 mg).[8] A Cochrane review of 24 randomized controlled trials (RCTs) in bacterial vaginosis showed that clindamycin is as effective as metronidazole[9] and six RCTs showed topical and oral antibiotic preparations to be equally effective.[10] Similarly, a

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Cochrane review of 19 RCTs reported no statistically significant differences in clinical cure rates of anti-fungals administered by the oral and intra-vaginal routes for the treatment of uncomplicated vaginal candidiasis.[11] Thus, currently CDC recommends oral or topical metronidazole or clindamycin for bacterial vaginosis, oral fluconazole or any azole topically for Vulvovaginal candidiasis and oral metronidazole for trichomoniasis.[12]

As topical therapies are minimally absorbed and associated with fewer side effects, coupled with equal effectiveness as compared to systemic therapies, their availability has obviated the need for systemic therapy in many patients with bacterial vaginosis and vulvovaginal candidiasis. Thus, combinations of various topical agents are being tested and marketed for empiric syndromic management of vaginal infections. One such combination contains clotrimazole along with clindamycin.

In addition to its activity against candida,[13] clotrimazole has also documented a weak activity against T. vaginalis.[14] Though CDC does not currently recommend the use of clotrimazole for treatment of trichomoniasis, some medical practitioners consider clotrimazole suppositories for patients with trichomoniasis when nitroimidazoles cannot be used due to hypersensitivity or in first trimester of pregnancy, whereby clotrimazole mainly offers symptomatic treatment but may cure as many as 50% of infections.[15,16] On the other hand, clindamycin is effective against anaerobes and Gram-positive aerobes [17] including organisms like group B streptococci and, S.aureus, involved in aerobic vaginitis, or mixed aerobic-anaerobic infection that responds poorly to metronidazole.[18-21] Thus, such a combination of clotrimazole and clindamycin may provide empiric coverage for majority of the organisms involved in vaginal infections.

Two different intravaginal formulations, ClinSupV3 (immediate release soft gelatin vaginal capsule) and ClinSupV3-ER (extended-release vaginal tablet that releases the drugs over eight hours), each containing a combination of clindamycin and clotrimazole, are available commercially and are commonly prescribed as empiric therapy for vaginal infection. Though the drugs contained in these two formulations are same, they differ in terms of release patterns which could possibly result in a difference in efficacy. Rapid release of drugs from vaginal formulations has theoretical limitations like greater systemic absorption [toxicity], leakage and wastage of drug, messiness and low residence time giving high local concentration of drug only transiently. As against this, the extended-release tablet avoids fluctuations in drug concentrations and provides continued presence for longer period. Secondly, therapeutic efficacy requires a drug to be present in right amounts, at desired site, for appropriate duration making pharmacokinetic-pharmacodynamic correlation of drug formulations quite pertinent for selecting appropriate dosage-forms. In case of clindamycin-clotrimazole combination, both drugs inhibit growth of respective organisms.[13,17] This static effect suggests that inhibition would last only as long as the drugs are present in vicinity of the organism, giving a theoretical advantage to an extended-release formulation.

Hence, the present pilot study compares these two formulations to gather clinical and microbiological evidence for making a choice.

## OBJECTIVES

To compare effectiveness and tolerability of three day treatment with ClinSupV3 versus ClinSupV3-ER in women with clinical diagnosis of bacterial, trichomonal, candidial or mixed vaginitis.

## SUBJECTS AND METHODS

This was a two-arm, randomized, comparative, prospective, single center pilot study, conducted at Sassoon General Hospitals, Pune, India between April 2011 and September 2011.

The study was open-labeled with reference to the clinician and study subjects, but the microbiologist evaluating vaginal swabs was blinded to study group allocation of the respective subjects.

The protocol was approved by Institutional Ethics Committee and informed written consent obtained from participants.

### Inclusion Criteria

The study included women attending gynaecology OPD with symptoms of vaginal discharge and a clinical diagnosis of vaginal infection [based on symptoms and per speculum signs], age at least 18 years, agreeing to abstain from intercourse for eight days from start of treatment, agreeing not to douche or use intravaginal products during study period.

### Exclusion Criteria

Exclusion criteria were post-menopausal state, menstruating at diagnosis, pregnancy, presence of intrauterine device, use of antifungal or antibacterial during previous 14 days or immunosuppressants within 4 months, presence of vaginal/vulval ulcer, medical condition or treatment that might confound response, inability to attend follow-up visits, hypersensitivity to clotrimazole/clindamycin, regional enteritis, ulcerative colitis or 'antibiotic associated' colitis, significant disease or acute illness that could complicate the evaluation.

### Study drug

Both dosage forms, ClinSupV3 (intravaginal soft gelatin capsule) [Softesule Pvt Ltd, Mumbai, India; Mfg. date 12/2010; Exp.Date 05/2012] and ClinSupV3-ER (intravaginal extended-release tablet) [Cure Medicines(I) Pvt Ltd, India; Mfg. date 02/2011; Exp. Date 07/2012] contained clotrimazole 200 mg plus clindamycin phosphate equivalent to 100 mg clindamycin and were supplied by Resilient Cosmeceuticals Pvt Ltd, India.

### Drug Administration

After baseline vaginal examination and sample collection, the eligible women were allocated to receive ClinSupV3 [SG-group] or ClinSupV3-ER [ER-group] using computer-based randomization codes.

First dose was inserted per vagina by the gynaecologist (Day 1). The procedure for drug administration was repeated by the women for two consecutive days (Day 2 and Day 3). All women were asked to refrain from strenuous activities for four hours after insertion of intravaginal formulations, and abstain from sexual intercourse and douching for eight days from initiation of drug administration.

### Follow-up

The women were reassessed on Day 8 of the study [second visit] and Day 29 [third visit]. A flexibility of -2 days to +7 days was permissible for the second visit and -7 days to +7 days for the third visit for women unable to report on the expected day of follow-up.

At each visit, the women filled a subjective evaluation form for questions related to vaginal discharge, and itching whereby they were asked to rate their Vaginal discharge quantity as Nil=0, little=1, moderate=2, profuse=3; Vaginal discharge odour as Nil=0, malodorous=1; and Itching as Nil=0, little=1, moderate=2, severe=3. Similarly, at visit 2, tolerability of the test formulation was evaluated by the asking the women about occurrence of various adverse effects such as vaginal irritation, burning micturition etc and rating them as absent, mild, moderate and severe.

### Sample Collection

At each visit, sample of vaginal discharge was collected from lateral wall of vagina for Whiff test and pH [using pH-paper]. Additionally, one swab was sent in 2 ml normal saline, for microbiological diagnosis (wet mount, culture on Sabourauds medium, and Gram stain). The smear was scored from Grade 0 to 4 using Hay/Ison criteria.[22]

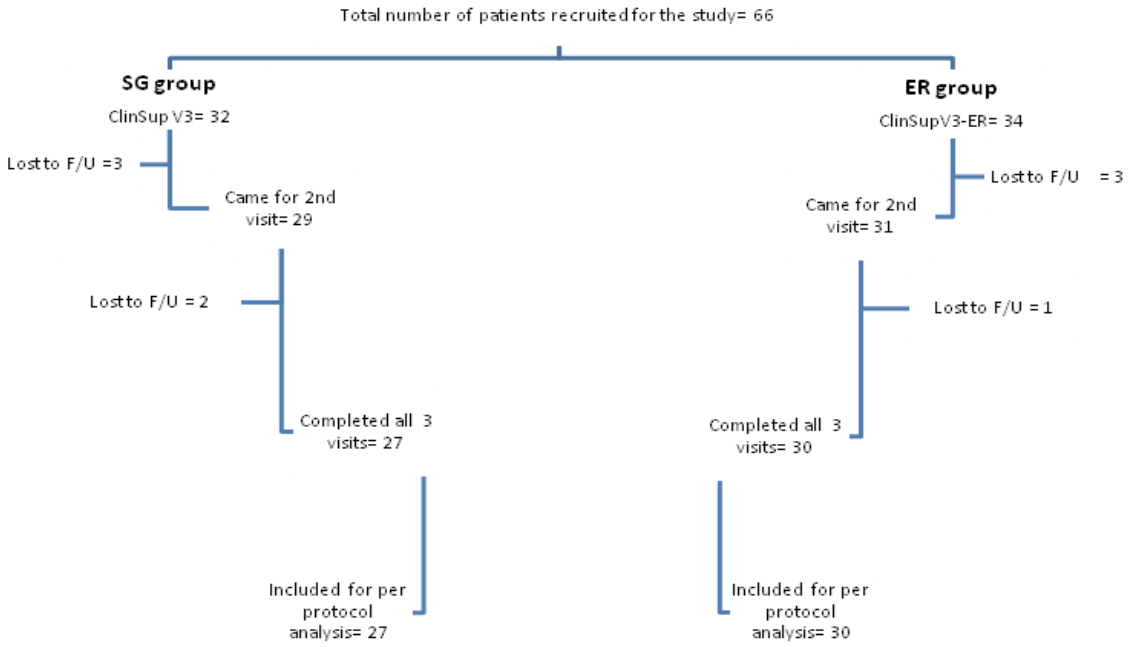


**Figure 1: Subject enrollment and follow-up**

## OUTCOME MEASURES

### *Primary outcome measure for Global effectiveness*

In women with microbiologically proven infection at baseline, if the vaginal swab was negative for bacterial, trichomonal and candidial vaginitis at second visit, with substantial improvement in clinical symptoms and regression of signs, it was considered as 'Global complete cure'. Partial or complete regression of signs and symptoms with partial microbiological remission [conversion from Grade 3 to Grade 2] was considered as 'Global partial remission'. Persistence of more than one symptom or sign of infection or microbiological evidence of infection was considered as 'Global failure of therapy'.

### *Secondary outcome measures for Global effectiveness*

In women with microbiologically proven infection at baseline and global complete cure/global partial remission at the second visit, if vaginal swab remained negative for bacterial, trichomonal and candidial vaginitis even at third visit and she remained free of signs and symptoms of vaginal infection, it was considered as 'Global maintenance of remission'.

If a woman who had global partial remission or global failure of therapy at second visit, met criteria for complete remission [vide primary outcome measure-'complete cure'] at the third visit, she was considered to have 'Global delayed cure'. Women with clinical or microbiological evidence of persistence of infection at second and third visit were considered as 'Global total failure of therapy'.

Conversion of global complete cure or global partial remission at second visit to global partial remission [in case of complete remission] or frank microbiological or clinical evidence of infection at the third visit was considered as 'Global relapse'.

### *Secondary outcome measures for tolerability*

If the woman completed the three day course without any break and did not experience intolerable side effects, this was considered as treatment success referring to our secondary endpoint for tolerability.

## STATISTICAL ANALYSIS

The results for primary and secondary outcome measures were analyzed on per-protocol basis. Considering the discrepancy between clinical and microbiological diagnoses and an apparently unequal distribution of microbiological findings between the two groups, despite randomization, we additionally analyzed microbiological findings and clinical responses for individual type of infection separately. This, however, was not a pre-specified outcome measure.

Unpaired t-test was used to compare the quantitative data in both groups. Descriptive data of the two groups were analyzed using Fisher exact test. Effect size was expressed as Relative risk and 95% Confidence interval. All statistical tests were performed using OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 2.3.1, (Updated 2010/19/09).

## RESULTS

66 women were recruited for the study of whom, 32 women were randomized to SG-group and 34 women to ER-group. Finally, 27 women from the SG-group and 30 women from the ER-group completed the study (Figure 1). Mean age of the study volunteers was 31.39 $\pm$ 7.5 years.

Of the 27 women in SG-group, 13 had microbiologically proven infection with isolated abnormal vaginal bacterial flora (ABVF) in three, candidiasis in five, trichomoniasis in one and mixed infection [ABVF+candidiasis] in four women while in the ER-group, 19 women had microbiologically proven infection with isolated ABVF in nine, candidiasis in five and mixed infection in five women [ABVF+candidiasis- three; ABVF+trichomoniasis- two]. Thus, the study participants randomized to the two groups were comparable with respect all relevant parameters though relatively more women from ER-group had grade3 ABVF (Table 1).

### *Primary outcome measure for global effectiveness*

In the SG-group 69.23% women had complete cure while 7.69% women had partial remission as compared to 73.68% women with complete cure in the ER-group (Table 2).

### *Secondary outcome measure for global effectiveness at 29$^{th}$ day*

In the SG-group, 88.89% women maintained remission while 11.11% women relapsed at third visit. Of the women who did not have complete cure at second visit, 25% had delayed cure. The ER-group had

**Table 1: Baseline demographic data of women who were eligible for final analysis**

| | SG group n (%) | ER group n (%) | p |
|---|---|---|---|
| Number of women | 27 | 30 | _ |
| Age [yrs] (mean + SD) | 32.07 ± 7.95 | 30.77 ± 7.17 | 0.5869 |
| Past history of similar illness [Yes/ No] | 12/15 | 16/14 | 0.6860 |
| Other Medical illness-Diabetes mellitus | 2 | 0 | 0.4398 |
| Clinical Diagnosis-<br>Bacterial vaginosis<br>Candidiasis<br>Mixed Infection | <br>1 (3.70)<br>7 (25.93)<br>19 (70.37) | <br>1 (3.30)<br>9 (30)<br>20 (66.67) | <br>>0.999<br>0.9648<br>0.9896 |
| Length of duration for visit 2 (days) | 8.56 + 2.81 | 8.21 + 5.09 | 0.734 |
| Length of duration for visit 3 (days) | 28.13 + 1.76 | 28.47 + 1.58 | 0.422 |
| pH>4.5 | 22 (81.48) | 22 (73.33) | 0.6806 |
| Malodorous discharge | 6 (22.22) | 5 (16.67) | 0.8437 |
| Itching at baseline | 16 (59.26) | 18 (60) | >0.999 |
| Microbiological findings [Mixed classified according to respective pathogens]: | | | |
| Abnormal vaginal bacterial flora | 7 (25.93) | 14 (46.67) | 0.1774 |
| Grade 2 | 4 (14.81) | 2 (6.67) | 0.5706 |
| Grade 3 | 3 (11.11) | 12 (40.00) * | 0.0271 |
| Pus cells | 11 (40.74) | 8 (26.67) | 0.3988 |
| Candidiasis | 9 (33.33) | 8 (26.67) | 0.7944 |
| Candida albicans | 7 (25.93) | 4 (13.33) | 0.3865 |
| Non-albicans Candida | 2 (7.41) | 4 (13.33) | 0.7749 |
| Trichomoniasis | 1 (3.70) | 2 (6.67) | >0.999 |

maintenance of remission in 85.71% women, relapse in 14.29% and delayed remission in 60% (Table 2).

Of all women with microbiologically proven infection at baseline, there was total failure of therapy in 23.08% of the 13 women in SG-group and 10.53% of the 19 women in ER-group.

### *Secondary outcome measure for tolerability*

None of the women complained of intolerable side effects or discontinued treatment because of side effects.

The two treatment groups did not differ statistically with respect to primary or secondary outcome measures.

## MICROBIOLOGICAL FINDINGS

Overall complete microbiological cure was seen in 76.47% women in SG-group and 83.33% women in ER-group at second visit and 82.35% versus 83.33% respectively at third visit.

On analyzing individual infections, it was observed that, at second study visit, 85.71% women with ABVF in both treatment groups showed complete microbiological cure. A similar proportion of women from both treatment groups had complete microbiological cure at third visit. One woman from SG-group developed de novo ABVF and one with partial cure at second visit showed relapse at third visit. In the ER-group, there was one woman with relapse and one with delayed cure.

Soft gelatin capsule produced cure in 77.78% women with candidiasis, which was maintained upto third visit. The extended-release tablet produced cure in 100% of women with candidiasis at second visit, but 25% of them relapsed providing net cure rate of 75% at third visit.

None of the women with trichomoniasis showed recovery at second visit but both the groups had a 100% cure at third visit

Thus, the two treatment groups did not differ with respect to the microbiological cures for various types of vaginal infections. Similarly, the two treatments did not differ with respect to delayed cure, relapse, new infection, and abolition of lactobacilli, grade 4 vaginal flora or effect on pus cells (Table 3, Figure 2).

## CLINICAL FINDINGS

At second visit, there was complete remission of clinical manifestations in 59.26% and partial remission in 40.74% women of SG-group.

**Table 2: Effect on Primary and Secondary outcome measures for effectiveness at 8th day [Visit 2] and 29th day [Visit 3] of the study**

| Treatment group | Visit 1 | Visit 2 | | | Visit 3 | | | |
|---|---|---|---|---|---|---|---|---|
| | Total cases with proven infection | Global complete cure n (%) | Global partial remission n (%) | Global failure of therapy n (%) | Global maintenance of remission n (%) | Global delayed cure n (%) | Global relapse n (%) | Global complete failure of therapy n (%) |
| SG group | 13 | 9 (69.23) | 1 (7.69) | 3 (23.1) | 8 (88.89) | 1 (25) | 1 (11.11) | 3 (23.08) |
| ER group | 19 | 14 (73.68) | 0 (0) | 5 (26.3) | 12 (85.71) | 3 (60) | 2 (14.29) | 2 (10.53) |
| Relative risk (95% CI) | - | 0.940 ( 0.598-1.475) | - | 0.877 ( 0.252-3.047) | 1.037 (0.757-1.421) | 0.417 (0.066-2.63) | 0.778 (0.082-7.376) | 2.192 (0.424-11.35) |
| p (Fisher exact) | - | >0.999 | 0.8125 | >0.999 | >0.999 | 0.7143 | >0.999 | 0.6334 |

**Table 3: Microbiological effects on vaginal bacterial flora**

| | SG group n (%) | ER group n (%) | Relative risk (95% CI) | p *(Fisher exact)* |
|---|---|---|---|---|
| **VISIT 2** | | | | |
| **Worsening of bacterial flora [Grade 2 to Grade 3]** | 0 (0.00) | 1 (50.00) | - | 0.667 |
| **Non-responding [no change in micro diagnosis + worsening]** | 0 (0.00) | 2 (14.29) | - | 0.867 |
| **Cases showing Abolition of lactobacilli [Grade 0]** | 10 (37.04) | 15 (50.00) | 0.7407 (0.403, 1.361) | 0.474 |
| **Abolition of lactobacilli in patients with proven BV on 1st visit** | 3 (42.86) | 6 (42.86) | 1 (0.351, 2.851) | >0.999 |
| **Recent Abolition of lactobacilli in patients with no BV on 1st visit** | 7 (35.00) | 9 (56.25) | 0.622 (0.298, 1.3) | 0.3488 |
| **Grade 4 [BV cured but Gram stain showed aerobic vaginitis flora]** | 1 (3.70) | 1 (3.33) | 1.111 (0.073, 16.91) | >0.999 |
| **Pus cells persisted** | 2 (18.18) | 4 (50.00) | 0.364 (0.087, 1.523) | 0.3313 |
| **New appearance of pus cells** | 2 (12.50) | 1 (4.55) | 2.75 (0.272, 27.77) | 0.759 |
| **VISIT 3** | | | | |
| **Delayed cure** | 0 (0.00) | 1 (7.14) | - | >0.999 |
| **Relapse** | 1 (14.29) | 1 (8.33) | 1.714 (0.126, 23.32) | >0.999 |
| ***De novo* abnormality of bacterial flora [Grade 2]** | 1 (5.00) | 0 (0.00) | - | >0.999 |
| **Non-responding [no change in micro diagnosis + worsening + relapse]** | 1 (14.29) | 2 (14.29) | 1 (0.108, 9.228) | >0.999 |
| **Sample showing GRADE 0- [TOTAL]** | 6 (22.22) | 9 (30.00) | 0.741 (0.303, 1.808) | 0.718 |
| **Persistent abolition of lactobacilli** | 4 (40.00) | 4 (26.67) | 1.5 (0.484, 4.651) | 0.786 |
| **Delayed abolition of lactobacilli at 3rd visit** | 2 (11.76) | 5 (33.33) | 0.353 (0.08, 1.559) | 0.298 |
| **Pus cells persisted after second visit** | 1 (25.00) | 1 (20.00) | 1.25 (0.109, 14.34) | >0.999 |

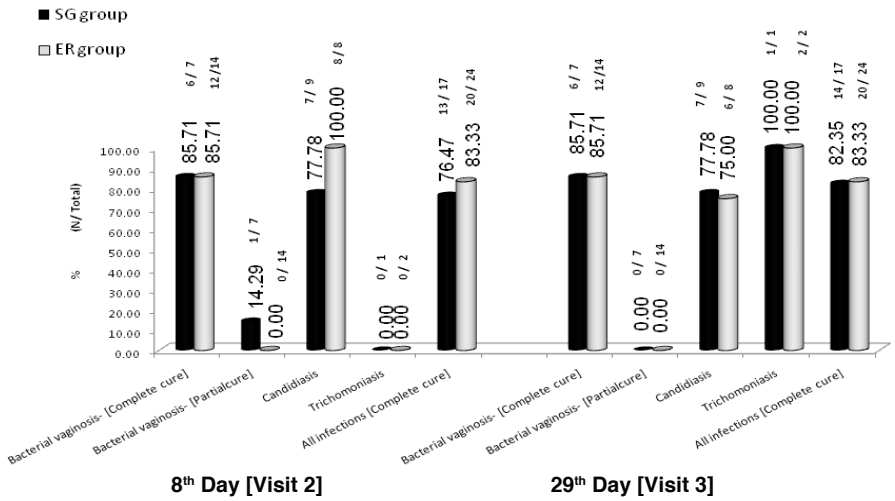


**Figure. 2: Microbiological cure at second and third visit - percentage of infections**

**Table 4: Clinical response**

| | SG group n (%) | ER group n (%) | Relative risk (95% CI) | p *(Fisher exact)* |
|---|---|---|---|---|
| **VISIT 2** | | | | |
| **Discharge reduced by atleast 1 unit** | 24 (88.89) | 24 (80.00) | 1.111 (0.889, 1.389) | 0.583 |
| **pH normalized [<4.5]** | 14 (63.64) | 16 (72.73) | 0.875 (0.583, 1.314) | 0.747 |
| **Discharge malodor treated** | 6 (100.00) | 5 (100.00) | 1 (1,1) | >0.999 |
| **Itching/ Pruritis reduced by atleast 1 unit** | 15 (93.75) | 15 (83.33) | 1.125 (0.883, 1.433) | 0.695 |
| **Adverse effect [patients]** | 3 (11.11) | 5 (16.67) | 0.667 (0.176, 2.53) | 0.830 |
| ***Leakage*** | 1 | 1 | | |
| ***Mild vaginal irritation*** | 1 | 1 | | |
| ***Mild lower abdominal pain*** | 1 | 1 | | |
| ***Mild burning/ irritation during micturition*** | 0 | 2 | | |
| **VISIT 3** | | | | |
| **Clinical Relapse** | 2 (7.41) | 1 (3.70) | 2 (0.193, 20.77) | >0.999 |
| **pH normalized [<4.5] by end of visit 3** | 15 (68.18) | 16 (72.73) | 0.938 (0.639, 1.375) | >0.999 |
| **pH remained normalized [<4.5] from visit 2** | 12 (85.71) | 11 (68.75) | 1.247 (0.841, 1.848) | 0.512 |
| **Discharge reduced by atleast 1 unit by end of visit 3** | 27 (100.00) | 26 (86.67) | 1.154 (1.003, 1.328) | 0.139 |
| **Discharge remained reduced by atleast 1 unit from visit 2** | 24 (100.00) | 22 (91.67) | 1.091 (0.967, 1.231) | 0.489 |
| **Discharge malodor treated** | 6 (100.00) | 5 (100.00) | 1 (1,1) | >0.999 |
| **Itching/ Pruritis reduced by atleast 1 unit** | 16 (100.00) | 18 (100.00) | 1 (1,1) | >0.999 |

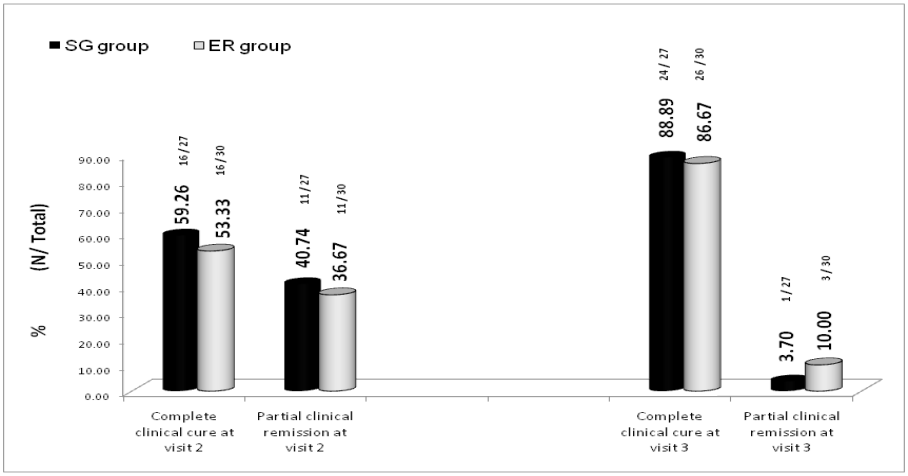


**Figure 3: Clinical response at second and third visit- percentage of subjects**

In ER-group, complete clinical remission was seen in 53.33% and partial remission in 36.67% women.

By third visit, overall complete clinical cure was observed in 88.89% women from SG-group and 86.67% women from ER-group; while partial remission was observed in 3.7% women from SG group and 10% women from ER-group. Two women from the SG-group and one woman from the ER-group showed clinical signs suggestive of relapse. Both treatment groups showed similar effectiveness at normalizing vaginal discharge, pruritis, malodor and vaginal pH (Table 4, Figure 3). Thus, the two treatment groups did not differ with respect to clinical cure in women at second or third visit.

## DISCUSSION

In the present study, there was a significant discrepancy in the clinical and microbiological diagnoses. According to clinical diagnosis only 3.5% cases had bacterial vaginosis, 28.07% had candidiasis; none had trichomoniasis and 68.42% had mixed infection, while according to microbiological diagnosis 37.5% women had abnormal vaginal bacterial flora, 31.25% had candidiasis; 3.13% had trichomoniasis and 28.13% had mixed infection. Furthermore, 32 women [56.14%] had a microbiological diagnosis of infection while the rest had symptoms but did not have microbiological evidence of vaginal infection. The clinical diagnosis matched with microbiological diagnosis in only 10 of 57 women. These findings are in concurrence with reports showing that microbiological diagnosis can't be reached using diagnostic approaches in 10-58% of the women with vaginal discharge[5] and classifications like candidiasis, trichomoniasis, and bacterial vaginosis are insufficient to explain all symptoms. In a study by Donders et al, a group of women with symptoms of vaginitis were found to have abnormal vaginal findings characterized by clue cell-negative, lactobacillus-negative, abundant pus cells, foul smelling vaginal discharge negative for Whiff test and pH> 6, in whom metronidazole was highly ineffective.[18] These women have aerobic vaginitis which is not detected by Amsel's criteria[23] or Nugent's score[24] resulting in a diagnostic dilemma. In our study, 19 out of 57 women had pus cells in the vaginal smear at baseline. The presence of pus cells, though normally suggestive of bacterial infection, was unrelated to presence of microbiological evidence of bacterial vaginosis and was thus indicative of some other infection.

In SG-group these pus cells disappeared in nine out of 11 cases [81.82%] but there was new appearance of pus cells in two more cases. One out of these four cases [25%] having pus cells at second visit showed persistence of pus cells at the third visit.

In ER-group these pus cells disappeared in four out of eight cases [50%] and there was one case with de novo appearance of pus cells. One out of these five cases [20%] with pus cells at second visit showed persistence of pus cells even at third visit.

Thus, in addition to comparing the two dosage forms, we also tried to find out whether empirical treatment of such women with an intravaginal combination of clindamycin and clotrimazole could provide clinical as well as microbiological cure.

The observations suggest that both intra-vaginal dosage forms containing clindamycin and clotrimazole combination produced clinical and microbiological cure in substantial number of women with clinical diagnosis of vaginitis and were able to maintain remission when used as empirical therapy. However, both the dosage forms caused marked abolition of lactobacilli. These findings are consistent with reports of inhibitory effects of clindamycin on lactobacilli in vitro.[25] Furthermore, this study did not find evidence that the two formulations differed with respect to their effects on microbiological findings, overall clinical cure, or individual symptoms and signs.

However, a closer look at the microbiological findings suggests a difference of greater than 20% in some parameters that did not reflect in the statistical tests, probably because of the small number of patients in subgroup analyses.

In case of women with grade 3 ABVF, extended-release tablet showed a complete microbiological cure in 91.67% (11 of 12) women against 66.67% (2 of 3) women receiving soft gelatin capsule [NNT=4]. On the contrary, in women with grade2 ABVF, the extended-release tablet produced complete microbiological cure in only 50% (1 of 2) women compared to 100% (4 of 4) women in the SG-group [NNH=2] and was associated with a relatively greater chance of worsening from grade 2 to grade3 ABVF as well as abolition of lactobacilli in case of women who did not have ABVF at baseline [NNH=4.7]. Therefore, it appears that the extended-release tablet, though more rapidly effective in women with grade3 ABVF, should be used judiciously. Further, the extended-release formulation was relatively slow in clearing pus cells.

In both groups, trichomoniasis showed no response at second visit but complete cure at final visit. This is probably because neither clindamycin nor clotrimazole have strong anti-trichomonal action or that the anti-trichomonal action, if any, follows a lag period. Also, as trichomonads may reside in the urethra, perivaginal glands and the crypts of the vagina, it is reasonable that topically applied antimicrobials may not work as well as the systemic treatments.[12]

## CONCLUSION

Empirical treatment with both intra-vaginal dosage forms containing clindamycin with clotrimazole produced clinical and microbiological cure as well as maintained remission in substantial number of women with clinical diagnosis of vaginal infection. Amongst individual infections, trichomoniasis showed least response. Neither of the two formulations could treat trichomoniasis by end of first week, though there was a delayed response of similar magnitude with both formulations. Thus, a clinical or microbiological diagnosis of trichomoniasis should essentially prompt systemic treatment of both sexual partners with metronidazole or tinidazole.

Secondly, although this study did not find evidence that the two formulations differed with respect to efficacy or tolerability, in the context of treatment of candidiasis, abnormal vaginal bacterial flora, and abolition of lactobacilli, the magnitude of difference (in terms of percentage) was large enough to be clinically relevant.

Being a pilot study, with a small sample size, it is not possible to draw valid conclusions regarding the differences between clinical and microbiological efficacy of the two formulations. Hence, an adequately powered study using a larger population should be conducted to further explore differences between soft gelatin capsule and extended-release tablet on these parameters.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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