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RESEARCH ARTICLE
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COMPARATIVE PROSPECTIVE STUDY SINGLE BLIND RANDOMIZED CONTROLLED TRIAL TO ASSESS THE EFFICACY AND SAFETY OF SECNIDAZOLE WITH N-ACETYL CYSTEINE IN PATIENTS WITH BACTERIAL VAGINOSIS AMONG REPRODUCTIVE WOMEN IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Secnidazole has been proven to have antimicrobial activity against many bacterial species that are involved in BV. Similar to other 5-nitroimidazoles, it has limited activity against lactobacilli, which are beneficial microbes crucial for re-establishing vaginal health post-treatment. However, the tolerability profile of secnidazole closely resembles that of other 5-nitroimidazoles. The most frequently reported adverse events in clinical trials were nausea, vomiting, glossitis, anorexia, epigastric pain, and a metallic taste. Whereas NAC (N-acetyl cysteine) stimulates glutathione synthesis, promotes detoxification, and acts directly as a scavenger of free radicals, making it a powerful antioxidant. some study also reported its choriodecidual protecting effect and its anti-inflammatory properties in the pregnant women with bacterial vaginosis.

Objective: To compare the effectiveness and safety of Secnidazole with N-acetyl cysteine for treating Bacterial Vaginosis in reproductive women at a Tertiary care hospital.

Methods: This was a single blinded randomized experimental stud. Patients received either Secnidazole (2g/day) alone (monotherapy) or the combination of Secnidazole (2g/day) with N-acetyl cysteine (600mg/day. The treatment period was four weeks, and both medications were administered orally once daily. Patients were requested to come for follow-up at the 2nd and 3rd month from the date of the end of the initial treatment for the assessment of recurrence. Safety evaluations were conducted to assess the incidence, intensity, and type of adverse events, as well as changes in the patients' physical examination findings, vital signs, and clinical laboratory findings in both groups.

Results: An Independent t-test was conducted to compare both groups. There was a statistically significant difference in the symptomatic cure (5 out of 45 patients in the secnidazole group, and none out of 45 patients in the secnidazole with NAC group; p-value < 0.01) and positive whiff test (4 out of 45 patients in the secnidazole group, and none out of 45 patients in the secnidazole with NAC

group; p-value < 0.01). Additionally, there were statistically significant differences in the mean ± SD of baseline Nugent score between the two groups (4.20 ± 1.37 in secnidazole group vs. 2.67 ± 0.87 in secnidazole with NAC group; p-value < 0.01*).

Conclusion: Our study recommends that the results of combining secnidazole with N-acetyl cysteine have been very promising for the broader clinical use of NAC as an adjuvant therapy for bacterial vaginosis

Keywords: Bacterial Vaginosis, Secnidazole, N-acetyl cysteine, Effectiveness, Safety

INTRODUCTION

Bacterial Vaginosis (BV) is a common vaginal infection caused by an overgrowth of harmful bacteria such as Gardnerella vaginalis, Mycoplasma hominis, and Prevotella species. This overgrowth disrupts the natural balance of bacteria in the vagina, leading to an increase in vaginal discharge.[1] The discharge is typically thin and watery and can be white or grey. It often has a distinct fishy odour, particularly noticeable after sexual intercourse. BV primarily affects women of reproductive age, with the highest prevalence among those aged 15 to 49. While some women with BV may not experience any symptoms, others may notice a change in their vaginal discharge, along with symptoms such as itching, burning during urination, and a strong odor.[1] Importantly, BV is not a sexually transmitted infection (STI), but having a new sexual partner or multiple sexual partners can increase the risk of developing BV.[2] Furthermore, BV is associated with adverse pregnancy outcomes, including a twofold increase in the risk of preterm labour and delivery, as well as a six-fold increase in the risk of miscarriage.[3] Therefore, prompt diagnosis and appropriate management of BV are crucial, especially for pregnant women or those planning to become pregnant.

BV also doubles the risk of other infections, including sexually transmitted diseases such as HIV/AIDS.[3] The first case of BV was documented in Africa and Europe in 1894.[3] In India, the infection is estimated to affect 5-70% of women in the reproductive age group.[3] The exact cause of BV is still unknown, but it is often linked to an imbalance of naturally occurring lactobacillus bacteria, which generally help maintain a healthy vaginal environment. When these bacteria decrease, it can lead to an overgrowth of other bacteria in the vagina.[4] Some theories suggest a decrease in lactobacillus species in cases of BV. The Centers for Disease Control and Prevention (CDC) recommend oral or vaginal forms of Metronidazole and clindamycin as the preferred treatments for BV.[5] However the effective treatment of BV is still a significant medical challenge. This is because of the high prevalence of the infection and the high rates of recurrence associated with currently available therapies.[6] In light of this, the CDC's 2006 guidelines suggest using new Nitroimidazole derivatives like Tinidazole, Secnidazole, and Ornidazole due to their lower recurrence rates.[7]

Secnidazole has been proven to have antimicrobial activity against many bacterial species that are involved in BV. Similar to other 5-nitroimidazoles, it has limited activity against lactobacilli, which are beneficial microbes crucial for re-establishing vaginal health post-treatment.[8] A single dose of 2 g of secnidazole is quickly absorbed and has not been shown to have drug interactions or interactions with alcohol. It has a longer half-life (17–39 hours in secnidazole vs. 8 hours metronidazole) compared to metronidazole and can be taken with or without a meal.[9] A randomized clinical study compared a single dose of secnidazole 2 g with metronidazole, and both demonstrated similar cure rates at day 28 (60.1% vs. 59.5%), based on criteria including vaginal discharge, positive whiff test, vaginal pH >4.5, and Nugent score.[10]

The tolerability profile of secnidazole closely resembles that of other 5-nitroimidazoles. The most frequently reported adverse events in clinical trials were nausea, vomiting, glossitis, anorexia, epigastric pain, and a metallic taste, occurring in 2-10% of patients.[11] Furthermore, studies revealed abnormalities in leucocyte counts and mild increase in blood urea nitrogen in adults treated with secnidazole, which were not deemed clinically significant.[11] On the other hand N-acetyl cysteine (NAC) is the acetylated precursor of the amino acid L-cysteine and reduced glutathione. It is a safe

and well-tolerated mucolytic drug that enhances glutathione S-transferase activity.[12] However, it has low bioavailability, ranging between 4% and 10%, due to deacetylation during first-pass metabolism in the small intestine and liver. NAC reaches its peak plasma level after 1 hour and disappears from the plasma after 12 hours. NAC stimulates glutathione synthesis, promotes detoxification, and acts directly as a scavenger of free radicals, making it a powerful antioxidant.[13] some study also reported its choriodecidual protecting effect and its anti-inflammatory properties in the pregnant women with bacterial vaginosis.[14] Considering this, the present study aimed to compare the effectiveness and safety of Secnidazole with N-acetyl cysteine for treating Bacterial Vaginosis in reproductive women at a Tertiary care hospital.

METHODOLOGY

Study design and population

The present study was a single blinded randomized experimental study conducted to compare the effectiveness of Secnidazole (2g/day) alone (monotherapy) and the combination of Secnidazole (2g/day) with N-acetyl cysteine (600mg/day) in treating Bacterial Vaginosis in reproductive women at Karpaga Vinayaga Institute of Medical Sciences & Research Centre, Chinnakolambakkam, Kanchipuram District-603 308, Tamil Nadu. The study took place from January 2020 to October 2020, spanning a total of 10 months, including follow-up visits. The study population consisted of reproductive women aged 20 to 50 years attending the gynecology OPD of the institute and diagnosed with Bacterial Vaginosis using Amsel's criteria after providing their informed consent

Inclusion and exclusion criteria

The study includes patients diagnosed with Bacterial Vaginosis who are between 20 and 50 years old and meet the Amsel criteria, which consists of any 3 out of 4 diagnostic factors: homogenous white discharge, vaginal pH of 4.5 or greater, absence of lactobacillus in vaginal smear, and positive whiff test with more than 20% clue cells in Sodium chloride (NaCl) wet mount. The following patients are excluded from the study: pregnant and lactating women, menopausal women, women with reproductive tract malignancy, immunocompromised women, and those who have withdrawn from the study (per protocol analysis)

Sample size calculation and sampling method

As this was the first study conducted in the local setting, there was no existing literature available to guide us in determining the sample size. Therefore, we conducted a pilot study with ten patients evenly allocated to both groups. Based on the pilot study results (measured by Nugent score) [4.06 + 0.98 in the secnidazole alone group vs. 3.42 + 0.85 in the secnidazole with NAC group], we utilized the sample size formula for the difference between two proportions for an unpaired sample. With 90% power and a confidence level of 5%, the total sample size was calculated to be 44 per group. Consequently, we completed the study with 45 samples in each group, allocated equally using the block randomization method.

Study instrument and data collection procedure

Informed consent was obtained after a detailed explanation of the study's purpose and methods. Patients received either Secnidazole or a combination of Secnidazole with N-acetyl cysteine. The treatment period was four weeks, and both medications were administered orally once daily. This is a single blinded study; therefore, patients were unaware of the treatment given to them. Patients were monitored during the 4th, 8th, and 12th weeks of the study. A pretested structured questionnaire was designed to gather information about the patients' demographic profile, clinical history, including present and past, personal and family history, and co-morbidities and given to patient for filling after one week of treatment. Patients were requested to come for follow-up at the 2nd and 3rd month from the date of the end of the initial treatment for the assessment of recurrence. Safety evaluations were

conducted to assess the incidence, intensity, and type of adverse events, as well as changes in the patients' physical examination findings, vital signs, and clinical laboratory findings in both groups.

Ethical consideration

All the investigational procedures and protocols used in this study were reviewed and approved by the Institutional Ethical Committee (IEC Reference No: 22/2016) and were in line with the declaration of Helsinki and Consort guidelines.

RESULTS

In this prospective randomized controlled trial, 133 women of reproductive age (between 20 and 50) with bacterial vaginosis were enrolled to compare the effectiveness of secnidazole (monotherapy) and secnidazole with N-acetyl cysteine. Out of the 133 women, 20 did not give informed consent to participate in the study, and 23 women were excluded for various reasons, as outlined in Figure No. 1. Ultimately, 45 women were randomized to the secnidazole (monotherapy) group and 45 to the secnidazole with N-acetyl cysteine (NAC) group, with an allocation ratio of 1:1.

Figure 1: Recruitment Flowchart of study participants (n = 90)

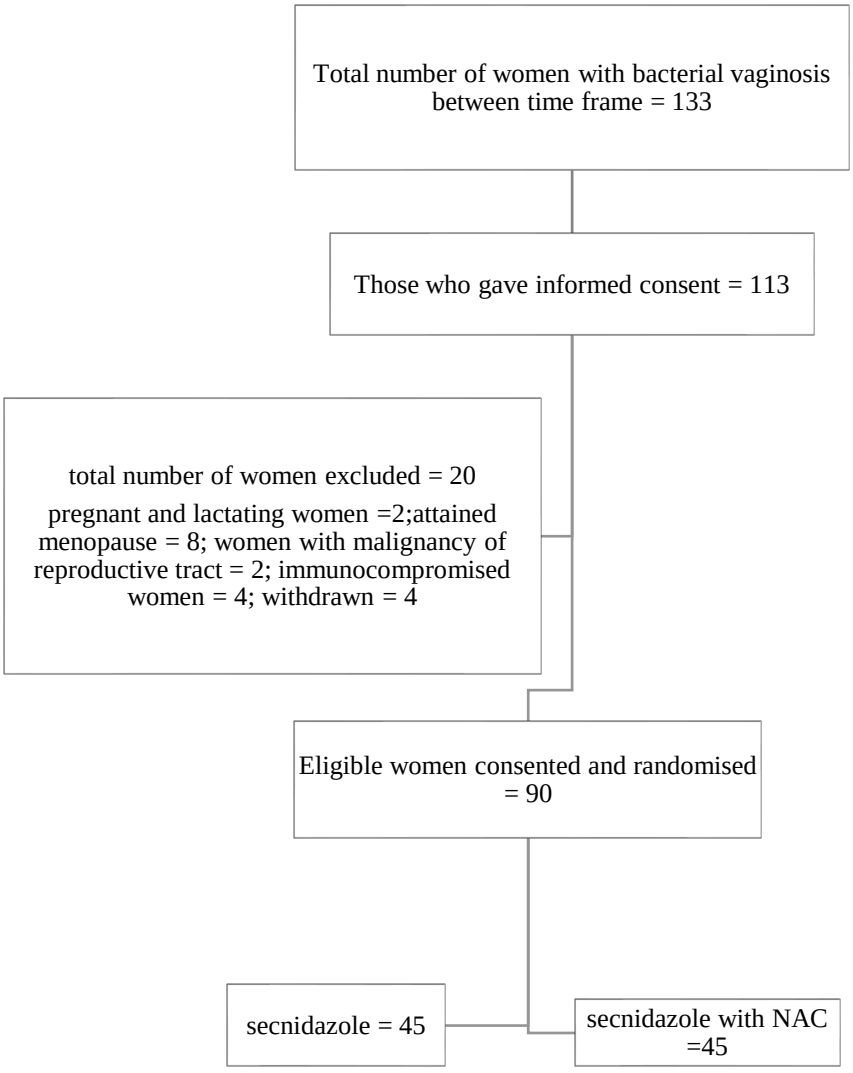


Table no.1: Baseline Demographic, maternal characteristics of study population

Characteristics	Secnidazole (n = 45)	Secnidazole with NAC (n = 45)
Age in groups, n(%)		
<25 years	2(4.4%)	3(6.7%)
26 – 30 years	22(48.8%)	24(53.3%)
31 – 35 years	7(15.6%)	7(15.6%)
36 – 40 years	8(17.8%)	8(17.8%)
41 – 45 years	3(6.7%)	1(2.2%)
>45 years	3(6.7%)	2(4.4%)
Clinical symptoms, n(%)		
Vaginal discharge	20(44.4%)	19(42.2%)
Vaginal pruritus	8(17.8%)	10(22.2%)
Vaginal bleeding	1(2.2%)	2(4.4%)
Abdominal pain	3(6.7%)	2(4.4%)
Others (dysuria, dyspareunia and vaginal malodor)	13(28.9%)	12(26.8%)
No. of BV episodes in last 12 months, n(%)		
< 3 episodes	29 (64.4%)	26 (57.8%)
≥ 3 episodes	16 (35.6%)	19 (42.2%)
Baseline Nugent score , mean (± SD)	7.24 (± 0.98)	7.13 (± 0.96)
Signs of bacterial vaginosis n(%)		
Vaginal PH >4.5	45 (100%)	45 (100%)
Presence of clue cells >20% per HPF	29 (64.4%)	30 (66.7%)
Positive whiff test	44 (97.8%)	41 (91.1%)
Homogenous discharge	30 (66.7%)	32 (71.1%)
Positive Amsel criteria	43 (95.6%)	44 (97.8%)

Table 1 compares the baseline demographic and treatment-related characteristics for both groups. Out of 45 women, most of them in both groups were aged between 26 and 30 years [22 women (48.8%) in the secnidazole group vs. 24 (53.3%) in the secnidazole with NAC group]. Among patients with clinical symptoms, most of them in both groups suffered from vaginal discharge [20 (44.4%) in the secnidazole group vs. 19 (42.2%) in the secnidazole with NAC group], followed by vaginal pruritis [8 (17.8%) in the secnidazole group vs. 10 (22.2%) in the secnidazole with NAC group]. When comparing participants with three or more episodes of bacterial vaginosis in the last 12 months, both groups had an equal number of participants [16 (35.5%) in the secnidazole group vs. 19 (42.2%) in the secnidazole with NAC group]. The baseline Nugent scores were almost similar in both groups, with a mean ± SD of Nugent score in the secnidazole group at 7.24 ± 0.98 vs. 7.13 ± 0.96 in the secnidazole with NAC group. When comparing the signs of bacterial vaginosis in both groups, all the women had vaginal pH > 4.5, and the majority of them had positive Amsel criteria [43 (95.6%) in the secnidazole group vs. 44 (97.8%) in the secnidazole with NAC group). Furthermore, most of the participants showed clue cells of more than 20% in their vaginal smears [29 (64.4%) in the secnidazole group vs. 26 (57.8%) in the secnidazole with NAC group].

The results of the treatment outcome with secnidazole (monotherapy) are summarized in **Table 2**. A paired test and z-test were conducted to compare the pre and post-treatment differences. In the

secnidazole group, there was a notable decrease in the presence of symptoms after treatment [45 (100%) pre-treatment vs. 5 (11.1%) post-treatment], and this difference was found to be statistically significant (p-value <0.01*). Additionally, there were statistically significant differences in the mean ±SD of vaginal pH [5.07 ± 0.39 pre-treatment vs. 4.40 ± 0.49 post-treatment; p-value <0.01*], number of patients with positive whiff test [44 (97.7%) pre-treatment vs. 4 (8.9%) post-treatment; p-value <0.01*], and clue cells >20% [29 (64.4%) pre-treatment vs. 3 (6.7%) post-treatment; p-value <0.01*]. The two groups also exhibited a statistically significant difference in the mean ±SD of baseline Nugent score [7.24 ± 0.98 pre-treatment vs. 4.20 ± 1.37 post-treatment; p-value <0.01*].

Table 2: Paired sample t-test and z-test were done to determine difference in the mean and proportion in the treatment variables of secnidazole group (before and after treatment)

Treatment Variables	Before treatment	After treatment	p-value
Clinical cure			
Clinical symptoms (+)	45 (100%)	5(11.1%)	**<0.01***
Vaginal PH	5.07 ± 0.39	4.40 ± 0.49	**<0.01***
Positive whiff test	44 (97.8%)	4(8.9%)	**<0.01***
Clue cells >20%	29 (64.4%)	3 (6.7%)	**<0.01***
<20%	16 (35.6%)	42 (93.3%)	**<0.01***
Microbiological cure			
Baseline Nugent score	7.24 ± 0.98	4.20 ± 1.37	**<0.01***

The results of the treatment outcome of secnidazole with NAC are outlined in **Table 3**. Within the group, a significant reduction in symptoms was observed after treatment [45 (100%) pre-treatment vs 0 (0%) post-treatment, p-value <0.01*]. There were also marked improvements in vaginal pH, whiff test results, clue cells, and Nugent score after treatment and these difference were found to be statistically significant (p-value <0.01*)

Table 3: Paired sample t-test and z-test were done to determine difference in the mean and proportion in the treatment variables of secnidazole with NAC group (before and after treatment)

Treatment Variables	Before treatment	After treatment	p-value
Clinical cure			
Clinical symptoms (+)	45 (100%)	0(0%)	**<0.01***
Vaginal PH	5.07 ± 0.25	4.31 ± 0.46	**<0.01***
Positive whiff test	41 (91.1%)	0(0%)	**<0.01***
Clue cells >20%	30 (33.3%)	2 (4.4%)	**<0.01***
<20%	15 (66.7%)	43 (95.6%)	**<0.01***
Microbiological cure			
Baseline Nugent score	7.13 ± 0.96	2.67 ± 0.87	**<0.01***

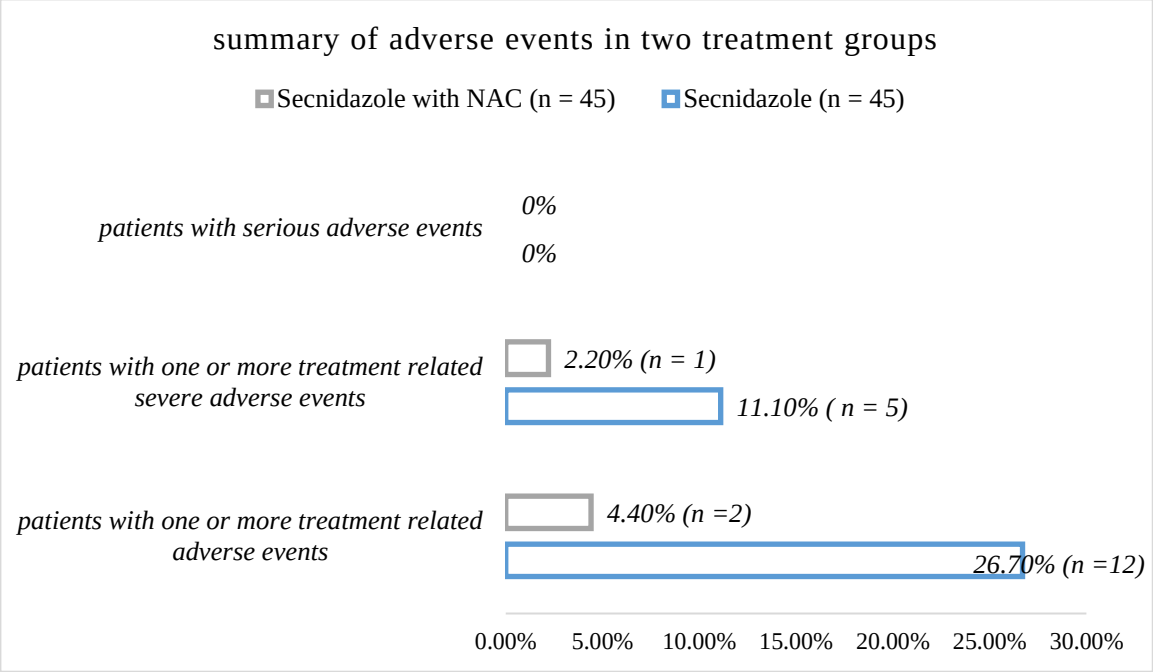
The treatment outcomes were compared between two groups: one receiving secnidazole alone and the other receiving secnidazole along with NAC. The results are outlined in **Table 4**. An Independent t-test was conducted to compare both groups. There was a statistically significant difference in the symptomatic cure (5 out of 45 patients in the secnidazole group, and none out of 45 patients in the secnidazole with NAC group; p-value < 0.01) and positive whiff test (4 out of 45 patients in the secnidazole group, and none out of 45 patients in the secnidazole with NAC group; p-value < 0.01). However, there was no significant difference in vaginal pH (4.40 ± 0.49 in secnidazole group vs. 4.31 ± 0.46 in secnidazole with NAC group; p-value = 0.37) and presence of clue cells <20 [42(93.3%) in the secnidazole group, and 43(95.6%) in the secnidazole with NAC group; p-value = 0.53). Additionally, there were statistically significant differences in the mean ± SD of baseline Nugent

score between the two groups (4.20 ± 1.37 in secnidazole group vs. 2.67 ± 0.87 in secnidazole with NAC group; p-value < 0.01*)

Table 4: independent t-test and z-test were done to determine treatment difference between secnidazole (monotherapy) group and secnidazole with NAC group [after treatment]

Treatment Variables	Secnidazole (n = 45)	Secnidazole with NAC (n = 45)	p-value
Clinical cure			
Clinical symptoms (+)	5(11.1%)	0(0%)	**0.02***
Vaginal PH	4.40 ± 0.49	4.31 ± 0.46	0.37
Positive whiff test	4(8.9%)	0(0%)	**0.05***
Clue cells >20%	3 (6.7%)	2 (4.4%)	0.17
<20%	42 (93.3%)	43 (95.6%)	0.53
Microbiological cure			
Baseline Nugent score	4.20 ± 1.37	2.67 ± 0.87	**<0.01***

In **Figure 2,** the summary of adverse events reported in both groups is depicted. No treatment-related severe incidents were reported in either group. However, in terms of treatment-related adverse events, 12 patients (26.7%) in the secnidazole group (monotherapy) experienced more episodes of nausea, headache, diarrhea, and abdominal pain compared to the patients who received secnidazole along with NAC [2 (4.40%)]. In the case of severe symptoms, only one patient on the secnidazole with NAC experienced them compared to those who received monotherapy [5 (11.1%)].



DISCUSSION

Our study was a randomized experimental study comparing the effectiveness of Secnidazole (monotherapy) and the combination of Secnidazole with N-acetyl cysteine in treating Bacterial Vaginosis (based on Amsel criteria) in women aged 20 to 50 years. Each group consisted of 45 participants who were single-blinded about treatment. The data collector and data analyst were not blinded, and the collected data were analyzed using per-protocol analysis. When we compared the baseline demographic and general characteristics for both groups, we found that most of the participants in both groups were aged between 26 and 30 years, and they commonly experienced vaginal discharge (44.4% in the secnidazole group vs. 42.2% in the secnidazole with NAC group). In

a randomized trial conducted by Hiller et al., the efficacy and safety of a single oral dose of 1 or 2 g secnidazole in women diagnosed with bacterial vaginosis was evaluated, and they found that the median age of the women in the study was 33 years.[15] Similarly, Eschenbach et al.in their research found that 69% of women with BV showed signs of homogeneous discharge.[16]

In our study, when comparing the recurrence rate of BV in both groups, we found that most of the subjects (16 out of 45, or 35.5% in the secnidazole group vs. 19 out of 45, or 42.2% in the secnidazole with NAC group) in both groups had a history of three or more episodes of bacterial vaginosis in the last 12 months. This finding is consistent with the results of Chavoustie et al.'s open-label randomized trial, which showed that 79.1% of women reported a recurrence of BV three times a year.[6] Similarly, the baseline Nugent scores were similar in both groups (7.24 ± 0.98 in the secnidazole alone group vs. 7.13 ± 0.96 in the secnidazole with NAC group). Additionally, Pentikis et al., in their double-blinded clinical trial, reported that the average number of BV episodes in a year was three, which aligns with our findings.[17] Almost all of the subjects in our study had positive Amsel criteria, elevated vaginal pH (>4.5), and most showed clue cells of more than 20% in their wet mount (29 out of 45, or 64.4% in the secnidazole group vs. 26 out of 45, or 57.8% in the secnidazole with NAC group). Hiller et al. also reported a median baseline Nugent score of 8, similar to our findings.[15] Similarly, Eschenbach et al. in his study found that all women with clue cells of more than 20% had a vaginal pH of more than 4.7.[16]

We analyzed the pre- and post-treatment outcomes of secnidazole (monotherapy) and secnidazole with the NAC group. In the secnidazole group, there was a significant change in the clinical symptoms [45 (100%) vs. 5 (11.1%)] and vaginal pH [5.07 ± 0.39 vs. 4.40 ± 0.49*] after the treatment. They also exhibited a statistically significant difference in their baseline Nugent score [7.24 ± 0.98 pre-treatment vs. 4.20 ± 1.37 post-treatment; p-value <0.01*]. Similarly, in the group administered with combination therapy also showed a significant reduction in symptoms after treatment [45 (100%) pre-treatment vs. 0 (0%) post-treatment, p-value <0.01*]. They also showed marked improvements in vaginal pH, whiff test results, clue cells, and Nugent score. Aziz et al. systematically reviewed secnidazole as a treatment for bacterial vaginosis. They outlined that the clinical, microbiological, and therapeutic cure rate of secnidazole (2g) was not different from metronidazole or secnidazole plus vaginal metronidazole or secnidazole plus vaginal ornidazole.[18] In our study, both groups showed better after treatment outcomes in terms of symptomatic and microbiological cures.

However, when we further compare the clinical and microbiological cure rate of secnidazole (monotherapy) with combined therapy (secnidazole with NAC), there was a statistically significant difference in the symptomatic cure and a marked reduction in clue cells <20 in the group treated with combined therapy. Additionally, there was a statistically significant reduction in baseline Nugent score between the two groups (4.20 ± 1.37 in the secnidazole group vs 2.67 ± 0.87 in the secnidazole with the NAC group; p-value < 0.01*). Mokhtari et al reviewed in this study that NAC generally reduces the inflammatory response, regardless of whether the infection started before or after treatment with the drug.[19] Similarly, according to Shahin et al., women with a history of preterm birth and bacterial vaginosis can take 0.6 g of NAC orally along with progesterone after week 16 of pregnancy to prevent preterm birth recurrence and improve neonatal outcomes.[14]This clearly demonstrates the antioxidant property of N-acetyl cysteine and its superiority in reducing the inflammatory response when given in combination with secnidazole.

Our study also evaluated the treatment-related adverse events. We found that patients in the secnidazole group (monotherapy) experienced more episodes of nausea, headache, and other gastrointestinal symptoms compared to the patients who received secnidazole along with NAC. Chavoustie et al. also pointed out in their study that the most frequently reported adverse events related to treatment with 2g secnidazole were vulvovaginal mycotic infection, nausea, and dysgeusia.[6] This suggests that the safety and efficacy of secnidazole in combination with NAC is better in addressing nausea and other gastrointestinal symptoms.

CONCLUSION

Our study recommends that the results of combining secnidazole with N-acetyl cysteine have been very promising for the broader clinical use of NAC as an adjuvant therapy for bacterial vaginosis. This is due to its antioxidant properties and its ability to inhibit biofilm formation. In addition, the group treated with Secnidazole and NAC showed a significant reduction in clinical symptoms compared to baseline therapy and a better response than when each drug was used individually, based on efficacy parameters such as Nugent's score, vaginal pH, and discharge. The safety of the combined treatment was assessed through laboratory findings and adverse events, and was found to be more favorable compared to the group treated with secnidazole alone.

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