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ORIGINAL ARTICLE

A Comparative Study of Ozonized Olive Oil versus Tazarotene Gel in the Treatment of Onychomycosis

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ABSTRACT

Background: Onychomycosis is a fungal infection of the nail bed that may end in nail dystrophy. Topical ozonized oil was reported to have antifungal effects. It delivers oxygen that kill fungus and bacteria. Tazarotene has anti-inflammatory and immune-modulating activities.

Objective: Evaluate the efficacy and safety of topical ozonized olive oils compared to topical tazarotene in patients with onychomycosis

Methods: This study included 32patients with onychomycosis. Patients were assigned into two groups; group I treated topically with ozonized oil, group II applied topical 0.1% tazarotene gel. Both medications were applied for 3 months. Patients were followed up for 6 months. Assessment was based on clinical and mycological evaluation by analysis of the culture taken before and after treatment.

Results: The mycological clearance at the end of treatment (12 weeks) occurred in 12 patients (75%) in group 1(ozonized oil) compared to 9 patients (56.25%) in group2 (tazarotene) ($p<0.03$). There was a significant improvement of all clinical parameters of the affected nails in both groups ($P<0.001$). Recurrence occurred in one patient (8.3%) in ozonized group and 2patients (33.3%) in tazarotene group.

Conclusion: Ozonized oil and tazarotene are new, safe, and effective in the treatment of onychomycosis but ozonized oil has a higher therapeutic effect.

Keywords: Ozone Therapy; onychomycosis; Ozonized olive oil; Ozonized sunflower; Tazarotene gel

INTRODUCTION

Onychomycosis is a frequently recurrent, handicapping disease and significantly associated with negative impact on the patient's quality of life. Failure to treat onychomycosis may lead to permanent nail plate damage and increase susceptibility for secondary bacterial infections. Furthermore, it may lead to some physical and occupational limitations. Onychomycosis is considered one of the most common disorders of the nails. Dermatophytes account for about 60-80% of cases. The most common causative agents are dermatophytes and Candida species. The distal and lateral subungual onychomycosis is the most prevalent type caused mainly by Trichophyton rubrum [1,2,3].

Topical treatments of the disease are often ineffective due to poor penetration as the fungus is deeply seated within the nail plate. Systemic agents are associated with the risks of side effects and poor patients' compliance [3,4].

There is continuous need for more effective and safe antifungal therapy. Natural therapies are among treatments that are currently being evaluated by the researchers to improve outcome in onychomycosis. Ozone, (O3) is a natural part of the atmosphere and is a highly reactive inorganic molecule. At the start, ozone was essentially used as a disinfectant in different fields but now it has been used in different medical diseases owing to its microbiologic properties. It was reported that ozone has antibacterial, antiviral, antifungal and anti-parasitic effects. The therapeutic effects of ozonized oils for treatment of recurrent vaginal candidiasis, tinea pedis, diabetic ulcers, leishmaniasis were previously investigated [5,6,7].

Different ozonized oils are successfully applied against different infections; olive oil and sunflower oils are most used in many countries [8]. In

National Institutes of Health in the United States, ozone was used as a complementary medicine. Ozonated oil is achieved by passing ozone as bubbling through olive oil via ozone generators and becoming ozonic cream or gel material. Ozone is unstable gas, easily dissolves and can't be stored but ozonized oil is stable at room temperature but melted in higher temperature so, it should be refrigerated. Ozone molecule reacts with carbon double bonds present in unsaturated fatty acid of olive oil producing several oxygenated compounds such as aldehydes and peroxides. These products are toxic and responsible for the wide antimicrobial activity of ozonized olive oil [9,10,11]. Previous studies revealed that olive oil has antioxidant effects that can neutralize the free radicals; harmful toxins that are released from the fungus. Tazarotene reduces epidermal hyperkeratinization, improving keratinocyte differentiation. Therefore, it facilitates deep penetration to reach diseased tissues which is the main cause of failure of topical antifungal drugs that can't pass down to hyperkeratotic nails. Tazarotene was reported as an effective topical treatment in onychomycosis owing to its keratolytic effect [12,13]. The aim was to evaluate the efficacy and safety of topical ozonized olive oils compared to topical tazarotene in patients with onychomycosis.

METHODS

Study design: A total of thirty-two patients suffering from onychomycosis were classified randomly into two groups, selected from Dermatology Outpatient Clinic from June 2016 to December 2017. The study was approved by the Institutional Review Board at Zagazig university hospital. The study was done according to (Declaration of Helsinki) for studies involving humans.

Informed consent was taken from both groups.

Inclusion criteria: Patients who had clinical and microbiological diagnosis of onychomycosis and aged from (21-70 years old) of both genders were enrolled in the study.

Exclusion criteria: Patients on tetracycline or systemic retinoids treatment, associated nail disorders such as lichen planus or psoriasis, Pregnancy, patients under chemotherapy or, immunosuppressive drugs, patients used topical or systemic anti-fungal therapy in the preceding 3months were excluded from the study.

Mycological examination

Identification of fungi was carried out using standard mycological procedures; the nail of the patient was decontaminated by 70% alcohol; the nail specimens were collected by nail clippings or scrapings. Direct microscopic examination by 20% potassium hydroxide was performed for identification of hyphae, conidia, and yeast cells. Scrapping is considered positive if hyphae, pseudohyphae, arthro-spores or yeast cells were observed. Mycological culture was performed on Sabouraud's dextrose agar medium with chloramphenicol and Cycloheximide (Mycobiotic agar-Conda-Spain). The isolates were incubated at 28 ± 2℃ and the culture was observed once weekly for 2-5 weeks for any growth. Identification of the growing fungi was carried out by macroscopic and microscopic examination [14,15].

Treatment with topical ozonized oil and tazarotene

Patients were randomized into two groups, each group included 16 patients; Group1 treated topically with ozonized oil (pure O3, olive unscented,2OZ, USA) applied on the affected nails plates and nail folds with a little massage, two times per day. Group 2 treated topically with 0.1% Tazarotene gel, applied once a day. Both medications were applied for 3 months.

Response to treatment was evaluated by

-Mycological culture every 4 weeks and at the end of treatment (3months).

-The clinical response was categorized as either cured, improved or no improvement according to the degree of improvement in the nail bed discoloration, thickness, and the growth of affected nails. Patients were considered cured; when the affected nails retained their normal color, growth and thickness, improved; when partial recovery of the affected nails was obtained and no improvement when there were not any changes in the affected nail.

Follow-up visits: All the patients were clinically evaluated every 4 weeks. Photographs were taken using digital camera (Nikon, Japan) at baseline, 4, 8 and12 weeks after treatment. The patients were followed up for 6 months for any side effects or recurrence.

STATISTICAL ANALYSIS

All analysis were performed with the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) using program version 18.0. Data were presented as means, standard deviations and range. Chi-square and McNemmar test were used. P value of less than 0.05 was significant for all previous tests.

RESULTS

A total of 32 patients enrolled into the study with mean age 35.7 ± 9.2 and 35.6±10.2 in ozonized oil and tazarotene groups respectively, the female gender predominates in both groups. Mean duration of the disease was 10.4 ± 5.2**.** The demographic, clinical data and predisposing factors are presented in (Table1). Fungal isolates were yeast (*candida*) in 13/16 patients (81.3%)(Figure 1),and dermatophyte infection in 3/16 patients (18.8%) in ozonized oil group, whereas in patients treated with tazarotene, fungal isolates were yeast in 14/16 patients (87.50%) and mould infection in 2/16 patients (12.5%) which was identified as *Aspergillus Niger* (Table2). There was complete clinical and mycological clearance occurred in twelve patients (75.0%) in ozonized group compared to nine patients (56.25%) in tazarotene group (p<0.27) at the end of 3months of treatment (Table3),(Figure2,3). Four patients (25%) still had positive culture in ozonized group compared to seven patients (43.75%) in tazarotene group with no significant difference (p=0.27) (Table3). In ozonized group,2 patients (12.5%) showed improvement compared to 5 patients (31.25%) in tazarotene group and 2 patients in both groups showed no improvement (P0.42) (Table4). Regarding improvement in nail plate thickness, color and nails growth, there was significant difference in early improvement in response to ozonized oil (group 1) than tazarotene (group2) (p 0.02). Whereas at the end of treatment, both groups showed improvement in the clinical changes of nail parameters (P<0.001) and the difference was insignificant (Table 5). After 6 months of follow up, recurrence occurred in one patient 1/16 (6.25%) in ozonized oil group compared to two patients 2 /16 (12.5%) in tazarotene group.

Safety: No side effects were observed in ozonized oil group whereas in tazarotene group, slight periangual erythema was reported in 4 patients (25%).

Table (1): Demographic and clinical data of the studied groups

	Group 1 (Ozonized oil) N=16	Group2 (Tazarotene) N=16	Test	P-value
Age (years) **Range** **Mean± SD**	 26-54 35.7 ± 9.2	 18-50 35.6±10.2	t 0.05	 0.96 NS
Gender **Male: N (%)** **Female: N (%)**	 6 (37.5) 10 (62.5)	 2 (12.5) 14 (87.5)	X^2 2.67	 0.10 NS
Residence **Rural: N (%)** **Urban N (%)**	 12 (75.0) 4 (25.0)	 13 (81.3) 3 (18.8)	X^2 0.18	 0.67 NS
Occupation **Housewives** **Working**	 11 (68.8) 5 (31.3)	 11 (68.8) 5 (31.3)	X^2 0.0	 1.0 NS
Predisposing factors **Prolonged immersion in water:N(%)** **Irritating chemicals and others: N(%)**	 12 (75.0) 8 (50.0)	 11 (68.8) 5 (31.3)	X^2 0.15 1.17	 0.69 NS 0.28
History of previous ttt: N (%)	9 (56.3)	8 (50.0)	0.31	0.58 NS
Fingernail:N%	14 (87.5)	13 (81.3)	0.24	0.63 NS
Toenails: N %	2 (12.5)	3 (18.8)	0.24	0.63 NS
Number of nails affected **Single nail affected:N %** **Multiple nails affected: N %**	 10 (62.5) 6 (37.5)	 11 (68.8) 5(31.3)	X^2 0.13	 0.71 NS
Duration **≤ 1 year (N)%** **1-2 years (N) %** **Mean ±SD** **Range**	 11 (68.8) 5 (31.3) 10.4 ± 5.2 3 – 24	 10 (62.5) 6 (37.5) 10.2 ± 7.5 3 - 24	X^2 0.13 MW 0.16	 0.71 NS 0.87 NS

Table (2): Identification of the fungal isolates among the studied groups

	Group 1(16) (Ozonized oil) N (%)	Group 2 (16) (tazarotene) N (%)	X^2	p-value
Candida (yeast)	13 (81.3)	14 (87.5)	5.04	0.08 NS
Dermatophyte	3 (18.8)	0 (0.0)		
Non-dermatophyte mould	0 (0.0)	2 (12.5)		

Table (3): Fungal culture among the studied groups at the end of 3 months

	(Ozonized oil) Group I N %	(Tazarotene) Group 2 N %	X^2	p-value
Culture positive patients	4 25	6 37.5	1.25	0.27 NS
Culture negative patients	12 75	10 62.5		

Table (4): Clinical improvement in patients of both groups

	Group 1 (Ozonized oil) N %	Group 2 (tazarotene) N %	X^2	p-value
No improvement	2 12.5	2 12.5	1.71	0.42 NS
Improvement	2 12.5	5 31.25		
Cured	12 75.0	9 56.25		

Table (5): Clinical response to treatment as regards thickness, color and growth of nail plate in patients of both groups during different times

	Thickness of nail plate Improved not improved	P^a	Color of nail plate Improved not improved	P^a	Growth of nail plate Improved not improved	P^a
1st month						
Group1	10(62.5) 6(37.5)	0.03*	8(50%) 8(50%)	0.02*	6(37.5% 10(62.5%)	0.71 NS
Group2	1(6.3) 15(93.8)		2(12.5%) 14(87.5)		5(31.3%) 11(68.8%)	
2nd month						
Group1	8 (50) 8 (50.0)	0.48 NS	14(87.5%) 2(12.5%)	0.001 **	8(50%) 8(50%)	0.72 NS
Group2	10(62.5) 6(37.5)		5(31.3%) 11(68.8%)		7(34.75%) 9(56.25%)	
3rd month		0.41 NS				
Group1	13(81.3) 3(18.8)		16 (100%) (0%)	0.14 NS	13(81.3%) 3(18.8%)	0.13 NS
Group2	11(68.8) 5(31.3)		14(87.5%) 2(12.5%)		9(56.25%) 7(34.75%)	
P^b	0.02*		<0.001**		<0.001**	
P^c	0.002**		<0.001**		<0.001**	

NS: non-significant; *: Significant; **: highly significant

P^a:Chi square test comparing group 1and group 2

P^b:McNemmar test comparing different month in group 1

P^c:McNemmar test comparing different month in group 2

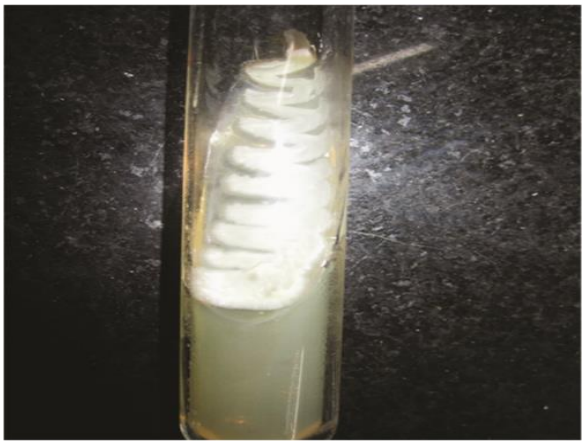
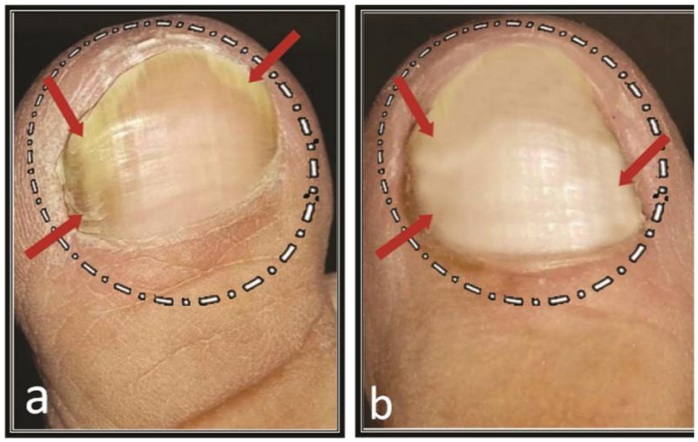


Figure (1)



Figure(2)

Figure (1): Yeast culture on Sabouraud's dextrose agar

Figure(2): (a) Shows right toenail of 54 yrs old female affected by distal lateral subungual onychomycosis (DLSO) before treatment, (b) the same toenail 3 months after treatment with ozonized olive oil

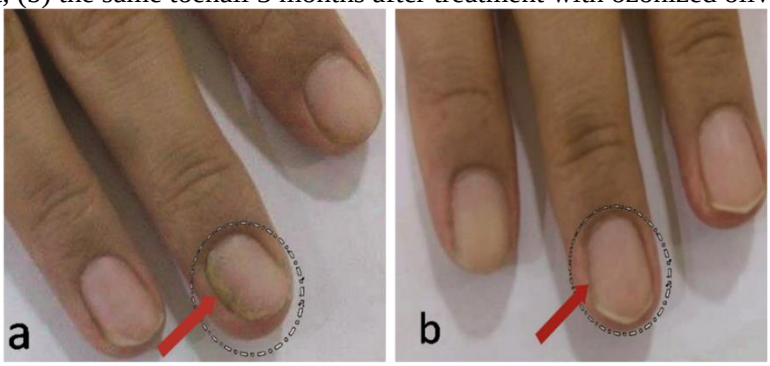


Figure (3): (a) Shows right middle fingernail of 26 yrs old female affected by distal lateral subungual onychomycosis (DLSO) before treatment, (b) the same nail 3 months after treatment with tazarotene

DISCUSSION

Currently available antifungal either topical or systemic are often of limited outcome, indeed there is continuous need for new drugs that offer a greater safety with rapid efficacy. Despite emergence of new antifungal therapies, onychomycosis is still difficult to eradicate; as systemic treatment is often associated with relevant adverse effects, emergence of drug resistance as well and often not suitable for older patients particularly who have low immunity and impaired liver function [16]. The use of ozonized oil for the treatment of onychomycosis is still a relatively new therapy with limited published clinical trials. To our knowledge, this is the 1st study that compared ozonized oil with tazaroten in onychomycosis treatment. In the literature, most of the available studies were in vitro study on bacterial and fungal cultures. Therefore, we tried to evaluate the efficacy and safety of ozonized oil versus Tazarotene in treatment of onychomycosis.

Ozonized oil was prepared by passing it into a reactor with bubbling ozone until they become solid for about 30 minutes; ozone reacts with the bonds in unsaturated fatty acids of the natural oil resulting in production of several oxygenated compounds such as hydroperoxides, ozonides, peroxides which are responsible for its wide biological activity. Free radicals released have high oxidizing activity which target unhealthy tissues. Ozone transforms those oils into a wide spectrum of antimycotic agents [17].

A total of 32patients were enrolled in this study with mean age 35.7 ± 9.2 years and 35.6±10.2 years in ozonized oil and tazarotene groups respectively. The incidence of onychomycosis in younger age groups is high since they are cosmetically more conscious about nail disfigurement. In addition, repeated trauma or wet work are one of the most predisposing factors at this age. However, other studies revealed that the older had the highest prevalence [1,2]. The fingernails were affected more often than toenails in both groups with no significant difference ($p>0.05$). The high incidence of fingernails onychomycosis in this study may be attributed to the predominance of female gender and most of them perform wet works. Yeast infection

was (81.3%) in ozonized oil group and (87.5%) in tazarotene group. In fact, our country is characterized by a hot and humid climate; so, *Candida species* are more frequently isolated. This reflects geographic difference in distribution of fungal isolates in onychomycosis between different regions of the same country. Three cases were reported to have dermatophyte infection (18.8%) in ozonized oil group, while in patients treated with tazarotene, non-dermatophyte mould infection was isolated (12.5%) and identified as *Aspergillus Niger*. Candidal species is considered one of the most important causative agents secondary to exposure to physical and chemical trauma. Some studies documented that candidal infection represents the principal etiologic factor in some tropical and subtropical areas [2,4,18,19]. However, other studies reported that dermatophytes are the most prevalent pathogens (72.73%) followed by candida and non-dermatophytic molds [16].

In the present study, the response was assessed both microbiologically; by analysis of cultures taken at the baseline, at 3 months (the end of the treatment) and clinically by the analysis of serial photographs of the affected nails by independent dermatologists. There was complete clinical and mycological clearance in (75.0%) of ozonized group whereas it was (56.25%) in tazarotene group at the end of treatment ($p<0.27$). There was early improvement in 1st 4 weeks in nail plate thickness and color in patients treated with ozonized oil than those with tazarotene ($P < 0.03$ and $P < 0.02$). Our study met with a randomized controlled trial used ozonated oil (sunflower oils, oleozon) versus ketoconazol cream 2% in patients suffering from onychomycosis for three months. In oleozon group (90.5%) were cured compared to (13.5%) of ketoconazol group with significant differences. The study demonstrated that ozonated oil was more effective than ketoconazol cream without any associated side effects[21]. Mendez et al. used ozonated sunflower oil whereas in our study, ozonized olive oil was used. It was found that both oils are effective, and they are similar in chemical and microbiological properties.

Ozonized oil could penetrate fungal cell walls, diffuse to the cytoplasm, and disrupt cellular function. Previous studies have shown that despite ozone being unstable; it can be trapped inside vegetable oils which are composed of triglycerides. These lipids could retain ozone; therefore, ozonated oils are more stable. Indeed, olive oil seems to be a suitable vehicle which could stabilize ozone since it is a highly reactive molecule[22]. The antioxidants found in olive oil not only kill the fungi but also they neutralize harmful toxins and free radicals released from the fungus. The oxygen delivered from ozone besides having fungicidal activity on different fungi, it activates local microcirculation, stimulates formation of granulation tissue, and induces tissues revitalization. Furthermore, ozone acts as immnuomodulator; it could stimulate some cells of the immune system[8].

Considering that ozonized oil has antifungal activity, and no fungus resistance has been reported against it. Some studies were performed on ozonized oils in the hope that they could be a new product for topical treatment of various fungi. Studies have been done to assess the antifungal activity of ozonized oil. At the start, Mendez et al.[21] evaluated the efficacy of ozonated sunflower in tinea pedis treatment on 200 patients and compared it with topical ketoconazol cream 2%. The results showed complete clinical and mycological cure in 75 for ozonated sunflower and 80% in ketoconazole.

In 2014, in vitro study using the disk diffusion method evaluated antifungal activity of ozonized oil and compared it with azole compounds. The results pointed to that both were effective against various fungal strains [23].

The effect of ozonized oil was examined on some specific properties of various dermatophytes such as sporulation and the fungal hydrolytic enzymes, lipase, keratinase, and urease. The result revealed decline in spore production and loss in the fungal hydrolytic enzymes [24].

The fungicidal effect of ozononated olive oil was compared to clotrimazol in treatment of 100 females with vaginal candidiasis in a randomized controlled trial. The results revealed that both were effective in treatment of vaginal candidiasis[24].

Tazarotene is a third-generation retinoid derived from vitamin A, which has beneficial effects in reducing inflammation, modulating keratinocyte proliferation and in regulating apoptosis. Tazarotene is used in the treatment of inflammatory skin diseases, in particular psoriasis, some skin tumors and acne. A clinical trial was carried out on the effect of topical tazarotene in patients with onychomycosis. The results revealed that six patients (40%) achieved a mycological cure in the 1st month after treatment. In addition, fungal cultures showed a central zone of inhibition in all patients after tazarotene treatment[12]. Another study evaluated the fungistatic activity of all-trans retinoic acid against *C. albicans* and *A. fumigates*.

The results showed that retinoic acid has a direct fungistatic activity [13]. The mechanism of action of tazarotene in onychomycosis may be related to its immunomodulating and anti-inflammatory effects. Tazarotene has a role in the immune response against fungal infections; it modulates cytokines production from macrophages and dendritic cells. It stimulates monocyte mediated immunity. Moreover, it could modulate innate and adaptive immune responses. It was reported that the antifungal activity of retinoic acid is owing to its inhibition of transcription of TNFα, IL6, and IL12 which are induced by fungi[13].

This study represents a great challenge for both medications (ozonated oils and tazarotene) because both are topical drugs used in such chronic disease that require compliance and patience. In addition to, difficulty in finding drug that has ability for nail penetration. Nevertheless, both drugs showed satisfactory results of treatment, good tissue diffusion and well tolerated by patients without any adverse reactions. Both drugs succeeded to reduce the fungal burden in the affected nails. At the end of treatment, there was no significant difference clinically in both groups. However, the mycological clearance was (75.0%) in ozonized group and (56.25%) in tazarotene group.

The antifungal activity of ozonized oil yielded promising results on onychomycosis. It has no risk of systemic adverse effects, drug interactions. Moreover, is far less expensive than current antifungals and could be considered as an effective antimycotic drug.

This study has highlighted the role of ozonized oil in onychomycosis. It might be an alternative treatment option for onychomycosis in particular the patients who are older or those with poor compliance to systemic antifungal drugs.

Further prospective studies on large numbers of patients are recommended. Longer duration of treatment period and follow-up time are needed for better results to be obtained. Correlating the effect of treatment on wider spectrum of fungal species as dermatophyte either in vivo or in vitro is advised. Comparing the effectiveness of ozonized oil or tazarotene with systemic or topical antifungal drugs as treatment of onychomycosis is also recommended.

CONCLUSIONS

Ozonized oil could be considered as a promising antifungal agent, safe, effective, and well tolerated alternative therapy against onychomycosis which is based on ozone rather than chemical drugs.

Conflict of interest: No
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