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A double-blind randomized clinical trial of novel Ayurvedic muco-adhesive extended release vaginal tablet (NA) for treatment of leucorrhea

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Abstract
Leucorrhea or vaginitis could be primarily caused by yeast infections, bacterial vaginosis or Trichomoniasis. The hydro-alcoholic extract of a novel vaginal herbal formulation was prepared by adding dried stems of *Azadirachta indica* A. Juss. and *Saraca asoca* Roxb., mentioned in Ayurvedic text Charak Samhita for treatment of excessive vaginal discharge. Pre-clinical studies revealed antimicrobial action, no toxicity, presence of phenolic compounds and sustained drug release pattern for this muco-adhesive vaginal tablet. This double-blind randomized clinical study was done on 363 females equally divided into the placebo, standard drug, and four research drug groups for 15 days. Subjective primary and secondary symptoms as well as objective biochemical parameters and vaginal fluid were analyzed before and after treatment.
Results of clinical study indicate that all four research drug groups exhibited comparable and sometimes better therapeutic efficacy compared to standard drug. The research formulation resulted in 80-90% inhibition of subjective symptoms and demonstrated strong and significant ($p < 0.05$) antimicrobial action validating its high therapeutic efficacy.

Keywords: Leucorrhea, vaginitis, ayurvedic, vaginal tablet, clinical trial

1. Introduction
Vaginitis or leucorrhoea is a common medical problem in women that is associated with substantial discomfort and frequent medical visits. The vagina normally contains a healthy balance of bacteria and yeast. The hormone estrogen helps bacteria called *lactobacilli* to grow and kill harmful organisms in the vagina. Substances from the vulvar, sebaceous, sweat, Bartholin's and Skene's glands, as well as exfoliated cells, cervical mucus, and secretions of the endometrial cavity and fallopian tubes constitute the normal physiologic secretions of the vagina. These secretions pool in the posterior fornix and do not adhere to the vaginal walls. Cervical mucus becomes more fluid around ovulation. In contrast, a pathologic discharge adheres to the vaginal walls and is often accompanied by irritation, pruritus, odour, or urinary symptoms such as dysuria or frequency. Common causes of an abnormal discharge include infectious causes of vaginitis such as yeast infection (caused by a fungus called Candida albicans), bacterial vaginosis, and trichomonas infection (caused by a protozoan parasite) apart from other pathological reasons [1-5].
The hydro-alcoholic (70:30) extract of Research Ayurvedic vaginal herbal formulation was prepared by adding equal amounts of dried parts of the stem bark of *Azadirachta indica* A. Juss. and *Saraca asoca* Roxb. since these two plants have been used since ancient times in the Ayurvedic system of medicine and elaborated in ancient texts such as Charak Samhita (Chikitsa Sthanam) as an astringent, anti-inflammatory & haemostatic and useful for arresting excessive abnormal vaginal discharge [6-8]. These plants are reported for their anti-inflammatory, antimicrobial, antioxidant, wound-healing, antifungal & antipyretic properties and efficacious in arresting excessive abnormal vaginal discharge, excessive bleeding disorders and other gynecological diseases due to the presence of tannin, alkaloids, flavonoidic chemical compounds in new formulation [9-11]. This new herbal vaginal formulation is likely to exhibit sustained and significant antimicrobial action due to the synergetic effect of the phenolic and flavonoidic compounds like nimbin, azadirachtin in Neem and Quercetin, saponin, tannin & hematoxylin in Ashoka plant present in this research drug [12-13]. The reported pharmacological properties of its constituent herbs include anthelmintic, anti-fungal, anti-diabetic, antibacterial, antiviral, contraceptive and sedative in Nimba tree and uterogenic, antibacterial, oxytocic, anti-tumor, anticancer, anti-progestational in Ashoka plant [14-17].

Many herbal plants and their combinations in the nature of Ayurvedic drugs have been prescribed for oral administration and external application in the Ayurvedic text for the treatment of menstrual problems and vaginitis or leucorrhoea.

The results of preclinical study relating to pharmacognostical evaluation and standardization of this vaginal formulation revealed substantial amounts of phenolic and flavonidic compounds. After detailed analysis of six possible types of muco-adhesive vaginal tablets having same amount of research drug and varying amounts of excipients, binders and developers, it was found that the research formulation F-V_{NA}(iv) is the most suitable formulation due to its high muco-adhesive strength, low swelling index and maximum sustained drug releasing pattern. Analysis of its in-vitro kinetic drug release pattern indicated similarity with the first-order Fickian diffusion model, while the in-situ kinetic release study revealed that maximum drug concentration remained in vagina mucus membrane even after 24 hours, indicating sustained release of anti-vaginitis and anti-leucorrhoea drug delivery system in the form of an effective muco-adhesive tablet. Comparison of efficacy of F-V_{NA}(iv) with standard Candid-V6 tablet using zone of inhibition method suggested comparable but slightly lower antibacterial and antifungal activity against E. coli and Candida albicans microbes. HPTLC analysis at 277 nm wavelength suggested the presence of phenolic compounds Gallic acid and Quercetin in F-V_{NA}(iv) which could be directly related to its antimicrobial, antioxidant and anti-inflammatory activities. These phenolic chemical compounds could be directly related to the antimicrobial, antioxidant and anti-inflammatory activities of the herbal vaginal tablet F-V_{NA}(iv). These findings during the pre-clinical phase indicated that this formulation was likely to provide sustained release of anti-vaginitis and anti-leucorrhoea drug delivery system in the form of an effective muco-adhesive vaginal tablet [18-20].

The purpose of the present clinical study was to evaluate the efficacy of this novel Ayurvedic formulation (NA) in the form of muco-adhesive extended release herbal vaginal tablet for the treatment of excessive abnormal vaginal discharge in female subjects through double-blind randomized clinical trials. The study also compared the efficacy of the research drug with the standard modern drug Candid using the intravaginal route. The clinical trials also assessed the additional therapeutic impact of administering the research drug through oral route or as ointment for local application to supplement the vaginal tablet in the treatment of excessive vaginal discharge, irritation, itching etc.

2. Materials & methods

2.1. Plant materials

The stem barks of *Saraca asoca* Roxb. and *Azadirachta indica* A. Juss. were purchased from the crude drug supplier of Katwa Chowrasta, Burdwan district and plant samples were authenticated as per Ref./no. BSI/Pharma/SD/Tech./2017 by the Botanical Survey of India, Howrah, India. Authenticated specimens were deposited bearing numbers IPGAE&R/ Dravyaguna/ M. Gupta/09 & IPGAE&R/ Dravyaguna/ M. Gupta/10 in the herbarium museum of the department of Dravyaguna at I.P.G.A.E.&R., Kolkata for future reference.

2.2. Preparation of extracts, muco-adhesive vaginal tablets and their standardization

The stem barks of both plants were washed, air-dried and pre-heated in oven before being powdered in a grinding machine to 40# mesh particle size and mixed in an equal ratio. This coarse powder was sequentially extracted with petroleum ether (60°C – 80°C), chloroform, acetone, ethanol and water using Soxhlet apparatus. The hydro alcoholic extract was also prepared in the ratio of 70:30. These extracts were filtered using a Buckner funnel and Whatman-1 filter paper at room temperature, concentrated at reduced temperature and pressure using rotary evaporator, and then stored in refrigerator below 8°C for subsequent experiments.

The basic physio-chemical & phytochemical properties of the research drug in powder form and its hydro alcoholic extract are given below in table 1. After formulating various combinations of excipients, binders and developers, the most suitable muco-adhesive tablet F-VNA (iv) shown in figure 1 was taken up for standardization. The comparison of the properties of this research formulation with standard marketed muco-adhesive vaginal formulation 'Candid-V6' have been given in table 2.

Table 1: Results of the basic physio-chemical & phytochemical studies of research drug

Parameter	Value
Total Ash value (in % w/w)	9.43
Acid insoluble Ash (in % w/w)	1.89
Water soluble Ash (in % w/w)	7.65
pH value	4.62
Moisture Content (in % w/w)	7.70
Extractive value of hydro-alcoholic extract (in % w/w)	8.17
Elemental N, S, Cl, Br, I and P analysis	Nitrogen & Sulphur present
Total Aflatoxin analysis	Not detected
As, Hg, Cd and Pb heavy metal analysis for Impurities	Found lower than acceptance limits
Phytochemical constituents analysis using standard methods	alkaloids, flavonoids, tannins carbohydrates & saponin present
Flavonoid content (µg Quercetin equivalent / mg of extract) (R^2 =0.999)	43.37 µg/mg
Phenol content (µg Gallic acid equivalent / mg of extract) (R^2 =0.997)	101.22 µg/mg

Table 2: Comparative data of properties of research tablet formulation F-V_{NA} (iv) with standard 'Candid-V6' muco-adhesive vaginal tablets

S. No.	Parameter	F-V_{NA} (iv) tablets	CANDID-V6
1	Weight variation (mg)	994.50 ± 10.20	1046.1 ± 15.2
2	Thickness (mm)	5.90 ± 0.03	6.00 ± 0.02
3	Hardness (kg/sq.cm)	10.2 ± 4.04	8.2 ± 1.5
4	Friability (%w/w)	1.16	0.06
5	Surface pH	4.82 ± 0.05	6.56 ± 0.04
6	Swelling Index at 24 hour (%w/w)	53.18 ± 3.28	10.41 ± 0.52
7	Mucoadhesive force (Newton)	0.788 ± 0.04	0.701 ± 0.018
8	Dissolution study at 12 hour (%w/w)	81.17 ± 2.85	-
9	In situ release study at 12 hour (%w/w)	28.12 ± 1.88	-
10	In situ release study at 24 hour (%w/w)	34.70 ± 0.83	-
11	Zone of Inhibition for *Escherichia coli* (mm)	8.75 ± 0.20	20.2 ± 0.1
12	Zone of Inhibition for *Candida albicans* (mm)	12.50 ± 0.34	16.6 ± 0.1

Fig 1: Prepared vaginal tablet

The research drug was also prepared in the form of capsules having average weight of ingredients 629.5 ± 1.94 mg and disintegration time of 2 minutes 45 seconds while the dissolution time is 30 minutes. Similarly, the ointment form of the research drug had a pH of 4.5 ± 0.08, in two different assays of 5% and 10%. After all the above mentioned pharmacognostical, standardization and pre-clinical studies yielded satisfactory results, the research formulation was taken up for clinical studies.

2.3 Clinical studies

Placebo-controlled double blind randomized clinical trials (CTRI Registration No: CTRI/2019/04/018852 registered on 30.04.19) were undertaken in the Outdoor patients' department of the hospital of I.P.G.A.E&R. Kolkata after getting approval from the Institutional ethical committee (No. SVP/564/2017 dated 29.05.17) involving female subjects who had given their informed consent in the prescribed proforma following the guidelines of the ICMR on biomedical research. 363 female patients in the 15-55 years' age group suffering from abnormal vaginal discharge, excessive vaginal irritation and itching were randomly selected subject to the following exclusion criteria: (i) pregnancy (ii) history of prolapsed uterus (iii) malignancy (iv) allergy or severe illness. 319 subjects finally completed the study in all respects. All subjects were randomly allocated to the 6 groups as detailed in figure 2 and table 3 and treated for 15 days with a follow-up period of 28 days.

The treatment allocation schedule was based on computer-generated random numbers. The study medication was provided in white paper boxes, numbered consecutively with a medication number. The treatment codes were residing with the principal investigator and the local investigators were not aware of treatment assignments.

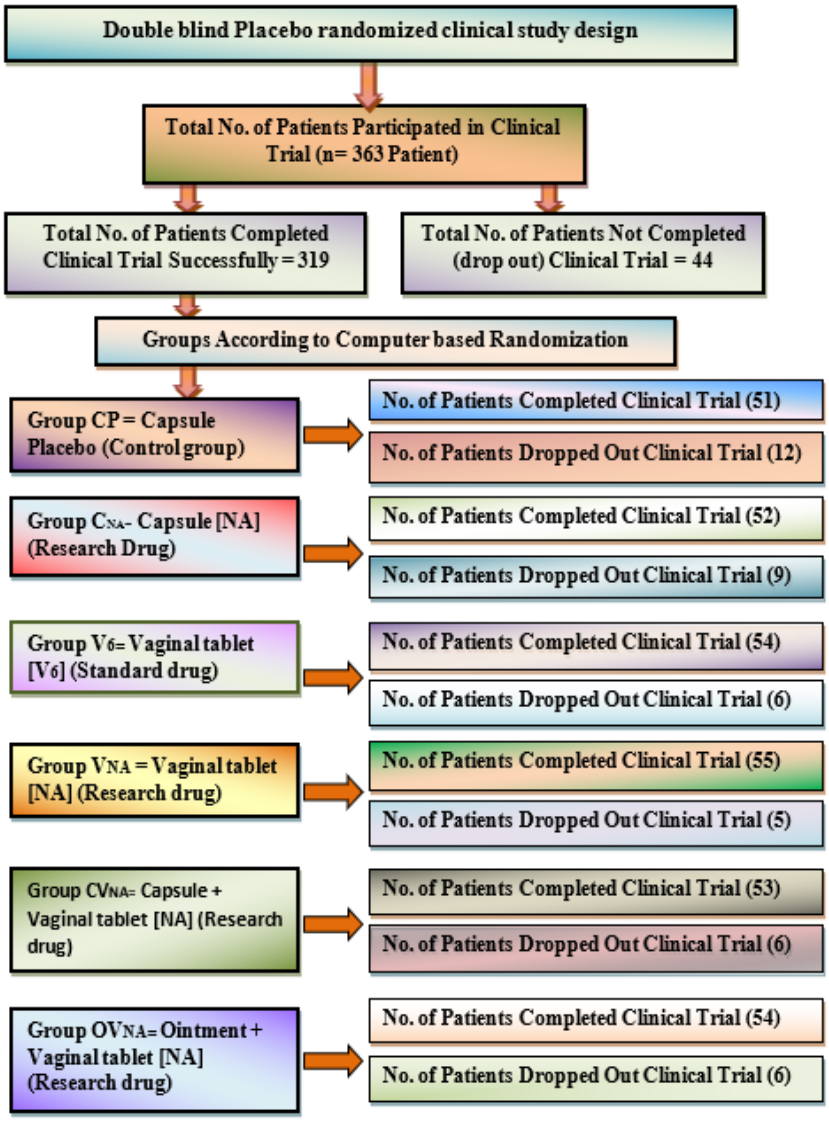


Fig 2: Distribution of patients among groups during clinical study

Table 3: Treatment Groups and route of administration

Treatment Group	Route of administration
Group CP	Oral
Group CNA	Oral
Group V_6	Intra-vaginal with applicator
Group VNA	Intra-vaginal with applicator
Group CVNA	Oral & Intra-vaginal with applicator
Group OVNA	Ointment (external) & Intra-vaginal with applicator

Subjective assessment of the primary and secondary symptoms of all the participants was carried out before and just after the study period. The primary symptoms studied included - excessive abnormal secretion of vaginal white discharge, itching around the external genital parts, swelling & redness of the genital parts, and odour. Evaluation was conducted of the following secondary symptoms - pain in the back region, constipation, loss of appetite, painful intercourse, and wellbeing of the patient. The severity of these physical symptoms was evaluated by using an arbitrary grading scale (0-25% (+), 25%-50% (++), 50%-75% (+++), 75%-100% (++++)).

Evaluation of objective parameters of each patient such as estimation of hematological parameters, liver function test, hormonal tests, vaginal discharge tests and routine urine tests was done pre and post treatment during this study. Analysis of vaginal fluid included vaginal swab study, determination of vaginal pH test, vaginal smear examination, vaginal wet mount (KOH) test and vaginal pap smear study. The presence of specific type of infection was assessed in each patient using the clinical symptoms, pH values and microscopic analysis as detailed below in table 4.

Table 4: General indicators of various types of infections

Parameter	Diagnosis		
	Candidiasis	**Trichimoniasis**	**Bacterial vaginosis**
Clinical	curdy", pruritus+++ no odour, white-yellow	no curds, pruritus+ + odour+++, yellow-green	no curds, pruritus+ odour+++, thin-gray
pH	< 4.5	> 5.0	> 5.0
Microscopic	KOH mount Hyphae & spores	WET prep motile trich "Whiff test"+	WET prep clue cells "Whiff test"+

2.4. Statistical analysis

The ANOVA test of variance was used for analysis of the obtained results. Statistical significance was benchmarked at $p < 0.05$.

3. Results

The demographic profile of the patients in terms of their age group, locality, religion, marital status, number of children, food habits and occupation is shown in figure 3.

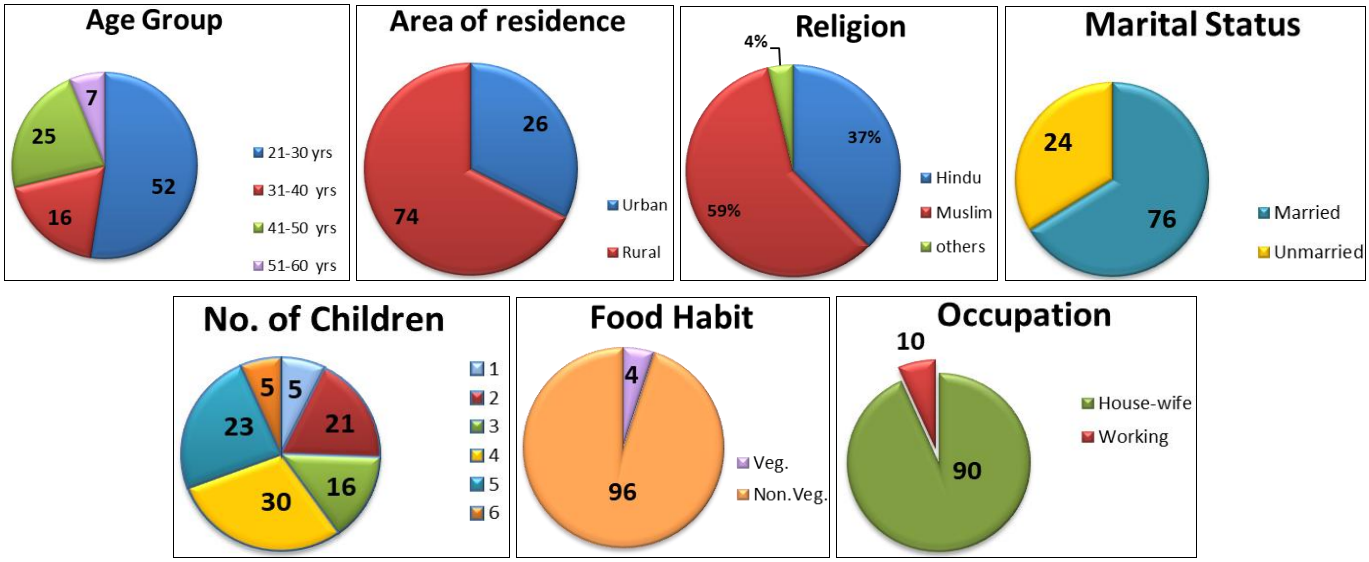
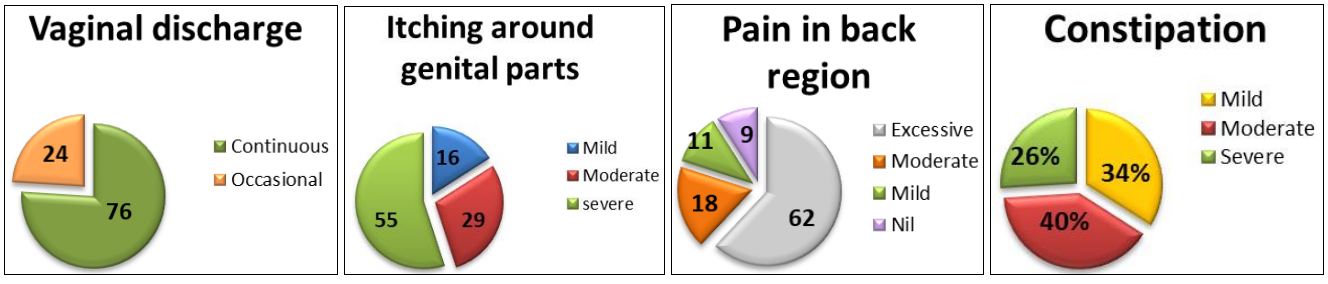


Fig 3: Percentage break-up of various demographic parameters

The symptoms of the patients were analysed in terms of their vaginal discharge, itching around genital parts, pain in the back region, constipation, loss of appetite, painful intercourse, and wellbeing of the patient, and the obtained results are shown in figure 4.



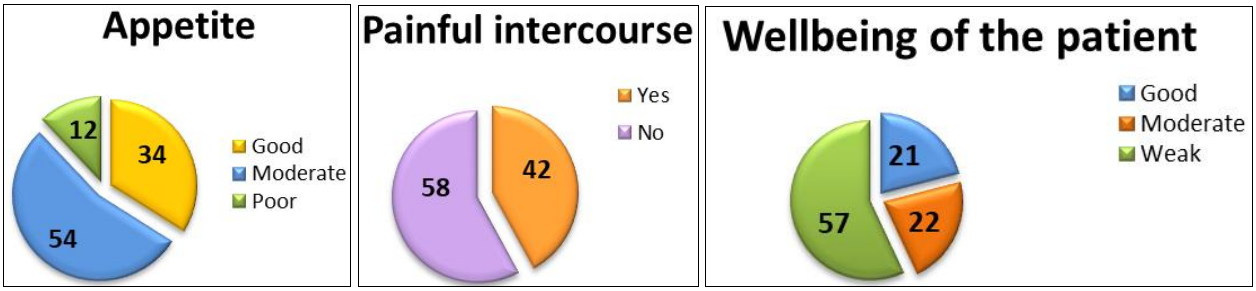


Fig 4: Distribution profile of symptoms of patients

3.1. Assessment of subjective parameters (primary and secondary symptoms)

3.1.1. Primary symptoms

The assessment of primary symptoms was done before and after the study period and their percentage inhibition during these 15 days was calculated as detailed in table 5, while the comparative position is depicted in figure 5.

Table 5: Percentage inhibition of primary symptoms in various groups

Primary Symptoms	% of Inhibition after 15 Days					
	CP	CNA	V6	VNA	CVNA	OVNA
Excessive vaginal discharge	25	75	96	94	92	93
Itching around genitals	27	59	87	89	85	94
Swelling & Redness of genitals	33	52	90	92	89	93
Odour of vaginal fluid	21	70	90	91	85	90

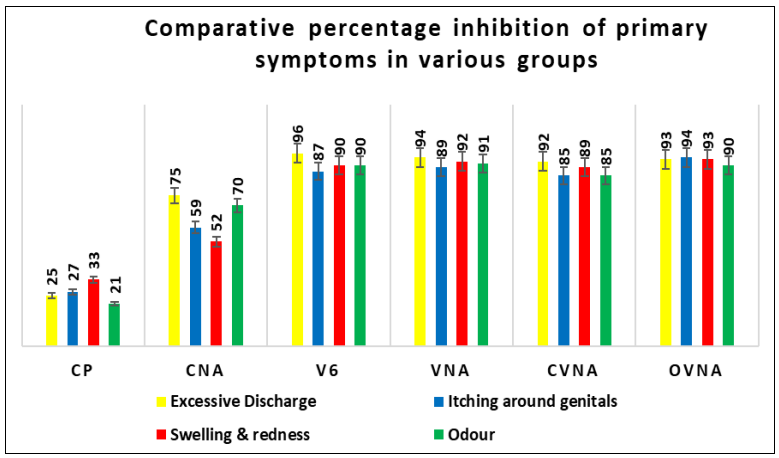


Fig 5: Inhibition of primary symptoms in various groups

Analysis of the data presented above indicates that inhibition of the primary symptoms was found to be lowest in Group CP (21 - 33%) followed by Group CNA (52-75%) as compared to the other four groups. Differences in inhibition among V6, VNA, CVNA and OVNA groups were small, but comparatively lower rates were observed in CVNA, followed by V6, and VNA while OVNA seemed to result in overall highest inhibition rates ($p < 0.05$).

3.1.2. Secondary symptoms

Evaluation of the inhibition rates in respect of the secondary symptoms is shown in figure 6.

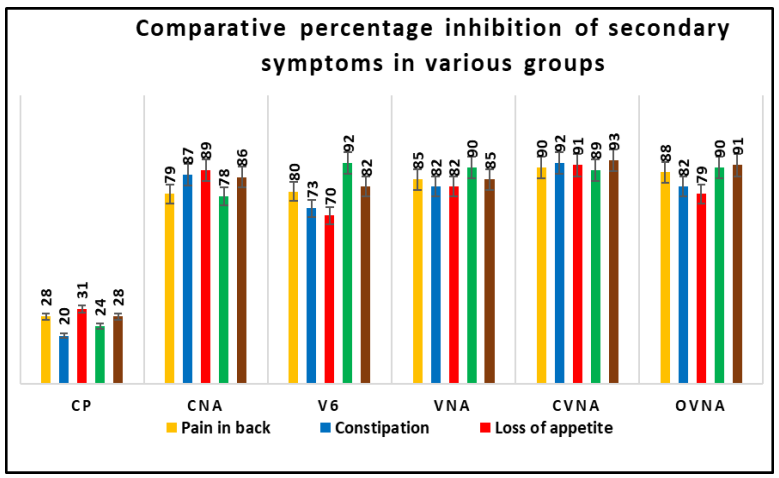


Fig 6: Inhibition of secondary symptoms in various groups

Analysis of data presented above indicates that inhibition of the secondary symptoms was found to be lowest in Group CP (20 - 31%) as compared to the other groups. Differences in inhibition among CNA, V6, VNA, CVNA and OVNA groups were small, but comparatively lower rates were observed in V6, followed by CNA, OVNA, and VNA while CVNA seemed to have significantly ($p < 0.05$) higher inhibition rates. The efficacy of various groups in terms of symptomatic relief where intra-vaginal route of drug administration was used is depicted in figure 7. Similarly, the percentage inhibition of the various primary and secondary symptoms in case of all treatment groups dealing with the research drug is shown in figure 8.

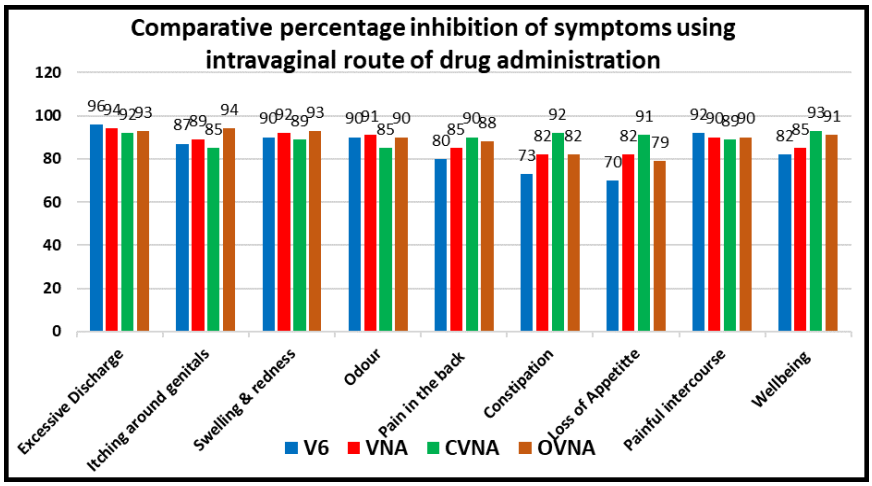


Fig 7: Inhibition of symptoms using intravaginal route drug administration

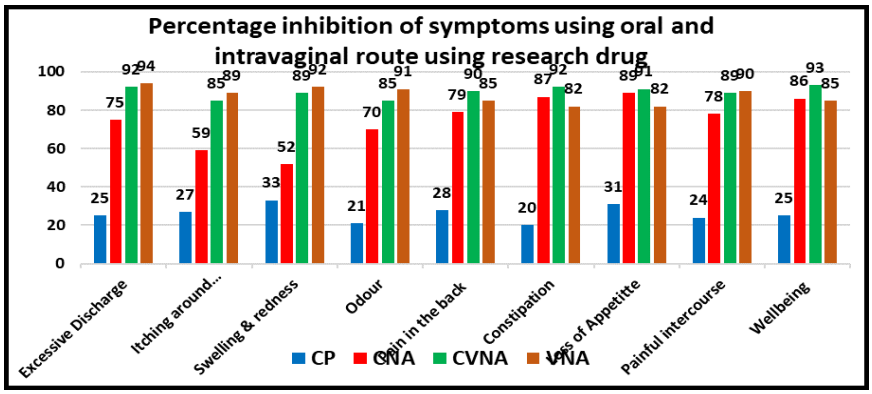


Fig 8: Inhibition of symptoms using oral & intravaginal route using research drug

3.2. Assessment of objective parameters

The results obtained during the hematological examination & liver function test are shown in table 6 while the changes in various parameters observed during the urine analysis are detailed in table 7.

Table 6: Percentage change in biochemical parameters during study

Parameter	Group					
	CP	CNA	V6	VNA	CVNA	OVNA
Total Count (per c.dm.)	2	3	2	3	2	-2
E.S.R. (mm 1hr.)	-0.5	-0.6	-1.5	-0.9	-0.5	-0.5
Blood glucose (mg/dl)	-0.2	-3	-0.2	-1.2	0.8	-0.9
Bilirubin (mg/dl)	-4.3	-7.5	-11.1	-25	0	18.9
Total Protein (gm/dl)	0.4	1.4	0.4	0.4	0.4	0.4
S.G.O.T. (u/ml)	1.5	2.5	4.5	3.5	2.5	-3.5
S.G.P.T. (u/ml)	-0.3	-2	-0.3	-0.3	-0.7	-6.3
Alkaline Phosphatase (IU/L)	2.23	-5.61	10.25	2.23	-4.91	-1.53

Table 7: Percentage change in urine parameters

Urine tests		% of Inhibition after 15 Days					
		CP	CNA	V6	VNA	CVNA	OVNA
Chemical Examination	Reaction (Acidic/Alkaline)	0	2	2.5	4	2	1.5
	Presence of any compound (Protein/Sugar/ Occult Blood /Crystal)	0	0	1	1.2	1	2
Microscopic Examination	Pus Cells / H.P.F.	0	1	2	1.4	2.2	1.4
	R.B.C. / H.P.F.	0	1.2	1.4	1.8	1	1.2

The changes noticed during the study in the hormonal levels of the subjects are shown in table 8.

Table 8: Percentage changes in hormonal parameters during study

Parameter	Group					
	CP	CNA	V6	VNA	CVNA	OVNA
Thyroid Stimulating Hormone (mcU/ml)	-2.02	0.68	1.57	-0.45	0.11	-0.03
FSH (mIU/ml)	-2	0.74	0.44	-1.21	0.11	1.66
LH (mIU/ml)	0.2	0.7	1	0.2	-2.1	-0.9
Prolactin (ng/ml)	-0.19	0.45	-1.78	0.44	-0.78	0.88

3.3. Analysis of vaginal fluid

The results obtained for various parameters of vaginal fluid swab analysis (including pH), microscopic analysis and the observed clinical symptoms provided a clear indication of the infection, namely candidiasis, trichomonas and bacterial vaginosis. The prevalence of each of these infections is shown in figures 9, 10 and 11.

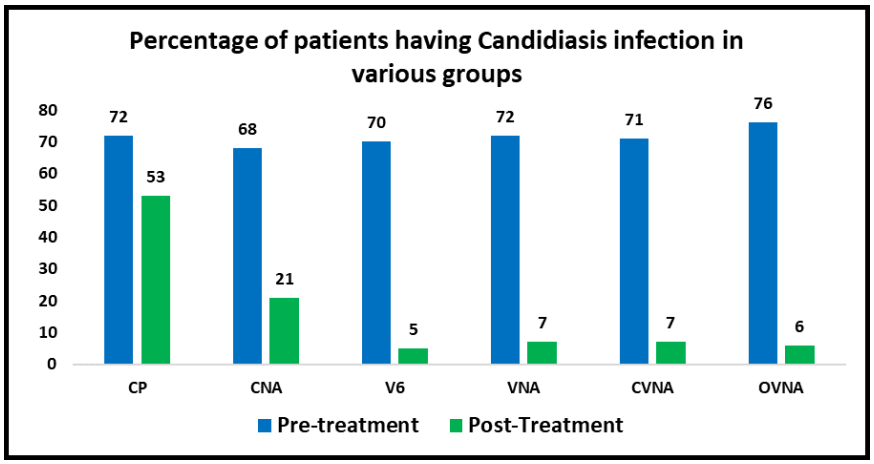


Fig 9: Percentage of patients having Candidiasis after treatment

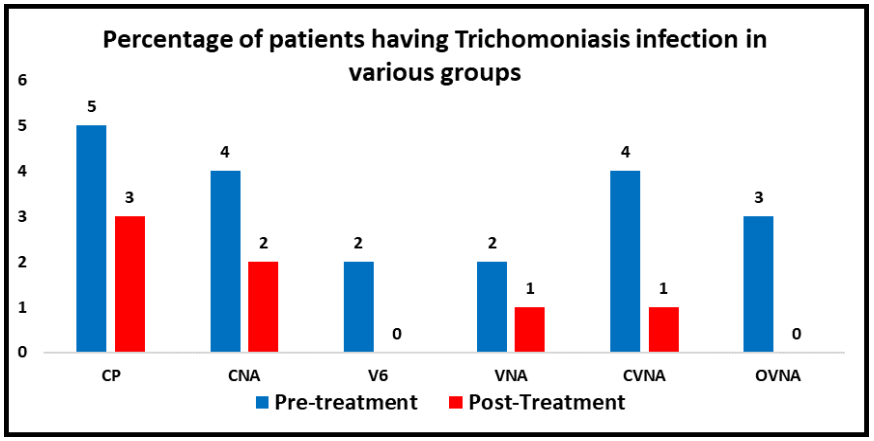


Fig 10: Percentage of patients having Trichomoniasis after treatment

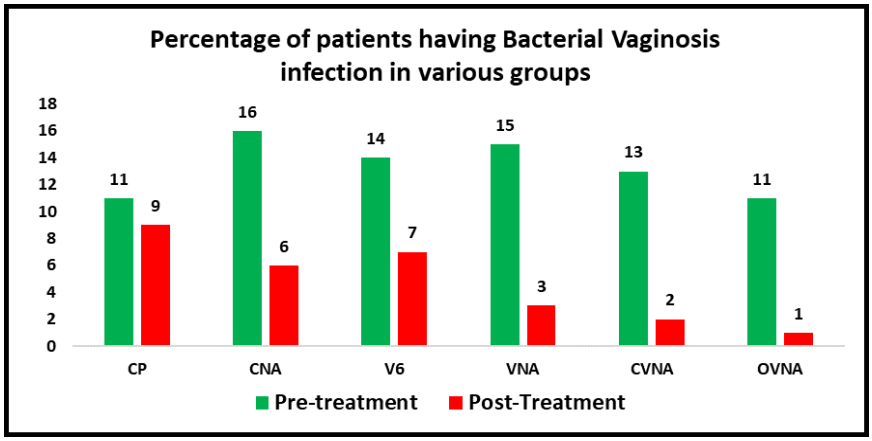
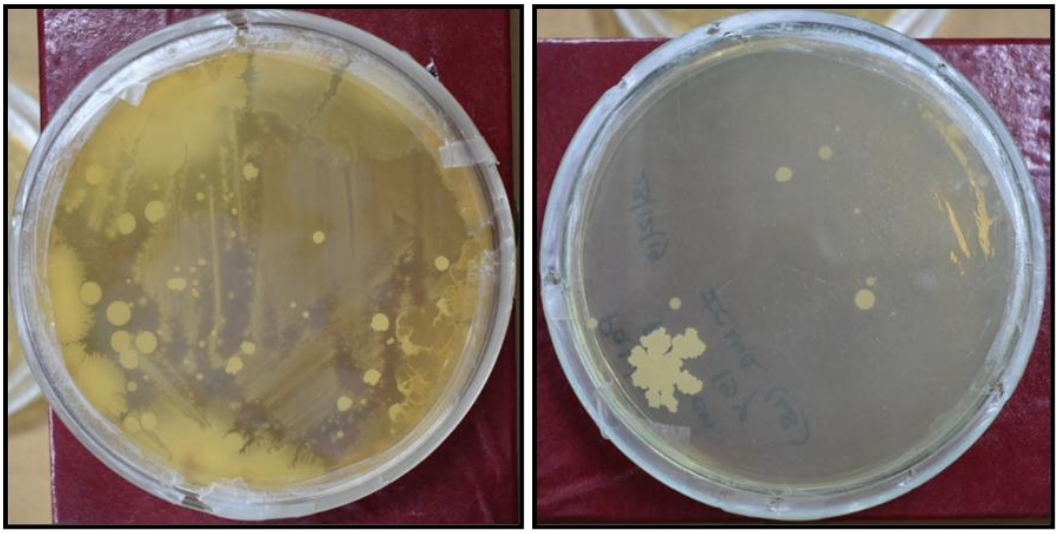


Fig 11: Percentage of patients having Bacterial Vaginosis after treatment

3.3.1. Vaginal wet mount (KOH) test

The photographs of the petri dishes used during this test before and after treatment are shown as figure 12. Vaginal swab study shows that the patients of various groups may have bacterial or fungal growth in the vaginal mucosa at the initial stage (pre-treatment phase) when tested at pathological laboratory. After treatment it is observed that all groups effectively reduced the growth of micro-organisms and showed better results in the post-treatment phase.

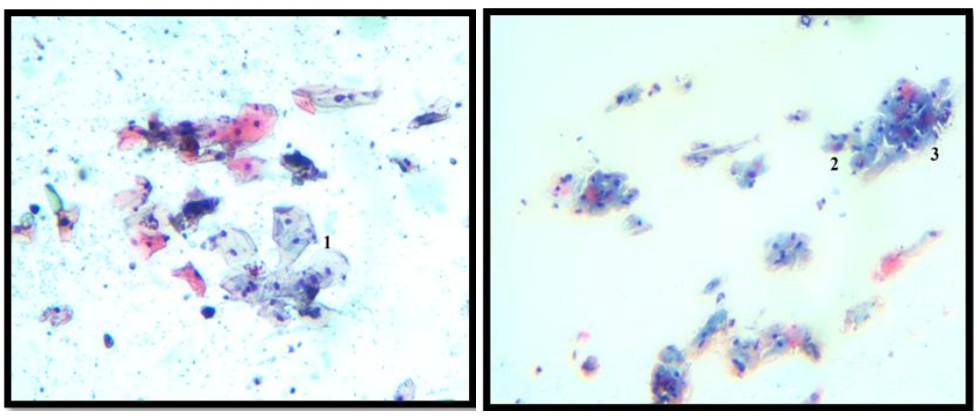


Pre-treatment **Post-treatment**

Fig 12: Condition of bacterial and fungal colonies before & after treatment

3.3.2. Vaginal Pap Smear Study

The findings after conducting vaginal pap smear test are shown in figure 13. After treatment, all important cell structures were found intact. Neither any special changes nor any necrosis was observed.



Pre-treatment **Post-treatment**

Fig 13: Images of the vaginal pap smear test under Olympus Microscope (10 X)

4. Discussion

The results of demographic classification of all the study subjects showed that most of patients belonged to the 21-40 years' age group, with 74% staying in the rural areas, mostly believing in Muslim religion, 76% were married women having more than 3 children, primarily non-vegetarian in their food habits and engaged in household works.

Analysis of the primary symptoms showed that 76% subjects had continuous excessive thick vaginal discharge while 55% were suffering from severe & 29% from moderate itching around external genital parts. 62% patients complained of severe while 18% had moderate pain in the back region. With regard to constipation, 26% had severe and 40% had moderate symptoms. 54% and 34% patients respectively exhibited poor and moderate appetite.

Among secondary symptoms, 58% of patients in this study reported the feeling of painful intercourse, while 57% subjects felt good and 21% felt weak as their overall state of wellbeing.

The evaluation of subjective primary parameters of the study participants indicated that maximum percentage of inhibition of the symptom excessive abnormal vaginal discharge was found in case of Group V6 (96%), followed by Group VNA (94%,) Group OVNA (93%), Group CVNA (92%), Group CNA (75%) & Group CP (25%) respectively.

The evaluation of subjective primary parameters of the study participants indicated that maximum percentage of inhibition of the symptom itching around the external genital parts was noticed in case of Group OVNA (94%), Group VNA (89%,) Group V6 (87%), Group CVNA (85%), Group CNA (59%) & Group CP (27%) respectively.

In case of the primary symptom swelling & redness of the external genital parts, maximum percentage of inhibition was found in Group OVNA (93%) followed by Group VNA (92%,) Group V6 (90%), Group CVNA (89%), Group CNA (52%) & Group CP (33%) respectively.

In case of the primary symptom odour of vaginal fluid, maximum percentage of inhibition was found in Group VNA (91%,) followed by Group OVNA (90%), Group V6 (90%), Group CVNA (85%), Group CNA (70%) & Group CP (21%) respectively.

The evaluation of subjective secondary parameters of the study participants indicated that maximum percentage of inhibition of the symptom pain in the back region was found in Group CVNA (90%) followed by Group OVNA (88%), Group VNA (85%,) Group V6 (80%), Group CNA (79%) & Group CP (28%) respectively.

The evaluation of subjective secondary parameters of the study participants suggested that maximum percentage of inhibition of the symptom constipation was found in case of Group CVNA (92%) followed by Group CNA (87%), Group VNA (82%,) Group OVNA (82%), Group V6 (73%), & Group CP (20%) respectively.

Analysis of the secondary parameters of the patients also suggested that maximum percentage of inhibition of the symptom loss of appetite was noticed in Group CVNA (91%) which was followed by Group CNA (89%), Group VNA (82%,) Group OVNA (79%), Group V6 (70%), & Group CP (31%) respectively.

Analysis of the secondary parameters of the patients also suggested that maximum percentage of inhibition of the symptom painful intercourse was found in Group V6 (92%), Group VNA (90%,), Group OVNA (90%), Group CVNA (89%), Group CNA (78%), & Group CP (24%) respectively.

In case of the secondary symptom wellbeing of the patient, maximum percentage of inhibition was found in Group CVNA (93%) followed by Group OVNA (91%), Group CNA 86%), Group VNA (85%,), Group V6(82%) & Group CP (25%) respectively.

Evaluation of the efficacy in treatment of the three common microbiological infections namely Candidiasis, Trichomoniasis and bacterial vaginosis among patients indicates that maximum curative result for candidiasis was obtained in Group V6 (93%), Group OVNA (92%) Group VNA (90%), Group CVNA (90%), Group CNA (69%) & Group CP (27%) respectively.

Similarly, maximum curative effect for Trichomoniasis was noticed in case of Group OVNA (100%) followed by Group V6 (100%), Group CVNA (75%), Group VNA (50%), Group CNA (50%) & Group CP (40%) respectively.

In case of Bacterial vaginosis, the highest efficacy was found in case of Group OVNA (91%), Group CVNA (85%), Group VNA (80%), Group CNA (63%), Group V6 (50%) & Group CP (18%) respectively.

5. Conclusion

The results of the clinical study clearly indicate that all the five treatment groups reported substantial improvement in clinical symptoms implying highly significant therapeutic effect as compared to the placebo group. When compared to the standard drug group V6, the four groups containing the research drug (OVNA, CVNA, CNA and VNA) were found to be having comparable and sometimes better therapeutic efficacy in terms of treatment of the three common antimicrobial infections associated with leucorrhea, except antifungal action since V6 is primarily antifungal in nature.

From the perspective of the primary and secondary symptoms studied during this trial, the four research drug groups resulted in around 80-90% inhibition of these symptoms implying very high treatment efficacy in respect of symptomatic relief. This very high inhibition of subjective symptoms combined with the strong antimicrobial action described above validates the anticipated high therapeutic efficacy of the research drug in this clinical trial.

Comparing the four research groups with each other, the results indicate that the efficacy is better when vaginal route of drug administration is used in comparison to the oral route, i.e. the performance of group VNA is overall better than group CNA. At the same time, the efficacy of vaginal route of drug administration is further improved when it is combined with oral administration of the research drug, since efficacy of CVNA group is better than VNA group. In fact, the clinical studies also clearly suggest that the highest therapeutic efficacy is exhibited by OVNA group, when research drug in the ointment form is used for external application together with the research drug in intravaginal application.

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