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A Randomized Clinical Trial on Therapeutic Effects of Myrtus communis L. Cream on Chronic Skin Lesions and Quality of Life of Sulfur Mustard-exposed Veterans

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HIGHLIGHTS

- This is the first study of the protective effects of myrtle cream against sulfur mustard-induces chronic skin complication including; itching and burning sensation.
- Myrtle therapy significantly decreased skin lesion symptoms such as excoriation.
- Myrtle therapy effectively improved quality of life of the sulfur mustard-exposed veterans.

Abstract: Sulfur mustard is one of the chemical warfare agent. It rapidly reacts with the cutaneous tissues and other tissues, leading to various devastating long-term effects on human health. Mustard-exposed veterans suffer from its chronic skin problems, including itching, burning sensation, and eczema. We aimed to evaluate the protective effects of Myrtus communis L. (myrtle) on chronic skin lesions and quality of life of sulfur mustard-exposed veterans. In this randomized, double-blind clinical trial, 60 sulfur mustard-exposed patients were evaluated. Thirty patients received myrtle essence 5% cream (case group) and 30 patients

received Eucerin cream (placebo group) twice in a day for one month. Then, We assessed the chronic skin problems and itching-related parameters (such as the itching time, severity, distribution, frequency, and calculated itching score), duration of sleep, number of waking up at night, and quality of life in the both groups. Our analysis of data revealed that application of myrtle cream effectively decreased skin problems including; itching and burning sensation. Additionally, myrtle markedly decreased skin lesion symptoms such as excoriation in the case group as compared with before treatment. Noticeably, myrtle cream significantly improved quality of life of the patients in the case group. The present study provides more in-depth information regarding the protective role of myrtle on the sulfur mustard-induces skin complication. Also, myrtle effectively improved quality of life of the sulfur mustard-exposed veterans.

Keywords: Myrtle; Skin lesions; Sulfur mustard; Itching.

INTRODUCTION

Sulfur mustard [bis(2-chloroethyl) sulfide; C4H8Cl2S; CASRN: 505-60-2], which is also called mustard gas, is a chemical warfare agent with the ability to form blisters on exposed skin and damage of various organs including; lungs, eyes and skin of victims [1, 2]. It is well accepted that sulfur mustard is a critical threat to both military and civilian populations. Malaviya and coauthors in 2014 reported that cytotoxic effects of sulfur mustard may associate with production of cytotoxic inflammatory markers including; cyclooxygenase-2, tumor necrosis factor-α, inducible nitric oxide synthase, and matrix metalloproteinase-9 (MMP-9). All of these inflammatory markers related to sulfur mustard toxicity [3]. Since, skin has the largest surface area, so it usually suffers more than any other organ in the body in exposed veterans. The process of gas penetration into skin is irreversible and the fixed chemical agent beneath the skin area cannot be collected or removed. Most of patients still refer to the clinic due to the chronic skin complications such as itching, burning, scarring, pigmentation, dryness and flaking [3, 4]. Although, the current topical and oral treatment methods are primarily supportive or symptomatic. Todays, treatment of sulfur mustard lesions involves local application of anti-inflammatory ointments or systemic administration of anti-inflammatory drugs or antibiotics; including cortisone, silver sulfadiazine, diclofenac, and cefazolin [5, 6, 7]. However, the current chemical drugs have low efficacy and also patients mainly suffer from itchy and dry skin, leading to a decrease in quality of life [5]. Herbal medicine, which are natural agents for treatment of many diseases, typically has the least side effects on body organs [8]. Therefore, any efforts towards substitution of chemical drugs with phyto-pharmaceuticals are really appreciated in the field of medicine. Myrtus communis L. (myrtle), which is an endemic medial plant of Mediterranean area, is a valuable traditional herbal drug with approved antioxidant, anti-inflammatory, anti-diabetic, anti-cancer and analgesic effects as well as antimicrobial, and antifungal properties [9]. Indeed, most of the therapeutic nature of myrtle comes from different useful compounds (such as monoterpens and polyphenols) that isolated from its essential oils. Essential oils are aromatic and evaporative mixtures that are extracted from branches and leaves of myrtle after steam distillation. Interestingly, it has been demonstrated that the antibacterial activity of essential oils isolated from myrtle was equal to the antibacterial properties of those antibiotics that are successfully employed against those bacterial strains (roughly 150 strains including the gram-positive Streptococcus aureus and the gram-negative Pseudomonas aeruginosa), which are naturally found in burned areas of skin [10, 11]. Furthermore, the antioxidant activity of myrtle is of huge interest, since oxidative stress and free radical-induced oxidation of bio-molecules are preliminary to initiation and progression of many diseases [12-19]. It is also reported that myrtle essence has protective effects in different skin diseases. It is identified that myrtle effectively decreased the twinge and itching symptoms in herpes. Chronic pruritus is the most common reason of patients' referral to dermatology clinics that might have undesirable effects on quality of life and general health of affected veterans [20]. Therefore, the present study evaluated the protective effects of myrtle cream on the chronic skin problems and itching-related clinical parameters in the mustard gas exposed victims in the Iraq-Iran warfare. We also assessed the effects of myrtle on the quality of life of patients. To our knowledge, this is the first report of the protective effects of myrtle on affected irritated skin of chemically-injured victims.

MATERIALS AND METHODS

Ethical consideration

All ethical issues were approved at ethical committee of. All patients were aware and satisfied with the present study. All patients had the right to withdraw from these experiments and/or to be aware of their results

at any time point of the present work. Nuremberg and Helsinki research ethical principles were strictly considered in the current trial. The current experiments were approved by Baqiyatallah University of Medical Sciences, Tehran, Iran at Iranian registry clinical trial (Date: 2014-11-21; IRCT code: 2014090819090N1).

Study design and data collection

The method of the current study was a randomized double-blind clinical trial. Before beginning the study, informed consent was obtained from each patient. Sixty patients who referred to Chemical Injuries Research Center of Baqiyatallah University of Medical Sciences, Tehran, Iran, were selected from November 2016 to March 2017. Sulfur mustard-induced skin problems was confirmed in patients by a dermatologist. Sixty patients (mustard-exposed veterans) were selected and randomly divided in to two groups: case and placebo groups (n=30 in each group). Neither physician nor patients were aware of both mentioned groups. Case group received myrtle cream at 5% concentration (as drug) [21] twice in a day for one month. Patients in the placebo group only were received Eucerin (as placebo, Abidi pharmaceutical laboratory, Tehran, Iran) twice in a day for one month. Myrtle cream at 5% concentration was prepared in the pharmaceutics department, Baqiyatallah University of Medical Sciences, Tehran, Iran. Both the drug and placebo cream were identical in the appearance, color and texture, amount. Furthermore, both patients and investigator were blinded to the treatment allocation throughout the study. Skin problems and itching in patients were mostly in the arms, trunk and legs, and in some patients in all mentioned areas. All patients were asked to apply the creams to their ulcers, twice per day for one month. Clinical data including; age, percent of war injuries, intensity of exposure to mustard gas, and pharmacological history of patients were assessed in the both of placebo and case groups. Additionally, we assessed the therapeutic effects of myrtle on skin problems, clinical features of skin lesion, itching-related parameters (such as the itching time, severity, distribution, frequency, calculated itching score), duration of sleep, number of waking up at night, and quality of life in both groups. Final itching score calculated by assessment of six itching-related parameters including; itching time, frequency, severity, distribution (at the morning, evening, night), sleep duration, and the number of waking up at night. The time of itching were divided into 4 following groups: itching in the morning (score 1), itching in the evening (score 1), itching at night (score 1), and itching at all-time (score 3). Severity of itching were divided into following 5 groups: itching with no need to scratch (score 1), itching with few needs to scratch (score 2), itching with many needs to scratch (score 3), itching without any relief with scratch (score 4), and itching with discomfort at all times (score 5). Distribution of itching were also divided into 5 groups: itching for any of the limbs including arms, trunk or legs (score 1), or total body itching (score 2-5). Frequency of itching were divided into 5 groups: itching for two times and less than ten minutes or one time more than ten minutes (score 1), and itching in ten times less than ten minutes or five times of more than ten minutes (score 2-5). The frequency of waking up were also categorized into 5 groups: one time wake up (score 1) and the maximum times of wake up (score 5). Any reduction of at least 5 grades in itching score was considered as a successful treatment. For the assessment of quality of life (related to skin complications) in both groups, a questionnaire for Dermatology Life Quality Index (DLQI) was gathered from chemically-injured veterans. The questionnaire is applicable for many skin disorders [9]. This method has been validated in Iranian population. It consists of ten questions that examine six subsets of emotion and symptoms, daily activity, opportunity, work and education, personal relationships, and treatment. The answer of each question is divided into “very much” (3 grades), “a lot” (2 grades), “a little” (1 grade), and “not at all” (0 grade). In addition, grade 0 was assigned to unanswered questions and “non-relevant” responses. The final grade was calculated by summing up the number of grades of answers to all questions ranging from 0-30 grades. Higher grades reflect a more worsening condition of quality of life. The reliability of this questionnaire is 0.77 based on the Cronbach's alpha coefficient.

Inclusion criteria

Our inclusion criteria were as follows: (1) a previous history of mustard gas exposure and itching complication that confirmed by a specialist, (2) no sensitivity to drug and derivatives, (3) no positive history of any autoimmune skin disease, pregnancy and breast feeding.

Exclusion criteria

Our exclusion criteria were as follows: (1) uncontrollable symptoms with herbal drug, (2) lack of patients' collaboration with procedure of treatment, and (3) itching caused by any other factor except mustard gas. Patients were also excluded if they were not accessible to be followed. Those patients who received all other

kinds of topical drugs except of Eucerin or myrtle for at a minimum of 4 weeks before the experiment were excluded from the present study. However, systemic oral drugs were not quitted throughout the experimental procedure.

Drugs

Eucerin (as placebo) and myrtle (as drug) creams were employed for placebo and case groups, respectively. The pre-made myrtle essence at 5% concentration was used due to its availability and cost-effectiveness. We mixed pre-made myrtle essence at 5% concentration and Eucerin cream, using a mixer in the pharmaceutics department, Baqiyatallah University of Medical Sciences, Tehran, Iran. Both the drug and placebo cream were identical in the appearance, color and texture, amount. Furthermore, both patients and investigator were blinded to the treatment allocation throughout the study. Indeed, we poured the creams in equal concentrations into tubes and coded them and gave them to the patients. Patients were treated twice in a day with the drug or placebo for one month. The fingertip unit (FTU) was employed as the measurement unit of both creams. About 0.45 g of cream (that was enough to cover the surface of both sides of one hand from wrist to finger tips) was applied to patients by using the index finger tip. Patients used drugs on affected areas of skin after training.

Statistical analysis

Data analyzed by SPSS software (IBM. SPSS Statistic., version 17.0). Qualitative and quantitative variables were analyzed using Pearson chi square and independent samples t-test tests, respectively. The differences were considered to be significant at $p< 0.05$.

RESULTS

Pharmacological history of patients

All patients in the present study were no longer treated with any other drugs at least 4 weeks before experiment. Most of the patients in the case group used steroids drugs (topical, injection and oral, 83.3%) and orally antihistamines (66.7%). Similarly, most of the patients in the placebo group used steroids drugs (topical, injection and oral, 86.7%) and orally antihistamines (50.0%). In the present study, the myrtle was pre-tested on the arms of patients before starting the experiment for prevention of the allergic reactions. We did not observed any side effects of drug in the patients.

The percent of war injuries, and intensity of exposure to mustard gas

There were 30 patients in each of case and placebo groups (total patients in the present study=60). The mean age was 55.23±16.45 and 54.73±13.38 in the placebo and case groups, respectively. In the present study, no age differences were observed between the two groups (P=0.898). Furthermore, the percent of war injuries were 41.50±18.20 and 48.62±13.22 in the placebo and case groups, respectively. There was no significant difference of war injuries between placebo and case groups (P=0.092). Our data analysis revealed that most of the patients were exposed to mild mustard gas in the both groups. The intensity of exposure to mustard gas was not significantly different between the two groups (P=0.883).

The effects of myrtle on the Skin problems

The protective effects of myrtle were assessed on various skin problems including; itching and burning sensation, eczema, and flaking (Table 1). Among 30 patients in each group, all patients (100%) had itching sensation before treatment. Application of myrtle significantly decreased itching sensation in case group (6.7%, $P< 0.001$). Similarly, application of myrtle significantly decreased burning sensation (13.3%, P=0.021) in case group as compared with placebo group (40%). However, the drug could not cause a significant change on eczema and flaking in patients of case group (Table 1).

Table 1. The protective effects of myrtle on skin problems in the placebo and case groups. N: number of patients.

Skin problem	Treatment status	Case group (N)	Placebo group (%)	P Value
Itching sensation	Before	(30) 100%	(30) 100%	0.121
	After	(2) 6.7%	(25) 83.3%	0.021
P Value		**0.001**	0.652	
Burning sensation	Before	(12) 40.0%	(6) 20.0%	0.091
	After	(4) 13.3%	(9) 30.0%	0.209
P Value		0.021	0.549	
Eczema	Before	(7) 23.4%	(6) 20.0%	0.754
	After	(1) 3.3%	(4) 13.3%	0.353
P Value		0.070	0.625	
Flaking	Before	(4) 13.3%	(1) 3.3%	0.353
	After	(1) 3.3%	(1) 3.3%	0.999
P Value		0.375	0.999	

The effects of myrtle on the clinical features of skin lesion

Clinical features of skin lesion including, erythema, fissure, lichenification, excoriation, and hyperpigmentation were evaluated from neck to waist in all patients (Table 2). Assessment of skin lesion identified that application of myrtle significantly decreased excoriation (0.0%, P=0.001) in the case group as compared with before treatment (23.3%) (Table 2). However, application of myrtle could not cause a significant protective effects on erythema, fissure, lichenification, as well as hyperpigmentation as compared with before treatment in the case group (Table 2).

Table 2. The protective effects of myrtle on clinical features of skin lesion in the placebo and case groups. N: number of patients.

Skin lesion	Treatment status	Case group (N)	Placebo group (N)	P Value
Erythema	Before	(7) 23.3%	(12) 40.0%	0.165
	After	(2) 6.7%	(10) 33.3%	0.010
P Value		0.125	0.50	
Fissure	Before	(5) 16.7%	(1) 3.3%	0.139
	After	(1) 3.3%	(2) 6.7%	0.999
P Value		0.219	0.786	
Lichenification	Before	(1) 3.3%	(1) 3.3%	0.999
	After	(0) 0.0%	(0) 0.0%	0.999
Excoriation	Before	(7) 23.3%	(0) 0.0%	0.011
	After	(0) 0.0%	(0) 0.0%	0.999
P Value		0.001	0.999	
Hyperpigmentation	Before	(6) 20.0%	(4) 13.3%	0.731
	After	(8) 26.7%	(5) 16.7%	0.347
P Value		0.791	0.999	

The effects of myrtle on the itching-related parameters

Neither myrtle nor Eucerin significantly reduced the time of itching in the all-time including; morning, evening, or night (data are not shown). Similarly, there was no significant reduction in itching severity of patients after treatment with myrtle cream (P=0.19) in the case group (data are not shown). Additionally, application of myrtle cream could not significantly reduce itching frequency in the case group (P=0.549) as compared with the before treatment (data are not shown). Generally, as shown in the table 3, the final calculated itching score was 18.61±3.72 for case and 18.71±3.62 for placebo groups before, and 17.66±4.71 for case and 19.10±2.33 for placebo after treatments (Table 3). There was no significant decline in the itching score of case group (p=0.388) after treatment (Table 3). Also, application of myrtle did not significantly reduce the final itching score as compared with Eucerin treatment (p=0.426).

Table 3. The effects of myrtle on itching calculated score in the placebo and case groups.

Treatment condition	Mean of itching score of case in all 30 patients	Mean of itching score of placebo in all 30 patients	P Value
Before treatment	18.61±3.72	18.71±3.62	0.523
After treatment	17.66±4.71	19.10±2.33	0.426
P Value	0.388	0.648	

The effects of myrtle on the duration of sleep

The application of myrtle did not significantly change the duration of sleep in the case group (P=0.999). Additionally, there was no significant reduction of the number of waking up at night between both groups after treatment (data are not shown).

The effects of myrtle on the quality of life based on DLQI questionnaire

Quality of life was 18.30±4.41 for case and 18.36±5.27 for placebo groups before treatment, with no significantly difference between them (Table 4). Additionally, after treatment both of case and placebo groups revealed 21.93±5.19 and 22.30±5.84 scores for quality of life with no significant difference between groups. Interestingly, both treatment (myrtle and Eucerin) significantly increased quality of life in both of case (P=0.003) and placebo (P=0.004) groups (Table 4).

Table 4. The effects of myrtle on the quality of life based on DLQI questionnaire in the placebo and case groups.

Treatment condition	Mean of DLQI of Case	Mean of DLQI of Placebo	P Value
Before treatment	18.30±4.41	18.36±5.27	0.523
After treatment	21.93±5.19	22.30±5.84	0.923
P Value	0.003	0.004	

DISCUSSION

Our analysis of data revealed that application of myrtle cream effectively decreased skin problems including; itching sensation, burning sensation, skin color change, and skin dryness. However, application of myrtle cream had no significant effect on eczema and flaking in case group as compared with before treatment. Additionally, administration of myrtle cream markedly decreased skin lesion symptoms such as excoriation and hypopigmentation in case group as compared with before treatment. Noticeably, application of myrtle cream significantly improved quality of life of the patients in the case group. Skin injuries inflicted by sulfur mustard as a chemical warfare agent can induce through several pathological factors. Three factors have important role in the physiopathology of sulfur mustard-induced skin problems and also other complications. The first important factor is oxidative stress and apoptosis, which are play a crucial role in the toxicity mechanism of sulfur mustard [22]. It can induce oxidative stress via either an increase reactive oxidative species (ROS) production or a decrease in antioxidant capacity [23]. Pohanka and coauthors reported that sulfur mustard-exposed rats exhibited depletion of glutathione (GSH), as an antioxidant peptide, and increase in caspase activity, as an apoptotic factor, in the various organs including liver, kidney, and muscles of animals [22]. Similarly, another research identified a marked decrease of GSH level in the blood of Iran-Iraq sulfur mustard-exposed veteran warfare [24]. The second factor is inflammation. The inflammatory role of sulfur mustard is supported by various documents [25, 26]. For example; Change and coauthors reported that sulfur mustard induced an accumulation of macrophages and neutrophils in the ear skin. They also identified that these inflammatory response in the ear skin was related to the increase in expression of the pro-inflammatory markers such as interleukin-1β, interleukin-6, and tumor necrosis factor α [25]. The third factor is alkylating activity of sulfur mustard. The alkylating activity of sulfur mustard can damage enzymes, proteins, lipids, and particularly DNA [22]. This activity can lead to inhibition of nucleic acid and protein biosynthesis, as well as ATP depletion which disruption of intracellular energy metabolism. Then, ATP depletion and cell energy sources deprivation lead to further oxidative stress [23]. Therefore, it is highly likely that herbal compounds that can target sulfur mustard-induced oxidative stress are important therapeutic options because oxidative stress is an immediate critical consequence of sulfur mustard exposure [27]. Hence, the important aim of the present study was assessment of the protective effects of myrtle cream, as an oxidant agent on itching-related parameters in the sulfur mustard-exposed veterans in the Iraq war against Iran (1980-1988). Myrtle is an evergreen shrub, which is widespread spontaneously throughout the Mediterranean area. This plant used for folk medicine, food and spice purposes [28]. It is reported that myrtle

extract has strong antioxidant activity [29]. Our study is in line with other studies, which are supported the protective effects of myrtle in skin diseases. For example; Ghadami Yazdi and coauthors in 2014 reported that topical treatment of myrtle decreased the number and the size of warts in patients [30]. Similarly, Raeiszadeh and coauthors investigated effect of ethanol extract of myrtle leaves on molecular mechanisms of the wound healing process. They identified that ethanol extract of myrtle leaves increased the angiogenic potential and also decreased expression of inflammatory genes (COX-2 and iNOS) in the LPS-exposed J774.A1 macrophage [31]. Recently, in one animal study, Ozcan and coauthors in 2019 identified that oral and topical myrtle extract treatment (100 mg/kg/day for 2 days) have protective role against burn-induced damage in the Wistar Albino rats [32]. Hear, our study revealed potent therapeutically activity of myrtle on chronic skin lesions and quality of life of sulfur mustard-exposed veterans. The exact underlying mechanism of protective role of myrtle on skin diseases is far from clear. However, using in vitro study, Raeiszadeh and coauthors in 2018 reported that application of myrtle extract have antioxidant, anti-inflammatory, and angiogenesis properties [31]. Similarly, several studies identified that berry and leaf extracts isolated from myrtle can decrease oxidative stress by its antioxidant activity [33]. Furthermore, Amensour and coauthors in 2009 identified that leaf extracts isolated from myrtle showed higher antioxidant activities than berry extracts. They also reported that antioxidant strength was in the order methanol > water > ethanol in leaf extracts isolated from myrtle and methanol > ethanol > water in berry extracts [34]. Hence, it is suggested that likely the protective role of myrtle on the sulfur mustard-induces skin complication is mediated by its anti-oxidant and anti-inflammatory activity. It is needed further study. Our limitations at the present study are the small sample, low cooperation for the exams, and lack of similar studies of chemical warfare veterans. Furthermore, a long time is passed from the date of the war. So, there is the possibility of recall bias.

CONCLUSION

The present study provides more in-depth information regarding the protective role of myrtle on the sulfur mustard-induces skin complication in the sulfur mustard-exposed veterans. Furthermore, application of myrtle effectively improved skin problems and quality of life of the sulfur mustard-exposed veterans. So, this plant can be used as an integrative and alternative choice for sulfur mustard-exposed veterans who suffering from skin problems. However, future studies are recommended to recruit larger sample to achieve more precise results.

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