

Clinical Efficacy of Topical *Avena sativa* Versus Betamethasone in Chronic Pruritus due to Sulfur Mustard Exposure

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Abstract

Background: *Avena sativa*, a well-known herbal medicine; has been used in various skin diseases such as eczema, burn and pruritus.

Objective: The objective of this study was to evaluate the effect of this herbal medicine for treatment of chronic pruritus in Sulfur Mustard (SM) exposed patients.

Methods: Veterans who referred to Baghiat-Allah dermatologic clinic for itching problems were examined by a dermatologist and randomly assigned in three different groups. Group A received ointment derived from *Avena sativa* plant, group B, placebo and group C, betamethasone 0.1% cream twice a day for 4 weeks. Twenty five patients were included in each group. A visual analogue scale were used for assessment of severity of pruritus and 2 questionnaire for quality of life and quality of sleep were filled for each patient.

Results: Pruritus severity after the study by VAS method was significantly decreased in all the groups, but betamethasone group showed the largest decrease (-2.4, P<0.001). The average quality of life based on DLQI criteria and quality of sleep based on PSQI after the treatment showed the most significant difference in betamethasone group (3.52, P<0.001 and 0.96, P=0.001 respectively). Although *Avena sativa* showed significant effect on these criteria but it was only superior to placebo and not as effective as betamethasone.

Conclusion: The result demonstrated that *Avena sativa* ointment reduced chronic pruritus, increased quality of life and quality of sleep in patients exposed to SM but betamethasone was superior in all aspects.

Keywords: *Avena sativa*, Chronic pruritus, Sulfur mustard

Introduction

Sulfur Mustard (bis (2-chloroethyl) sulfide) (SM) is a blister-forming agent that was widely used during the World War I and in the Iran–Iraq war between 1983 and 1988 [1]. SM is highly lipophilic and penetrates mucosal surfaces easily, and the organs most commonly affected are the skin, eyes, respiratory tract and sometimes the gastrointestinal tract [2, 3]. SM promote severe inflammatory effect as erythema, itching and vesicles in acute phase as a result of damage to hydrolipid barrier of the skin [4] and production of inflammatory cytokines such as interleukin (IL)-1 β , IL-6, IL-8 and tumor necrosis factor alpha (TNF α) [5].

Skin is one of the organs with most exposure to SM gas and as a result suffers the most damage [6]. Xerosis, itching, rash and hypo-hyper pigmentation occurred in chronic phase [7]. Changes in trans-epidermal water loss (TEWL) which has been reported in patients exposed to SM is one of the main factors in development of xerosis followed by pruritus [8]. Also hyperpigmentation with increase in the skin melanin level is another symptom of chronic phase [9].

In the chronic phase, treatment is mainly symptomatic including antihistamines, moisturizers and topical corticosteroids [10]. Although betamethasone, a topical corticosteroids has been used in these patients but chronic application may results in adverse effects such as striae, atrophy of the skin and acne routinely [11, 12]. Various studies indicated effective topical products for the treatment of itching skin lesions in SM exposed veterans [13, 14].

Avena sativa (L. Geraminae) (oat) is one of the popular traditional medicinal herbs and has been generally found in different part of the world. In Iran, *Avena sativa* green herb commonly known as "Jow-dosar" in Iran and used in traditional medicine to treat nervous exhaustion, insomnia and also as a bath for eczema. *Avena sativa* seed contains high amount of soluble silica, minerals, steroidal compounds [15], and oats polyphenols (avenanthramides) are potent anti-inflammatory agents with anti-irritant effects [16, 17]. However its efficacy in chronic skin complication of SM exposed patients has not been assessed in other studies.

The aim of this study is to evaluate clinical efficacy of topical *Avena sativa* extract in the treatment of inflammatory skin lesions and pruritus in comparison to betamethasone in veterans with chronic SM exposure.

Materials and Methods

This double-blind clinical trial was conducted on chemical veterans suffering from skin lesions due to sulfur Mustard, such as xerosis and pruritus, in dermatology clinic of Baqiyat-Allah hospital from February 2012 to February 2013 (1 year). The study was approved by ethic committee of Baghiat-Allah university. All the participants were informed about aspects of the study and signed a consent form. Patients with previous exposure to sulfur mustard suffering from chronic pruritus were included in this study. Previous exposure to SM was proven by the medical commission of foundation of martyrs and veterans affair's

records. Exclusion criteria of the study were primary pruritic skin disorders, medical conditions associated with pruritus and psychocutaneous syndromes. Also patients with a history of topical treatment within one month of the trial were excluded.

Patients were assigned in three different groups based on the computer-generated random number. Group A treated with the ointment derived from *Avena sativa* plant extract, group B received placebo (Eucerin) and group C treated with betamethasone 0.1% cream (Sina Darou pharmaceutical Co., Tehran, Iran). In this study each group used one finger tips of topical creams locally, two times a day for 4 weeks. For more precision in amount of drug which were applied by patients, we used Finger Tip Unit, amount of cream applied from the distal skin-crease to the tip of the index finger, which almost equals to 0.47 g [18]. Twenty five patients were included in each group. All patients were instructed about the correct amount of use in the first clinic visit.

The plant of *Avena sativa* (L. Graminae) was collected in the beginning of summer in Iran and extraction was conducted by using a Ethanol 70% as solvent and the extracted fluid was filtered and concentrated in vacu. Then *Avena sativa* %5 w/w ointment was prepared with the base of Eucerin.

A visual analogue scale (VAS) was designed to evaluate the severity of pruritus. A 100 mm horizontal line, which zero meant no itch and 100 meant worst experienced itch [19, 20]. Also timing of pruritus during the day was recorded.

For quality of life assessment, Dermatology Life Quality Index (DLQI) was employed which validity and reliability of this

questionnaire has been confirmed in Iranian population and also SM exposed patients with chronic skin lesions [21, 22]. DLQI questionnaire includes 10 questions (symptoms and feelings [2 question], daily activities [2 question], leisure [2 question], work and school [1 question], personal relationships [2 question], and treatment [1 question]). Each question has four options for answer 3 for “very much”, 2 for “a lot”, 1 for “a little”, and zero for “not at all”. By summing all the scores of questionnaire, score of 0– 30 can be obtained where the higher the scores the more severe impairments of life quality gets. Effects on patient’s quality of life are categorized as below; DLQI scores of 0-1 (no), 2–5 (small), 6–10 (moderate), 11–20 (very large), and 21–31 (extremely large).

For sleep quality, Pittsburg Sleep Quality Index (PSQI) (23) was employed which validity and reliability of this questionnaire also has been confirmed in Iranian population and also in SM exposed patients with chronic skin lesions [24, 25]. The questions include difficulty of sleep due to pruritus, general quality of sleep (reversely scored) and usage of sleep medication. Total scores range from 0 to 9.

SM exposed veterans were examined by an expert dermatologist in the first visit in the clinic and at the end of study (4 weeks later). A check list consists of skin complications (Xerosis, erythema, scaling, lichenification and hypo-hyper pigmentation) and outcomes of the study including reduced severity of itch, frequency of itching, improvement in quality of life and quality of sleep were completed by the dermatologist. Patients and physician remained

blinded to treatment allocation during the study.

Statistical analysis

After the collection of data, IBM SPSS Statistics for windows, version 22.0 (Armonk, NY: IBM Corp) were used for analysis. The results of the study were shown as mean±SD or Number (%). The Chi-square test was used for categorical variables. The three-way ANOVA was used to determine the interaction between variables. $P < 0.05$ was considered statistically significant.

Results

In this prospective, randomized double blinded trial among SM exposed patients who referred to Baghiat-Allah dermatology clinic with chief complaint of pruritus, 82 patients were included from which 7 were dropped out of study due to various reasons and finally 25 patients were included in each group.

All of our patients were male. Average age of patients enrolled in the study in group A (*Avena sativa* ointment), group B (placebo) and group C (betamethasone) was 45.8 ± 5.7 , 44.7 ± 3.8 and 43 ± 5.8 years respectively and there was no significant difference between groups ($P = 0.17$). All the patients were exposed to sulfur mustard 25 to 31 years ago and referred to dermatology clinic due to the chronic skin complications.

The region with most frequent itching was upper extremities. The pruritus was also reported in lower extremities, head and face, anterior trunk, posterior trunk, flexures, genitalia and as well as generalized pruritus. The frequency of itching in these areas is depicted in Table 1 and the timing of pruritus is shown Table 2.

The average (mean±SD) of pruritus severity before the study by VAS method in group A and B and C was 8.04 ± 1.59 , 7.44 ± 1.23 and 7.48 ± 1.12 respectively there was no significant difference ($P > 0.05$). Pruritus severity after the study by VAS method in group A, B and C was 6.52 ± 1.73 , 6.20 ± 1.06 and 5.08 ± 1.08 respectively and there were a significant difference between group A and B compared to C ($P = 0.003$) (Table 3).

There are a significant difference in quality of life between betamethasone and another two groups ($P = 0.001$), based on DLQI criteria, The average quality of life before the treatment was 18.04 ± 3.51 , 17.12 ± 1.98 , 17.36 ± 1.89 in group A, B and C respectively, with no significant difference ($P > 0.05$) however after the treatment the most significant difference was observed in betamethasone group 18.52 ± 1.98 ($P = 0.001$) (Table 3).

In Table 4 Pittsburg Sleep Quality Index (PSQI) is depicted. The betamethasone group had the most significant improvement in quality of sleep.



Table 1- Frequency of pruritus in different anatomical regions of patients in each group

Location of lesion	Groups			P value
	A	B	C	
Head and neck	4 16%	4 16%	3 12%	0.89
Anterior Trunk	1 4%	3 12%	2 8%	0.58
Posterior Trunk	1 4%	1 4%	4 16%	0.19
Upper Extremities	8 32%	10 4%	6 24%	0.47
Lower Extremities	4 16%	8 32%	2 8%	0.08
Flexures	3 12%	1 4%	0 0%	0.15
Genitalia	5 20%	3 12%	5 20%	0.68
Generalized	4 16%	9 36%	8 32%	0.24

Table 2- Timing of pruritus in each group

Time of pruritus	Groups			P value
	A	B	C	
Morning	2 8%	2 8%	3 12%	0.85
Evening	5 20%	2 8%	3 12%	0.44
Night	11 44%	16 64%	17 68%	0.18
All the time	7 28%	5 20%	2 8%	0.18

Table 3- Compared efficacy of *Avena sativa*, betamethasone and placebo on severity of pruritus and quality of life

Variables	Groups	Before		After		diff	P value	P-value
		Mean	SD	Mean	SD			
Severity of pruritus	A (A. Sativa)	8.04	1.59	6.52	1.73	-1.52	<0.001	0.003
	B (Placebo)	7.44	1.23	6.20	1.06	-1.24	<0.001	
	C (Betamethasone)	7.48	1.12	5.08	1.08	-2.4	<0.001	
Quality of life	A (A. Sativa)	18.04	3.51	19.68	3.19	1.64	<0.001	0.001
	B (Placebo)	17.36	1.89	18.52	1.98	1.16	0.001	
	C (Betamethasone)	17.12	1.98	20.64	2.36	3.52	<0.001	

Table 4- Pittsburg Sleep Quality Index (PSQI) in each group before and after the treatment

Group		Before		After		Diff	P value	P-value
		Mean	SD	Mean	SD			
PSQI	Avena	4.9231	2.54438	4.4615	2.50169	-.4615	0.058	
	Placebo	5.8696	2.30226	5.4348	2.25280	-.4348	0.060	0.206
	Beta	6.3600	2.28910	5.4000	2.04124	-.9600	0.001	

Discussion

Most patients, who were exposed to mustard gas, are suffering from inflammatory skin lesions and itching problems, that are resistant to most of systemic or topical treatments [26]. Our trial on the effect of topical extract of *Avena sativa* in SM exposed patients showed that, although this herbal medicine decreased pruritus and improved quality of life and quality of sleep but topical betamethasone was more effective in all these areas after 4 weeks of study.

Chronic pruritus, one of the late complication of sulfur mustard gas exposure, is a common problem among chemical veterans [8]. Degraded epidermal barrier function follows by a variety of inflammatory cutaneous symptoms such as erythema and pruritus [27]. In order to suppress these symptoms, anti-inflammatory therapies are often suggested. Systemic and topical immunomodulators such as glucocorticoids, cyclosporine A, tacrolimus, pimecrolimus and ultraviolet light therapy continue to be the most effective antipruritic agents [28, 29]. Administration of topical or systemic corticosteroids, antihistamines or local anesthetics in long-term may lead to suppression of immune system and cause other difficulties, including fungal and bacterial infections [29]. For this reason some studies

have evaluated other therapeutic options for chronic pruritus in SM exposed patients. In one study comparing topical doxepin 5% with betamethasone 1%, significant reduction of pruritus observed with topical doxepin which might be considered as an alternative to topical corticosteroids for treatment of pruritus [30]. In another study, immunotherapy with interferon-gamma (IFN- γ) reduced DLQI and showed effectiveness in treatment of SM-induced chronic skin lesions [31].

Recently herbal medicine with lower profile of adverse effect has gained more attention in this field. In a study by Panahi et al, phytochemicals were used for treatment of pruritus which showed that phenol and menthol have significant therapeutic effects in chronic pruritus [32] and in another study revealed the impact of curcumin on serum inflammatory biomarker, interleukins 8 (IL-8) and antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase [33]. In chronic skin complication of SM, curcumin supplementation can reduce these factors and improve quality of life [34]. Capsaicin isolated from pepper plants (genus capsicum), when frequently used, prevents the release of substance P from C fiber and caused reduction of pain and itch [35] and one study showed its efficacy to reduce pruritus perceived

in chronic skin lesion from sulfur mustard exposure [36].

Leaves of oat plant contain silicon dioxide, polyphenols, flavonoids, monosaccharide and pectin with topical anti-inflammatory effect [37]. Colloidal Oatmeal is extracted from seeds of *Avena sativa*, contains essential fatty acids, flavonoids, phospholipids and sterols that exert a moisturizing and emollient activity associated with a protective action on the skin, maintaining the hydrolipidic property of the skin and reducing the transepidermal water loss, insoluble proteins contained in colloidal Oatmeal have buffering properties, maintaining cutaneous PH at physiologic values [38]. In a study by Matheson et al. patients using the product made of colloidal oatmeal had significantly less itch than those using oil containing liquid paraffin [39]. Inflammatory cytokines such as interleukin-8 (IL-8) lead to pruritus and overexpression of these cytokines may result in pruritic skin disease [40]. A recent study on colloidal oatmeal demonstrated a decrease in IL-8 and NF-KB which is a nuclear

receptor responsible in production of pro-inflammatory factors [40].

The result of our trial showed a significant effect in all groups, even the placebo group. The reason for this finding might be the use of lanolin, an emollient, in our placebo formulation. This reveals the influence of skin dryness on chronic pruritus and importance of skin hydration in the process of treatment.

Although oatmeal was inferior to betamethasone in this study but *Avena sativa* lotion includes anti-inflammatory and emollient properties and are able to increasing moisture in the skin, and as a result we may be able to administer it concomitant with corticosteroids and anti-histamines.

Conclusion

In conclusion *Avena sativa* ointment reduced chronic pruritus, increase quality of life and quality of sleep in patients exposed to sulfur mustard. However the effect was not as significant as betamethasone.

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