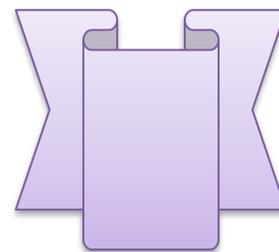
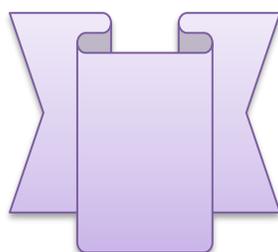
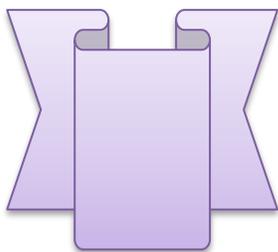
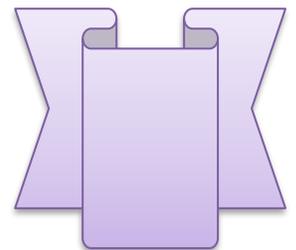
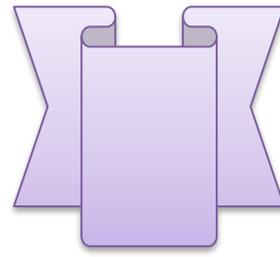
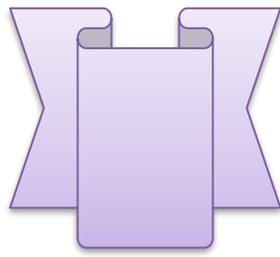
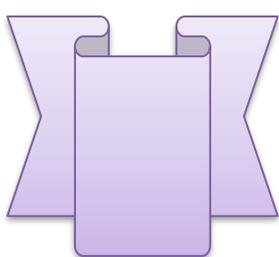
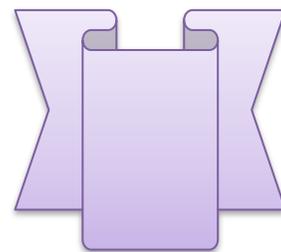
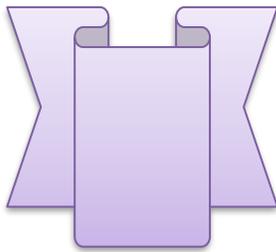
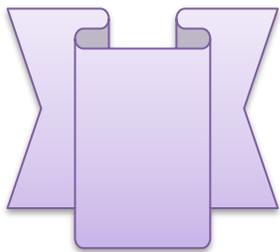


INTERNATIONAL JOURNAL OF MEDICAL ARTS



Volume 5, Issue 10, October 2023

<https://ijma.journals.ekb.eg/>



Print ISSN: 2636-4174

Online ISSN: 2682-3780



Available online at Journal Website
<https://ijma.journals.ekb.eg/>
 Main Subject [Gynecology and Obstetrics]



Original Article

Use of Povidone Iodine Vaginal Swabbing in Treatment of Recurrent Vulvovaginal Candidiasis

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ABSTRACT

Article information

Received: 20-06-2023

Accepted: 15-09-2023

DOI:
10.21608/IJMA.2023.219025.1713.

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Citation: Younis SMK, Mahmoud MS, Elshorbagy AM. Use of Povidone Iodine Vaginal Swabbing in Treatment of Recurrent Vulvovaginal Candidiasis. IJMA 2023 October; 5 [10]: 3763-3768. doi: 10.21608/IJMA.2023.219025.1713.

Background: Recurrent vulvovaginal candidiasis [RVVC] is a common condition affecting millions of women worldwide. It is associated with significant morbidity. Vulvovaginal candidiasis affects up to 75% of women of childbearing age once in their life, and up to 9% of women in different populations experience more than three episodes per year, which is defined as recurrent vulvovaginal candidiasis [RVVC].

The Aim of the work was to test efficacy of povidone iodine vaginal swabs in treatment of recurrent vaginal candidiasis.

Patients and Methods: This study included 210 women, who suffered from symptomatic acute episode of RVVC, and attended Obstetrics and Gynecology Department, Al-Azhar university hospital Damietta. They were divided into three groups: Group A [70 women] who were treated with povidone iodine vaginal swabs. Group B [70 patients] who were treated with oral fluconazole and topicalazole therapy. Group C [70 patients] who were treated with a combination of povidone iodine swabs and fluconazole. The overall clinical cure rate and improvement were assessed and compared between groups.

Results: There was no significant difference between study groups, regarding overall clinical cure rate, which was higher in group C. As the clinical cure, improvement and no improvement percentage were in group A, 62.8%, 27.2%, 10% respectively. In group B, the values were 60.0%, 28.5%, and 11.5%, respectively. The values in group C were 65.7%, 31.3% and 3.2% with the same order. However, the recurrence rate 6 months after treatment was significantly different between groups [it was 7.9%, 3.2% and 1.47% in groups A, B and C, respectively].

Conclusion: Povidone iodine swabs were effective in treatment of RVVC as medical treatment almost with lower cost and lower side effects with good compliance.

Keywords: Povidone iodine; Vulvovaginal; Candida Albicans; Antifungals; Antiseptics.



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INTRODUCTION

Recurrent vulvovaginal candidiasis [RVVC] is a common disease, affecting millions of women of different social classes worldwide. The RVVC was significantly reduced or even prevented by the onset of menopause. The widespread use of hormone replacement therapy [HRT] is associated with an extended at-risk period [1]. Up to 75% of women at childbearing age are affected by vulvovaginal candidiasis [VVC], at least once in their life. However, 9.0% of women, in general, reported more than three episodes of VVC per year. These are defined as RVVC, which had a profound effect on patients' quality of life [2].

Candida albicans is the dominant species responsible for RVVC. However, the optimal management strategy needs determination of candida species and use of species-specific treatment measures. The understanding of different risk factors and pathogenic mechanisms for RVVC showed significant progress during the last decade [3, 4]. The main clinical manifestations of VVC include vaginal irritation, pruritus, discharge and dyspareunia. On examination, there is vulval erythema, edema, excoriation, and formation of fissures. In addition, introital and vaginal erythema are commonly present [5]. The VVC-associated vaginal discharge is usually white in color, and clumpy. However, beside other clinical manifestations, it is not-specific. Thus, the diagnosis should not be dependent only on the clinical manifestation and detection of specific pathogen is mandatory [6].

RVVC due to *C. albicans* respond to short courses of oral or topical azoles. However, a longer duration of treatment [one to two weeks of topical therapy or oral fluconazole [10-200 mg/day] every third day for a maximum of total doses] is required to obtain a mycologic remission before starting a maintenance antifungal regimen [the recommended is oral fluconazole [100-200 mg/day] once weekly for 6 months]. However, in low compliance with this regiment, intermittent topical treatments are considered. Susceptibility tests are recommended for VVC-azole-resistant infections despite maintenance therapy, and treatment plan should be tailored according to the results [7-9].

Original antifungal agents are associated with marked toxicity due to the narrow toxic therapeutic ratio. Additionally, the local formulations may lead to itching, redness with

low efficacy. Advanced agents improve tolerability and widen the toxic therapeutic ratio [10, 11].

Povidone iodine is a wide-spread anti-septic solution used mainly for skin disinfection before and after surgery to prevent wound infection [12]. However, it is tried for its potential as an antifungal agent on a very-limited scale. For example, a previous trial used povidone-iodine paint for 13 patients with a definite dermatological fungal infection. The mycological study revealed pityriasis versicolor [10 patients], trichophyton rubrum [2 patients] and *M. Canis* [one patient]. 70% of patients in pityriasis versicolor group were improved or cleared up from the clinical point of view within 7 days, with no adverse effects and quite acceptability. Scanning electron micrographs confirmed the clinical results [13]. Three decades later, Philip *et al.* [14] supported the use of povidone iodine as a topical anti-fungal in the treatment of otomycosis. Subsequently, its effectiveness against trichomonal infections and candida albicans, as well as other vaginal bacteria was demonstrated [15]. In addition, it had a good tolerability with low adverse events when used for treatment of vaginal infections of different etiologies including fungal agents [16]. However, it is not tested in the RVVC.

THE AIM OF THE WORK

The aim of this work is to evaluate the efficacy of using povidone iodine vaginal swabbing in treatment of recurrent vulvovaginal candidiasis.

PATIENTS AND METHODS

This was a prospective comparative study. It was carried out at the Obstetrics and Gynecology Department [outpatient clinic], Al-Azhar University Hospital [Damietta] from 1st of May to the 30th of November 2022.

Woman was included if she and her husband gave their informed consent, her age is 18 years or older, suffering symptomatic acute episode of RVVC. However, we excluded virgins, women who had bleeding at the time of examination, other vaginal infections, pregnant or breastfed mothers and women with other diseases [e.g., immunodeficiency, diabetes mellitus or estrogen-dependent tumors].

According to sample size justification [described later], we included a total of 210 women, who were divided into three equal

groups [each 70 women], according to the type of provided treatment. They were group A for povidone iodine vaginal swabs, group B for oral fluconazole and topicalazole therapy, and group C for Povidone Iodine swab and oral fluconazole.

After an informed consent, each woman was subjected to full history taking, thorough general and local vaginal clinical examination.

The local clinical examination was performed in the lithotomy position. Areas of erythema, edema, fissures, or ulcers were noticed during inspection of the vulva, vaginal walls and fornix using a speculum. All secretions were documented by their color, contour, and odor. The speculum was inserted sideways [blades closed, angled downwards and backwards] by the left hand [index and thumb fingers were used to separate labia]. Then, blades were opened to obtain the optimal view of the cervix. Then, the blades position was fixed by tightening and holding in place the locking nut. All secretions were cleaned by a sterile cotton, followed by swabbing of the vaginal walls and fornix by cotton swabs immersed in povidone iodine 10% many times till complete removal of the discharge. At the end, the swab was removed carefully without touching any surface. Finally, the speculum was removed.

The povidone iodine treatment was applied twice weekly for one month or disappearance of symptoms whichever was longer. The second group was treated by fluconazole [initial treatment 7–14 days of topical therapy and a 150-mg oral dose of fluconazole every third day for a total of 3 doses [days 1, 4, and 7]. Then 150 mg of oral fluconazole as maintenance dose weekly for 6 months]. The third group was treated by a combination of treatment as in the first and second groups. The clinical symptoms were evaluated [itching and vaginal discharge] and self-reported by the patients as present or absent.

The evaluation of efficacy was based on clinical overall cure rate defined as the ratio between the number of women without vaginal discharge or itching and negative culture and all women present in the treatment group. Recurrence rate was calculated as ratio between the number of women experiencing at least one symptom during the 6-month follow-up period, confirmed by culture, and all women present in the treatment group. Safety was assessed by

recording all side effects [i.e., adverse events, serious adverse events, and suspected unexpected serious adverse reactions]. An adverse event would be considered severe if it is requiring hospitalization or led to permanent injury.

Follow-up and test of cure for patients with acute VVC was unnecessary if symptoms resolve. Patients with recurrent VVC were advised to return if they experience poor or partial response to therapy; repeat microscopy and culture is indicated to assess for microbiological cure or new resistance. Patients who demonstrated microbiological response but not clinical response to therapy should be reassessed for alternative causes of their symptoms.

Ethical considerations: The study protocol was reviewed and approved the institutional review board [IRB] of Damietta Faculty of Medicine, Al-Azhar University [Damietta, Egypt]. Each patient signed an informed consent, and the study was completed according to ethical codes of Helsinki declaration for research conduct and reporting.

Statistical considerations

Sample size calculation: This study was based on a study carried out by **Russo *et al.*** [6], Epi Info STATCALC was used to calculate the sample size by considering the following assumptions: - 95% two-sided confidence level, with a power of 80%. & an error of 5% odds ratio calculated = 1.115. The final maximum sample size taken from the Epi- Info output was 200. Thus, the sample size was increased to 210 subjects to assume any drop out cases during follow up.

Data analysis: Data were checked, entered and analyzed using SPSS version 23 for windows [IBM®, Armonk, Chicago, USA]. Data were presented by their relative frequencies [numbers] and percentage for qualitative variables. Otherwise, mean + standard deviation [SD] were used for presentation of quantitative variables. For comparison between groups, the one-way analysis of variance and post-hoc least significant differences [LSD] were calculated for quantitative variables, and Chi square test or its equivalent were used for qualitative data. Paired comparison [e.g., before and after treatment] was compared by paired samples [t] test or Wilcoxon signed ranks. P value < 0.05 was considered significant to interpret results.

RESULTS

Table [1] described the patient characteristics among study groups. The patient age ranged between 19 and 40 years, while parity ranged between 1 to 4, and most women had middle education. The major contraception type was COC among all the study groups. Groups were comparable as patient characteristics including patient age, parity, education level, contraception method, weight, height or body mass index [BMI] [i.e., no significant difference was recorded between groups.

The differences between groups were statistically non-significant regarding the results of culture, overall cure rate and dizziness. However, the recurrence rate was significantly reduced among the third group than the second and first groups [1.47% vs 3.2% and 7.9%, respectively]. Nausea was not reported with topical povidone iodine group but was recorded for 8.5% and 7.14% of B and C groups respectively. The vaginal burning on the other side was significantly increased with local povidone iodine [groups A and C], and not registered at all in the B-group [tables 2-4].

Table [1]: Patient characteristics among studied groups

		Group A	Group B	Group C	test	P
Age	Mean± SD	32.3±6.1	32.4±6.4	31.9±6.1	0.212	0.89
	Min.-max.	20-40	20-39	19-40		
Parity	Mean± SD	2.52±0.81	2.49±0.79	2.54±0.80	0.04	0.97
	Min.-max.	1-4	1-4	1-4		
Education	Illiterate	5 [7.1%]	4 [5.7%]	6 [8.5%]	0.48	0.97
	Middle education	56 [80%]	57 [81.4%]	56 [80%]		
	Graduated	9 [12.8%]	9 [12.8%]	8 [11.4%]		
Contraception type	COC	33 [47.14%]	31 [44.28%]	32 [45.71%]	0.62	0.99
	Injection	21 [30%]	20 [28.57%]	22 [31.4%]		
	IUD	10 [14.28%]	11 [15.71%]	10 [14.28%]		
	POP	6 [8.5%]	8 [11.4%]	6 [8.5%]		
Height [m]	Mean± SD	1.65±0.1	1.64±0.13	1.67±0.12	4.77	0.09
	Min.-max.	1.5-1.75	1.5-1.75	1.5-1.75		
Weight [kg]	Mean± SD	77.5±7.2	76.9±6.9	77.7±7.1	0.12	0.93
	Min.-max.	65-80	65-80	65-80		
BMI [Kg/m²]	Mean± SD	29.5±0.58	29.9±0.6	30.1±0.72	3.84	0.14
	Min.-max.	24-32	25-33	25-33		

Table [2]: Culture result at the end of the treatment course

		Group A	Group B	Group C	X ² test	P value
Culture	Positive	14 [20%]	16 [23%]	12 [17%]	0.71	0.69
	Negative	56 [80%]	54 [77%]	58 [83%]		

Table [3]: Clinical cure rate at the end of the treatment course

		Group A	Group B	Group C	test	P
Overall cure	Clinical cure	44 [62.8%]	42 [60%]	46 [65.7%]	0.48	0.78
	Improved	19 [27.2%]	20 [28.5%]	22 [31.3%]	0.32	0.850
	Not improved	7 [10%]	8 [11.5%]	2 [3.2%]	3.96	0.13

Table [4]: Recurrence rate and adverse side effects among studied groups

Variable	Results	Statistics
Recurrence rate	5/63 [7.9%]	2/62 [3.2%]
Adverse effects	Nausea	6 [8.5%]
	Dizziness	5 [7.14%]
		4 [5.7%]

DISCUSSION

We performed this study aiming to test safety and efficacy of povidone iodine vaginal swabs for the treatment of RVVC. The stud groups were comparable regarding age, parity,

education, or contraception type. The overall cure rate did not differ significantly between groups [all three regimens were effective]. However, the recurrence rate was significantly reduced when povidone iodine was used with systemic anti-fungal when compared to the sole use of povidone iodine or systemic anti-fungal agents.

In line with the current work, **Kandil et al.** [17] evaluated the effect of oral versus topical antimycotics for treatment of RVVC. They reported no significant difference between groups regarding patient age, parity or contraception type. Similar results were reported by **Fardyazar et al.** [18]. **Kandil et al.** [17] showed no significant difference between groups regarding a mycological cure rate, as in the current work. However, **Petersen et al.** [16] reported that, the use of povidone iodine swabs was associated with a significant reduction of recurrence rate from 6.3 ± 2.0 at the entry to 1.3 ± 1.1 and 0.5 ± 0.9 after one week and one month of treatment, respectively, indicating significant efficacy of the use of povidone iodine in treatment of VVC. **Lirio et al.** [8] in two studies included in their meta-analysis showed failure of fluconazole treatment to induce long-term remission. This was ascribed to azole resistance by some species [e.g., *Candida glabrata* and *Candida krusei*].

The efficacy of povidone iodine as antimicrobial agent is explained by its unique structure as it consisted of a complex of povidone, hydrogen iodide and elemental iodine. It works on microbial structures critical for survival and replication of the micro-organism [e.g., amino acids, nucleic acids, and membrane components]. Fungi also have these structures, and this was the rationale about the use of povidone iodine as anti-fungal agent. A marked and confirmed finding with povidone iodine use is the lack of microbial resistance. This was thought to be due to the sheer diversity of susceptible targets within each pathogen, an important manifestation to be considered in the face of rising concerns for antimicrobial resistance. It is even used as an anti-viral agent [19].

In an interesting recent study carried out by **Salehi et al.** [20], a synergistic interaction was reported for concurrent use of micafungin and chlorhexidine against azole-resistant fungi [mainly *C. Albicans*]. They suggested this as an alternative approach to overcome resistance of fungi to antifungal drugs. But their study was in-vitro and in vivo confirmation was required. Our study could be the required confirmation as both povidone iodine and chlorhexidine share the antiseptic properties and efficacy. However, povidone iodine is less-irritant, favoring its use. **Hacioglu et al.** [21] tested the efficacy of different antiseptics compounds as a potential anti-fungal for isolates of VVC and reported that N-Chlorotaurine was the most effective

agent followed by octenidine dihydrochloride and povidone iodine. They advocated the use of N-Chlorotaurine. However, they used a povidone iodine 8%, which could explain its lower efficacy when compared to the current study [we used 10%].

The current study has the limitation of small number of cases, although the sample size was justified. Thus, future large-scale studies are recommended. Additionally, the study's findings may not be generalizable to a wider population due to the specific characteristics of the participants and the single-center design.

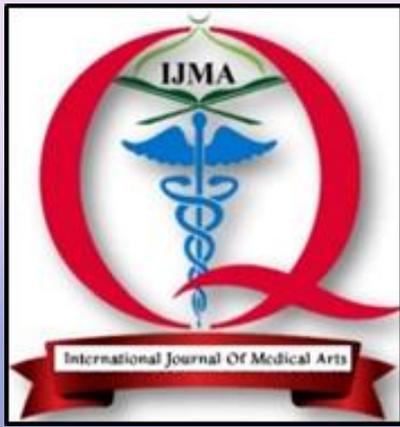
Conclusion: Our results showed that povidone iodine vaginal swabbing was effective in treatment of recurrent vulvovaginal candidiasis with lower cost and lower side effects and good compliance. The prospective nature of the study with justification of the sample size represented a powerful point of the current work. However, sample size remains insufficient to globalize results. Thus, future studies are recommended.

Financial and non-financial relations and activities of interest: None

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Print ISSN: 2636-4174

Online ISSN: 2682-3780

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