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"RANDOMIZED CONTROL TRIAL ON SYSTEMIC USE OF ITRACONAZOLE VERSUS TERBINAFINE IN VULVOVAGINAL CANDIDIASIS"

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INTRODUCTION

Vagina is generally distinguished by relationships between Lactobacillus acidophilus and the metabolic by products of endogenous flora, oestrogen, vaginal pH and glycogen. L. acidophilus keeps the vaginal pH acidic by producing hydrogen peroxide, which is harmful to the pathogens. [1]

The species of Candida are found commonly in the healthy vagina in lesser amount. When any imbalance happens, like change in pH of vagina, hormonal balance, there is multiplication of Candida.[2]

After bacterial vaginosis, the next most common cause of vaginal infection is vulvovaginal candidiasis. Around 75% female face minimal single episode of vulvovaginal candidiasis in their period of fertility. [3]

The most common cause of vulvovaginal candidiasis is Candida albicans (85-90%) and other causes include Candida glabrata, Candida guilliermondii, Candida krusei and Candida tropicalis.[4]

Around 21-32% of healthy women are carriers of asymptomatic vaginal infection. Pregnant females, females treated with antibiotics previously and females with diabetes mellitus showed increased rates of colonisation. [5] In immunodeficient females, Candidiasis was found to be the most familiar opportunistic fungal infection. [6]

This infection generally presents with symptoms like dryness in vulva, itching, pain in abdomen, dryness, painful coitus, soreness and burning sensation. [7] The most common risk factors are uncontrolled sugar level, decreased immunity, hormonal therapy, oral contraceptives, decreased neutrophil count, pregnancy and frequent use of antibiotics. [8]

Vulvovaginal candidiasis is because of an excess growth of yeasts within the vagina[9]. It causes symptoms like curdy white discharge per vaginum, dryness, redness, soreness, burning sensation, itching, pain in abdomen and painful coitus. Vulvovaginal candidiasis commonly seen with patients with human immunodeficiency virus(HIV) infection .[10]

The diagnosis of vulvovaginal candidiasis is made by clinical features and microscopic examination of KOH smear and fungal culture.[11]

The treatment of vulvovaginal candidiasis consists of various antimycotic drugs which can be given locally as well as systemically. [12]

Antifungal agents cause change in permeability of cell membrane of the fungus. Currently, polyene antifungal drugs and pyrrole ring are the two main drugs used in the management of vulvovaginal candidiasis. The first set of drug consists of amphotericin B. It has high antifungal role and broad spectrum of antibacterial coverage. However, it is very toxic. The second class of drugs is the azoles which include fluconazole, itraconazole and ketoconazole. These are also very frequently utilized and have extensive antibacterial spectrum coverage. [13]. They work by preventing the synthesis of ergosterol by inhibiting CYP450- based lanosterol. It is important for the structure and function of fungal cell membrane. Fungal cell death occurs if there is excess assimilation of this enzyme in the cell. [14]

Terbinafine belongs to new allylamine group of fungicidal. Terbinafine inhibits 'squalene epoxidase' and is a comparatively new drug with good efficacy. It is used for the management of tinea corporis, tinea pedis and tinea cruris (cutaneous dermatophytosis), onychomycosis and very newly tinea capitis. It has also been used in cases of systemic and superficial mycoses. [15] There are very few side effects noted from the use of Terbinafine.

Hence, we conducted a randomized control trial between systemic use of Itraconazole and Terbinafine (a comparatively new antifungal drug) in Candida vulvovaginitis.

OBJECTIVES

- To assess the safety and effectiveness of itraconazole.
- To assess the safety and effectiveness of terbinafine.
- To compare the effectiveness, adverse effects and prevention of recurrence of fungal vulvovaginitis using these two drugs.

MATERIALS AND METHODS

STUDY DESIGN: A Randomized Control Trial Study.
STUDY SETTING: The department of Obstetrics and Gynecology at Teerthanker Mahaveer Medical College & Research Centre.
STUDY POPULATION: Women coming with thick white discharge per vagina.
STUDY DURATION:12 months after approval and clearance from (CRC and EC).
SAMPLE SIZE: 94 in each group with absolute error 10% and 95% confidence level.

INCLUSION CRITERIA

All Patients with suspected vulvovaginal candidiasis confirmed by 10% KOH mount test after taking informed written consent.

EXCLUSION CRITERIA

1. Pregnant and lactating female.
2. Patients with mixed vulvovaginal infection.
3. Patients who have received systemic or topical antifungal treatment within the previous month.
4. Patients with active liver and renal impairment.
5. Patients on H2 blockers, PPIs, rifampicin, phenytoin, phenobarbitone.
6. Known cases of hypersensitivity to azoles and allylamines.

METHODOLOGY

After taking detailed history and informed written consent of all study subjects, patients were enrolled on the basis of inclusion and exclusion criteria.

Patient's evaluation of vaginal discharge was done on the basis of duration, colour, consistency, smell and other symptoms like itching, dyspareunia, soreness and swelling. Patients previously treated for same problem and information regarding type of drug used that time was noted.
After evaluation of vaginal discharge clinically, vaginal swab was taken and 10% KOH mount was prepared. Patients diagnosed with vulvovaginal candidiasis were randomly divided into two groups by chits and box method. One group was prescribed tablet itraconazole 200mg twice a day
for 1 day and other group was given tablet terbinafine 250mg once a day for 7 days.
After treatment they were followed up on day 8, day 21 and at 3 months and evaluated for each signs and symptoms. KOH test was repeated on day 21 and at 3 months.
Spontaneously reported adverse event were documented.
Patients were asked to report at 3 months. Patients with no significant improvement in the clinical and mycological parameters were considered as failure to therapy of that particular drug and were dealt separately.

OUTCOME

- To measure the clinical cure rate of each drugs.
- To assess the mycological cure rate of each drugs.
- To record the adverse effects if any.
- To compare which drug is more efficient for treatment of vulvovaginal candidiasis with minimal side effects and in prevention of relapse.

OBSERVATIONS AND RESULTS

The mean age was compared between itraconazole and terbinafine groups using the unpaired t-test. There was no significant difference in mean age between itraconazole and terbinafine groups. [Table No. 1]

Table 1: Distribution of study population according to age

	Age				
Groups	Mean	Std. Deviation	Mean Difference	t-test value	p- value
Itraconazole	38.73	9.37	0.29	0.203	0.839
Terbinafine	38.45	9.99			

Unpaired t-test # Non-significant difference

The mean Fasting Blood sugar was compared between itraconazole and terbinafine groups using the unpaired t-test. The mean fasting blood sugar did not differ significantly between terbinafine and itraconazole groups.[Table No. 2]

Table 2: Distribution of study population according to fasting blood sugar

	Fasting Blood Sugar				
Groups	Mean	Std. Deviation	Mean Difference	t-test value	p- value
Itraconazole	115.88	21.69	-15.62	-2.100	0.077
Terbinafine	121.50	23.37			

Unpaired t-test #Non -significant difference

The distribution of clinical features day 8, day 21, follow-up >21 days and and <3 months and 3 months was compared between itraconazole and terbinafine groups using the chi-square test. Clinical symptoms present at follow-up >21 days and <3 months and 3 months significantly more among terbinafine group compared to itraconazole group.[Table No. 3]

Table 3: Distribution of study population according to clinical features at day 8, day 21, Follow-up >21 days and , Follow-up >21 days and < 3 months and 3 months

		Groups		Total	Chi-square value	p- value
Clinical Features		Itraconazole	Terbinafine			
Day 8	No	10	11	21	0.529	0.971
		10.6%	11.7%	11.2%		
	Curdy white discharge present, cervix-Hypertrophied, unhealthy, erosions present	25.5%	24.5%	25.0%		
	Curdy white discharge present, foul smelling	25	27	52		
		26.6%	28.7%	27.7%		
	Curdy white discharge present, foul smelling	21	22	43		
		22.3%	23.4%	22.9%		
	Relieved of symptoms	14	11	25		
		14.9%	11.7%	13.3%		
Day 21	No	10	11	21	2.740	0.254
		10.6%	11.7%	11.2%		
	Relieved of symptoms	30	20	50		
		31.9%	21.3%	26.6%		
	Symptoms persists	54	63	117		
		57.4%	67.0%	62.2%		
>21 days and	No	10	11	21	14.081%	0.003*
		10.6%	11.7%	11.2%		
	No recurrence of symptoms	33	21	54		
		35.1%	22.3%	28.7%		
	Relieved of symptoms	20	8	28		
		21.3%	8.5%	14.9%		
	Symptoms persists	31	54	85		
		33.0%	57.4%	45.2%		
3 months	No	10	11	21	13.296	0.001*
		10.6%	11.7%	11.2%		
	No recurrence of symptoms	53	29	82		
		56.4%	30.9%	43.6%		
	Symptoms persists	31	54	85		
		33.0%	57.4%	45.2%		

Chi-square test * Significant difference

The distribution of adverse effects was compared between itraconazole and terbinafine groups using the chi-square test. There was no significant difference in adverse effects between terbinafine and itraconazole groups.[Table No. 4]

Table 4: Distribution of study population according to complications

Complications		Groups		Total	Chi-square value	p-value
		Itraconazole	Terbinafine			
Vomiting	No	89	91	180		
		94.7%	96.8%	95.7%		
	Yes	5	3	8	0.522	0.470
		5.3%	3.2%	4.3%		
Diarrhea	No	92	90	182		
		97.9%	95.7%	96.8%		
	Yes	2	4	6	0.689	0.407
		2.1%	4.3%	3.2%		
Nausea	No	92	89	181		
		97.9%	94.7%	96.3%		
	Yes	2	5	7	1.335	0.248
		2.1%	5.3%	3.7%		

Chi-square test * Significant difference

The distribution of KOH test at day 8, day 21 and 3rd month was compared between itraconazole and terbinafine groups using the chi-square test. KOH test at day 8, day 21 and 3rd month was found to be negative significantly more among itraconazole group compared to terbinafine group.[Table No. 5]

Table 5: Distribution of study population according to KOH test

		Groups		Total	Chi-square value	p-value
KOH		Itraconazole	Terbinafine			
8TH day	Negative	63	31	94	10.179	0.001*
		67.0%	33.0%	50.0%		
	Positive	31	63	94		
		33.0%	67.0%	50.0%		
21st day	Not done	10	11	21	15.396	0.001*
		10.6%	11.7%	11.2%		
	Negative	39	15	54		
		41.5%	16.0%	28.7%		
	Positive	45	68	113		
		47.9%	72.3%	60.1%		
3 months	Not done	10	11	21	16.957	0.001*
		10.6%	11.7%	11.2%		
	negative	53	26	79		
		56.4%	27.7%	42.0%		
	Positive	31	57	88		
		33.0%	60.6%	46.8%		

Chi-square test

* Significant Difference

DISCUSSION

The pathogenesis of vulvovaginal candidiasis is not clear even though the incidence rate and recurrence rate is high.[16] Currently, it is found that the pathogenesis and the relapse of vulvovaginal candidiasis are due to many causes, like the increased resistant nature of Candida, the regional immunity of the host against species of Candida & the changing virulence of Candida. [17] The data available shows, 75% females experience vulvovaginal candidiasis once in their lives, 50% of females experience relapse of infections, and the most affected were highest in females of reproductive age.[18]

In the overall cases of vulvovaginal candidiasis, age is a significant factor among socio-demographic variables. In the study by Bitew and Abebaw, [19],71 of the 87 patients with candidiasis were in their second to fourth decade of life, accounting for 81.6 % of the total.

In this study, the clinical symptoms present at follow-up after 21 days and less than 3 months and 3 months significantly more among terbinafine group compared to itraconazole group. Arca et al [20] observed that clinical healing rates were 81.3 percent in the drug terbinafine group, 77.8 percent in the drug itraconazole group, and 37.5 percent in the drug fluconazole group, as similar to our findings.

KOH test at day 8, day 21 and 3rd month was found to be negative significantly more among itraconazole group compared to terbinafine group. Arca et al [26] assessed the safe use and efficient nature of drug fluconazole, terbinafine and itraconazole. It was found that the mycological healing rates were 75%, 31.2%, and 61.1% respectively.

In our study, there wasn't any difference which was significant in harmful effects amongst the terbinafine and itraconazole lists. Vomiting was reported among 5.3% and 3.2% subjects in terbinafine and itraconazole groups respectively, diarrhoea was reported among 2.1% and 4.3% % subjects in terbinafine and itraconazole groups respectively. Ellis et al. [21] found that itraconazole has a good level of tolerance with some small harmful effects like nausea, mild headache and pain in the abdomen being complained by few patients which was in similarity to our study.

CONCLUSION

Vulvovaginitis is the inflammation of vulva and vagina which is caused by an imbalance in the vaginal flora present normally by any form of infection or the less oestrogen levels due to menopause. The present clinical trial compares the effectiveness and safety of systemic use of itraconazole versus terbinafine in treatment of vulvovaginal candidiasis.

Our study findings were compared with the various other studies showing that itraconazole was more effective whereas contradictory results have been seen in some studies. Though, majority studies along with our study findings have established that itraconazole therapy is much more effective in the vulvovaginal candidiasis.

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