

The Effects of Ozonated Olive Oil and Clotrimazole Cream for Treatment of Vulvovaginal Candidiasis

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ABSTRACT

Context • Vulvovaginal candidiasis is the most common infection of the vulvovagina, which manifests with itching, a burning sensation, and leucorrhea. Some infections have been reported to be tolerant to conventional treatments, especially in immunosuppressed patients. New studies have suggested that ozone, which is the allotropic form of oxygen, may have antifungal effects.

Objective • The study intended to compare the effects of ozonated olive oil and clotrimazole in the treatment of vulvovaginal candidiasis.

Design • Patients were randomly assigned either to an ozone group or to a clotrimazole group in a randomized, controlled trial.

Setting • The study took place in the Department of Gynecology of the School of Medicine at Mashhad University of Medical Sciences in Mashhad, Iran.

Participants • Participants were 100 female patients who had been referred to the women's gynecology clinic at the Omolbanin and Ghaem Hospitals and who had confirmed vulvovaginal candidiasis.

Intervention • Patients in the ozone group were treated with ozonated olive oil or those in the clotrimazole group were treated with clotrimazole for 7 d.

Outcome Measures • Patients were evaluated through an interview and a paraclinical examination at baseline and postintervention. The study measured changes in itching, burning, and leucorrhea using a questionnaire that patients completed at the end of the study and determined the presence of an infection with vaginal candidiasis through a culture both before acceptance into the study and after the treatments, if accepted.

Results • Ozone and clotrimazole both reduced symptoms significantly and led to a negative culture for vaginal candidiasis ($P < .05$). No significant differences existed between the 2 groups in their effects on the symptom of itching and leucorrhea and on the results of the culture ($P > .05$). However, clotrimazole decreased the burning sensation significantly more than did ozone ($P < .05$).

Conclusions • Considering the potential efficacy of ozonated olive oil in the improvement of the clinical and paraclinical aspects of treatment of patients with vulvovaginal candidiasis, the research team suggests that the treatment can be an effective topical treatment for those patients. (*Altern Ther Health Med.* 2016;22(4):44-49.)

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Vulvovaginal infections caused by different types of *Candida* are the most common infections of women's genital systems. Cases of it have frequently been observed to be tolerant of its conventional treatments. Seventy-five percent of women experience an infection with vulvovaginal candidiasis at least 1 time in their lives, and 45% of women experience it 2 times or more.¹ Because of the prolonged treatment required for *Candida* and its drug tolerance, offering a treatment for removing the fungal infection that (a) is low in cost, (b) has no side effects, and (c) significantly affects the infection can have benefits for a society's health.

Recently, in new studies, evidence of the benefits and efficacy of ozone has been observed for treatment of different infections and inflammations. Ozone therapy has been suggested since 1995 in the United States as a complementary medicine for treatment of the infection. Moreover, ozone has been shown to have effects on the treatment of infections because it causes oxygen to reach the tissues and also decreases inflammation. Because the cost of treatment for the infections has been increasing in various societies, and because the drug tolerance of the infection is increasing, ozone therapy has received considerable notice because not only does it have a definite effect but also the infection does not tolerate it.²

In 1995, Rodriguez et al³ reported at a Cuban congress that ozonated oil was able to treat vulvovaginal candidiasis. Also, De Las et al⁴ and Morris et al⁵ showed positive effects for ozone on the treatment of vulvovaginitis. A study in 2006 compared ozonated olive and sunflower oils chemically and microbiologically. It showed that the antimicrobial activity was similar for both ozonized oils, except for a minimum bacterial concentration of *Pseudomona aeruginosa*, where sunflower oil at low peroxide value had better antimicrobial activity, whereas ozonized olive oil was better to high peroxide value. The composition of the fatty acids in both of the ozonized oils showed a gradual decrease in the unsaturated fatty acids.⁶

The results of a study performed in 2010 at Mashhad University of Medical Sciences (MUMS) in Mashhad, Iran, showed that ozonated olive oil had a prohibitive effect on 3 types of *Candida*. The effects were dependent on the concentration, with those effects being observed in a shorter time at a higher concentration. The types of *Candida* most sensitive to the ozonated olive oil were *Candida krusei*, *Candida glabrata*, and *Candida albicans*.⁷

In a study performed in 2008 at MUMS, the efficacies of an ozonated gel and of metronidazole were compared for the treatment of trichomoniasis vulvovaginitis. The effects of the ozone were found to be better than the oral tablet of metronidazole for improving the symptoms and culture smears of the patients with that infection.⁸

Because the antifungal effects of ozone and its cost effectiveness and lack of side effects had been reported in the previous studies, the research team performed the current study with the aim of comparing the efficacies of ozonated olive oil and clotrimazole cream for treatment of vulvovaginal candidiasis.

METHODS

Participants

The research team had calculated that the study required 82 patients who had had a positive culture for vaginal candidiasis, 41 patients in each group, according to the formula:

$$n = \frac{(P_1 [1 - P_1] + P_2 [1 - P_2])(Z_{1-\frac{\alpha}{2}} - Z_{1-\beta})^2}{(P_1 - P_2)^2}$$

$$P_1 = 64\%, \alpha = .05 \quad Z_{1-\frac{\alpha}{2}} = 1.96$$

$$P_2 = 92\%, \beta = .2 \quad Z_{1-\beta} = .84$$

P_1 and P_2 values were based on the results of previous studies. To be assured of sufficient power, the team determined that it needed 50 women in each group (ie, a total of 100 patients).

Potential participants were women who had been referred to the women's gynecology clinic at the Omolbanin and Ghaem Hospitals. Candidates were interviewed and given a paraclinical examination by the corresponding author, who also reviewed the women's medical charts. The first author determined whether or not each candidate met the inclusion criteria. A total of 200 women were interviewed. Among them, 150 were eligible clinically and underwent culture. Of those candidates, 50 were negative for *Candida* or showed other or mixed infection.

To be included, the women had to (1) be of fertile age, (2) have received a clinical diagnosis of vaginal candidiasis, (3) have had a positive culture for vaginal candidiasis upon testing at baseline, (4) be willing to avoid intercourse during the treatment period, and (5) be willing to avoid taking a vaginal bath during the study. Patients were excluded if they (1) were currently using drugs for treatment of *Candida*; (2) had diabetes, vascular collagen diseases, or immunosuppressive diseases; (3) were using corticosteroids or antibiotics; (4) were using antifungal treatments from 1 week before the study; (6) had taken a vaginal bath during the week prior to the start of the study; and (7) were pregnant or breastfeeding.

The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of MUMS. Written informed consent was obtained from all patients.

Procedures

Ozonated olive oil is an ivory-colored viscous jelly that remains unchanged at room temperature for 3 years. It keeps its ozone content even after melting. The medicated ozone used in the current study was produced in the research laboratory of the Pharmacy School at MUMS using an ozone-producing machine that had the capacity of making 13.6 g/hour of ozone. The machine conducts ozone bubbles

through the olive oil for 72 hours. It changes the liquid olive oil to solid. Glycozone, a superoxide, is released, and trepan gases are trapped inside the olive oil, which oxidizes it to peroxide O-O-H.⁹ The oxidative power of the ozonated olive oil was determined using iodometry with sodium thiosulfate.

After explaining the conditions of the study to the potential participants and obtaining informed consent, the research team obtained a vaginal culture for vaginal candidiasis. Women with a positive culture for vaginal candidiasis at baseline were included in the study. Participants were asked to visit the clinic on the tenth day after the start of treatment (ie, 3 days after the treatment ended) to allow the research team to evaluate the treatment. The patients underwent a clinical examination and a culture for vaginal candidiasis. At the end of the study, participants were also asked to record any changes in the symptoms of itching, burning, and leucorrhea, using a questionnaire.

Intervention

The women with a positive culture at baseline were randomly divided into 2 groups: (1) one that received treatments of ozonated olive oil, applied using a vaginal applicator containing 5 g of the treatment (ozone group); and (2) one that used clotrimazole cream, applied using a vaginal applicator containing 5 g of the drug (clotrimazole group). The participants applied the treatments themselves, with 1 applicator used every night for 1 week.

Outcome Measures

The study's outcomes were (1) measures of the changes in the clinical symptoms of itching, burning, and leucorrhea that were obtained using a questionnaire; and (2) the results of a culture for vaginal candidiasis.

Questionnaire. The questions about itching, burning, and leucorrhea each asked participants to classify their symptoms as to their degrees of severity, which were (1) none, (2) mild, (3) moderate, (4) severe, and (5) very severe.

Culture for Vaginal Candidiasis. The culture medium was sabouraud dextrose agar with chloramphenicol in the laboratory temperature of 22°C to 25°C. The waiting time for culture was at least 72 hours and at most 10 days.

Statistical Analysis

Data were analyzed using the SPSS software, version 17 (SPSS Inc, Armonk, NY, USA). A Student's *t* test was used for quantitative variables, and χ^2 and Fisher tests were used for qualitative variables. The Mann-Whitney *U* test, Wilcoxon signed-rank test, and logistic regression were used for analyzing the data.

RESULTS

The current study enrolled 100 women, all with cultures that had confirmed the presence of an infection with vaginal candidiasis. All 100 women who started the study also completed it. Before treatment, the demographics of the

2 groups of participants were not significantly different (Table 1).

Table 2 shows data for the 2 groups for the severity of itching at baseline and postintervention. No significant differences existed between the ozone and the clotrimazole groups, either at baseline ($P = .82$) or postintervention ($P = .74$) using Mann-Whitney *U* test. The drugs were comparable in their treatment of the itching.

The study also compared the changes in the severity of itching from baseline to postintervention for each group. For the ozone group, the changes from baseline to postintervention were as follows: (1) none—from 2 women (4%) to 38 women (76%), (2) mild—from 17 women (34%) to 11 women (22%), (3) moderate—from 12 women (24%) to 1 woman (2%), (4) severe—from 10 women (20%) to no women (0%), and (5) very severe—from 9 women (18%) to no women (0%). For all categories of the severity of itching, a significant difference was observed in terms of the reduction in the severity of itching for the ozone group ($P = .0001$).

The changes in the severity of itching between baseline and postintervention were also compared for the clotrimazole group, and for all categories of severity, results similar to those of the ozone group were found ($P = .0001$).

Table 3 shows data for the 2 groups for the severity of burning at baseline and postintervention. Significant differences were observed between the 2 groups at baseline ($P = .041$) and postintervention ($P = .032$). The ozone decreased the burning sensation significantly more than did clotrimazole (ie, the 2 drugs were not similar in their efficacies in decreasing the severity of burning).

The study also evaluated the changes in the severity of burning from baseline to postintervention for each group. For the ozone group, the changes from baseline to postintervention were as follows: (1) none—from 15 women (30%) to 47 women (94%), (2) mild—from 14 women (28%) to 2 women (4%), (3) moderate—from 8 women (16%) to 1 woman (2%), (4) severe—from 10 women (20%) to no women (0%), and (5) very severe—from 3 women (6%) to no women (0%). For all categories of the severity of burning, a significant difference was observed in terms of the reduction in the severity of burning for the ozone group ($P = .0001$).

The changes in the severity of burning were also compared for the clotrimazole group, and for all categories of severity, results similar to those of the ozone group were found ($P = .0001$).

Table 4 shows data for the 2 groups for the severity of leucorrhea at baseline and postintervention. The 2 groups were not significantly different at baseline ($P = .14$) or postintervention ($P = .75$). The efficacies of the 2 drugs were similar in decreasing the severity of leucorrhea.

The study also evaluated the changes in the severity of the leucorrhea from baseline to postintervention for each group. For the ozone group, the changes from baseline to postintervention were as follows: (1) none—from 4 women (8%) to 42 women (84%), (2) mild—from 9 women (18%) to 7 women (14%), (3) moderate—from 13 women (26%) to

Table 1. Baseline Characteristics of Participants

Characteristics	Ozone Group n (%)	Clotrimazole Group n (%)
Age, mean \pm SD, y	34.1 \pm 7.9	34.4 \pm 8.1 ^a
Having recurrences of vaginal infections in the year prior to the study	13 (26)	15 (30) ^b
Using contraceptive methods	8 (16)	11 (22.9) ^b
Using antifungal drugs in the month prior to the study	8 (16)	6 (12) ^b

^a $P > .05$ using a *t* test.

^b $P > .05$ using the χ^2 test.

Abbreviation: SD, standard deviation.

Table 2. Comparison of the Severity of Itching Pre- and Postintervention for the Groups (n = 50 in Each Group)

Itching	Ozone Group		Clotrimazole Group	
	Preintervention n (%)	Postintervention n (%)	Preintervention n (%)	Postintervention n (%)
None	2 (4)	38 (76)	5 (10)	37 (74)
Mild	17 (34)	11 (22)	14 (28)	10 (20)
Moderate	12 (24)	1 (2)	9 (18)	2 (4)
Severe	10 (20)	0 (0)	10 (20)	0 (0)
Very severe	9 (18)	(0)	12 (24)	1 (2)

Note: No significant differences existed between the ozone and the clotrimazole groups in the severity of itching, either at baseline ($P = .82$) or postintervention ($P = .74$) using the Mann-Whitney *U* test. Within-group analysis showed a significant difference in the severity of itching before and after the treatment with ozone, using the Wilcoxon signed-rank test ($P = .0001$). Within-group analysis showed a significant difference in the severity of itching before and after the treatment with clotrimazole, using the Wilcoxon signed-rank test ($P = .0001$). There was no significant difference between the 2 groups in the severity of itching before and after the study using logistic regression ($P = .89$).

Table 3. Comparison of the Severity of Burning Pre- and Postintervention for the Groups (n = 50 in Each Group)

Burning	Ozone Group		Clotrimazole Group	
	Preintervention n (%)	Postintervention n (%)	Preintervention n (%)	Postintervention n (%)
None	15 (30)	47 (94)	10 (20)	42 (84)
Mild	14 (28)	2 (4)	11 (22)	6 (12)
Moderate	8 (16)	1 (2)	6 (12)	1 (2)
Severe	10 (20)	0 (0)	14 (28)	0 (0)
Very severe	3 (6)	0 (0)	9 (18)	1 (2)

Note: Significant differences existed between the ozone and the clotrimazole groups in the severity of burning at baseline ($P = .04$) or postintervention ($P = .11$) using the Mann-Whitney *U* test. Within-group analysis showed a significant difference in the severity of burning before and after the treatment with ozone, using the Wilcoxon signed-rank test ($P = .0001$). Within-group analysis showed a significant difference in the severity of burning before and after the treatment with clotrimazole, using the Wilcoxon signed-rank test ($P = .0001$). There was a significant difference between the 2 groups in the severity of burning before and after the study using logistic regression ($P = .032$).

Table 4. Comparison of the Severity of Leukorrhea Pre- and Postintervention for the Groups (n = 50 in Each Group)

Leukorrhea	Ozone Group		Clotrimazole Group	
	Preintervention n (%)	Postintervention n (%)	Preintervention n (%)	Postintervention n (%)
None	4 (8)	42 (84)	6 (12)	33 (66)
Mild	9 (18)	7 (14)	13 (26)	13 (26)
Moderate	13 (26)	1 (2)	12 (24)	2 (4)
Severe	20 (40)	0 (0)	17 (34)	2 (4)
Very severe	4 (8)	0 (0)	2 (4)	0 (0)

Note: No significant differences existed between the ozone and the clotrimazole groups in the severity of leukorrhea at baseline ($P = .14$) but significant difference was seen postintervention ($P = .03$) using the Mann-Whitney U test. Within-group analysis showed a significant difference in the severity of leukorrhea before and after the treatment with ozone, using the Wilcoxon signed-rank test ($P = .0001$). Within-group analysis showed a significant difference in the severity of leukorrhea before and after the treatment with clotrimazole, using the Wilcoxon signed-rank test ($P = .0001$). There was no significant difference between 2 groups in the severity of leukorrhea before and after the study using logistic regression ($P = .75$).

1 woman (2%), (4) severe—from 20 women (40%) to no women (0%), and (5) very severe—from 4 women (8%) to no women (0%). For all categories of the severity of leukorrhea, a significant difference was observed in terms of the reduction in the severity of in the ozone group ($P = .0001$).

The changes in the severity of leukorrhea were also compared for the clotrimazole group, and for all categories of severity, A significant difference in the severity of leukorrhea before and after the treatment with clotrimazole was found, using Wilcoxon signed-rank test ($P = .0001$).

Table 5 shows the results for the cultures performed after treatment for the 2 groups. No significant difference existed between the 2 groups in terms of the results for the culture postintervention ($P = .62$).

DISCUSSION

The current study was performed to compare the efficacies of ozonated olive oil and clotrimazole cream for treatment of vulvovaginal candidiasis. Before treatment, the 2 groups were similar in terms of ages, recurrences of the infection, contraceptive methods, and use of antifungal drugs. The changes in patients' symptoms (ie, in the severity of burning, itching, and leukorrhea) and in the results of the cultures for vaginal candidiasis were considered to be the outcomes for the study.

The present study has shown that the 3 symptoms significantly improved after treatment for the group receiving the ozonated olive oil, with $P = .0001$ for all measures. The ozone was as effective as clotrimazole in reducing the severity of both the itching ($P = .89$) and leukorrhea ($P = .75$), as well as reducing the number of women with a positive culture for *Candida*; however, the ozone decreased the burning sensation significantly more than did the clotrimazole ($P = .032$) (ie, the 2 drugs were not similar in their efficacies in decreasing the severity of burning). No side effects occurred during the study for either group.

The results of the current study confirmed the findings of a study performed by Minocheher⁷ in 2010 that evaluated

Table 5. Results of Cultures for Vaginal Candidiasis Postintervention for the Groups (n = 50 in Each Group)

Results	Ozone Group n (%)	Clotrimazole Group n (%)
Positive	9 (18%)	13 (26)
Negative	41 (82%)	37 (74)

the fungal-removing effects of ozonated olive oil for 3 types of *Candida*. Also, the results of the current study are comparable to a study performed by Rajabi⁸ in 2007 that compared the effects of ozonated olive oil and clotrimazole cream on trichomoniasis infections and showed that 100% of the patients treated with ozone had improved symptoms. In that study, the 2 groups were not significantly different in terms of clinical symptoms after treatment, but in terms of the laboratory tests, the rate of negative smears was significantly higher for the ozone group than for the clotrimazole group. Rajabi's study was very similar to the current study because it evaluated the treatment of vulvovaginitis and its symptoms using ozone. The reduction in symptoms by ozone in Rajabi's study was similar to that in the current study, but the results in terms of the laboratory testing were different, because the present study showed that the treatments received by the ozone and clotrimazole groups were not significantly different in terms of obtaining a negative culture postintervention.

The results of the current study were in accordance with a study by Rodriguez et al³ in 1995. For 5 days, the researchers treated 12 patients with *Candida* vulvovaginitis that was tolerant to conventional treatments with ozonated oil and repeated the treatments for 2 additional cycles of 5 days. *Candida* vulvovaginitis was completely removed in all patients. The researchers evaluated the infection recurrence during an 18-month follow-up, and in only 1 case was the

recurrence of symptoms observed, without confirmation of a *Candida* infection.³

In a study performed by De Las et al⁴ in Cuba, 60 patients with vulvovaginitis were placed in 3 treatment groups: (1) ozonated flower seed oil, (2) a conventional treatment, and (3) flower seed oil without ozone as a placebo group. Positive results were observed for 100% of the patients in the ozone group within 5 to 7 days. No changes occurred for the placebo group, and for the group receiving the conventional treatment, the changes were smaller and occurred later than in the ozone group.⁴

Bailey has indicated that the reaction of ozone with vegetable oils such as olive or sunflower oils occurs exclusively within the carbon-carbon double bonds that are present in unsaturated fatty acid.¹⁰ That reaction produces several oxygenated compounds, including hydroperoxides, ozonides, aldehydes, peroxides, deperoxides, and polyperoxides. Those oxygenated compounds also could be responsible for the wide biological activity of ozonized vegetable oils.

The yield of oxygenated compounds from unsaturated oils depends on the reaction conditions, such as the type of medium where the reaction takes place, the presence of additives, the reaction temperature, the type of reactor, the agitation of the reaction mixture, and the applied ozone doses.^{6,10,11}

A study by Sadowska et al¹² confirmed Bailey's¹⁰ findings that the reaction of ozone with vegetable oils occurs almost exclusively with the carbon-carbon double bonds present in unsaturated fatty chains. The viscosity measurements in that study showed that viscosity is a function of the dimension and orientation of molecules. The decrease in the degree of unsaturation and the increase in the molar mass both contributed to the increase in viscosity of the ozonated oils.

Because ozone itself does not penetrate cells but immediately reacts with polyunsaturated fatty acids, its effects should be the result of oxidative reaction. For that reason, ozonated oils could be a way to deliver ozone messengers to tissue. Valacchi et al¹³ concluded that treatment with moderately ozonated sesame oil provided faster rate of wound closure in the first 7 days than did treatment with an oil containing either a lower or a higher peroxide value and even provided a faster rate than did the controls.

The limitations of the present study are technical problems related to maintaining the ozonated olive oil in a cold place, not having placebo group, and not making the study blinded. The current research team recommends the performance of a study to evaluate the rate and time of infection after treatment with ozone and to evaluate the side effects accurately. Repeating the current study with a placebo group could help to determine the efficacy of ozone in the treatment of candida vaginitis more accurately. Further, the research team recommends the performance of a new study that repeats the culture for vaginal candidiasis at several, frequent, consecutive points after starting the treatment, to determine better the required period for treatment with ozone. Moreover, the team also suggests the performance of a study about the efficacy of ozone for patients with an

infection that is tolerant to antifungal treatments, both oral and local.

Moureu et al¹⁴ found that the antibacterial activity of oils ozonized with water was better than the one with the oils ozonized alone. The current research team also suggests that future studies use water within ozonated oil to determine whether it enhances the antifungal activity.

CONCLUSIONS

Ozone appears to be as effective as clotrimazole for treatment of *Candida* vulvovaginitis both clinically (ie, resulting in reduced symptoms) and in terms of a laboratory culture. Because the efficacy of ozone has been confirmed in the current study, because recent reports have indicated the tolerance of the infection to new antifungal drugs, because ozone is a common drug that is widely used in most developed countries, and because no side effects have been recorded so far, the current research team suggests the introduction of ozone as an alternative and cost-effective treatment.

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