Phenol and menthol in the treatment of chronic skin lesions following mustard gas exposure

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ABSTRACT

Introduction: Chronic skin lesions are common late complications of sulphur mustard exposure in veterans injured in chemical warfare. Pruritus is the most common complaint in the chronic phase, with significant effects on the patient's quality of life. The current study evaluated the efficacy of a combination of one percent phenol and one percent menthol in the control of pruritus in these affected patients.

Methods: This randomised, double-blinded clinical trial was performed in chemical warfare-injured veterans with mustard gas-induced pruritus. 80 subjects were selected randomly and divided into two equal groups. One group was treated with a combination of one percent phenol and one percent menthol twice a day, while the other group received a placebo. The therapeutic effects and side effects were evaluated during a six-week treatment course. Pruritus score with a range of 1-48 points was used to calculate the severity of pruritus before and after treatment in both groups.

Results: The final pruritus score in the drug group was significantly different, compared with the placebo group (p-value equals 0.03). There was also a statistically-significant difference between the pre-treatment (19 points) and post-treatment (15.5 points) pruritus scores in the drug group (p-value equals 0.001), but there was no significant difference in the response in the placebo group (p-value equals 0.66). Only a few patients had complaints about the drug, and these were generally minor. The most common complaints were of the greasy nature of the drug and its intolerable odour.

Conclusion: A phenol one percent and menthol one percent combination has significant therapeutic effects for mustard gas-induced pruritus in chemical warfare-injured veterans, in comparison with the placebo.

Keywords: menthol, mustard gas, phenol, pruritus, skin lesions, sulphur mustard

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INTRODUCTION

Sulphur mustard (SM), also known as mustard gas, is one of the agents used for chemical warfare. Its toxic effects may be systemic, local or both, depending on environmental conditions, the system involved and the extent of involvement.[1-3] The skin is one of the first organs to be exposed to mustard gas and because of its high surface area in comparison with other systems, suffers the most damage. Approximately 80% of liquid mustard on the skin surface would evaporate, 10% would be absorbed and fixed to the skin, while the remainder would be absorbed systematically. Cutaneous fixed and absorbed mustard can almost never be removed.[4-6] Skin involvement by mustard gas can be divided into two categories, namely: acute and chronic. The acute type may be seen more commonly in warm and wet skin regions, such as the groin, scrotum and armpit, due to rapid decrease in mustard evaporation rate and its accelerated cycle formation in the mentioned areas. The most common cutaneous complaint in the chronic type is itching, which may be concomitant with dryness. Sometimes, the patients' complaints are a burning sensation and/or bulla formation, especially in tropical areas and during warm seasons. Skin pigmentation changes are seen in both the hyper- and hypopigmentation forms. Eczema and chronic urticaria with no specific pattern may be seen more frequently in chemical warfare-injured veterans and is probably resistant to the common types of treatment.[7-9]

Treatment of chronic involvement is symptom therapy. In patients suffering from pruritus, oral anti-histamines are administered, and in patients with dry skin, local moisturisers and decrease in washing of the involved site are necessary.[10,11] Since the most common chronic skin lesion is pruritus and its presence would significantly

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decrease the quality of life of chemical-injured veterans and because of the low efficacy and high side effects of common therapeutic methods, finding a safe treatment for chronic skin lesions with low adverse effects and high effectiveness would greatly improve the patient's quality of life. Therefore, we evaluated the efficacy of a local combination of 1% phenol and 1% menthol for chronic skin lesions (especially itching) resulting from SM in chemical-injured veterans.

METHODS

The current study was performed as a randomised clinical trial. Our sample population included 80 SM-injured veterans suffering from related chronic skin lesions. Selected patients were randomly placed in two groups consisting of 40 subjects each: one group was treated with 1% phenol and 1% menthol, and the other group received a placebo (containing Eucerin as base and almond oil as solvent). The proposal was accepted by the ethical committee of Baqyatallah Medical Sciences University. After obtaining consent for participation in the study, a questionnaire including demographical variables was given to the patients. Our inclusion criteria were male gender, being chemically injured, having established SM-related skin lesions (according to previous medical documents) with resistance to routine treatment including oral anti-histamine and topical corticosteroids, and/or complications due to long-term consumption of topical corticosteroids. Exclusion criteria included hypersensitivity to the drug or placebo, and itching which resulted from systemic or cutaneous non-chemical diseases.

In order to determine an effective drug amount, we used the finger tip unit (FTU) which was equal to 0.47 g in males and 0.42 g in females, so that one FTU was enough to cover both sides of a hand from the wrist to finger tips. Indeed, because among the several problems due to chemical injuries in veterans, pruritus was so important that we calculated a pruritus score (maximum 48 points) for each patient (Table I). We finally categorised the patients into three groups, namely: mild (1–16 points), moderate (17–32 points) and severe (33–48 points).[12] SM-injured veterans were treated with 1% phenol and 1% menthol twice a day for six weeks, then another pruritus score was calculated at the end of the course of

Table I. Pruritus score (Maximum 48 points)[19]

Parameters	Morning	Afternoon	Night	Total
Period	1	1	1	3
Severity	5	5		10
Distribution	5	5		10
Frequency	5	5		10
Sleeping			10	10
Waking up			5	5
Total	16	16	16	48

Points were awarded for:
Severity: Itching without need to scratch (1 point); itching with occasional need to scratch (2 points); frequent scratching (3 points); no itching relief with scratching (4 points); itching with discomfort all the time (5 points).
Distribution: For each body part: arms, trunk or legs (1 point); generalised itching (5 points).
Frequency: Itching in two periods of less that ten minutes or one period of more than ten minutes (1 point); itching in ten periods of less than ten minutes or five periods of more than 10 minutes (5 points).
Sleeping: Sleeping disorder total one day (10 points); seven hours or more of night sleep (5 points).
Waking up: For each time of waking up (5 points).

Table II. Comparison of skin disorders before and after treatment in both groups.

Skin disorder	Phase	Drug group (%)	Placebo group (%)	Significance
Pruritus	Before	100	100	–
	After	85.0	100	0.02
Burning sensation	Before	30.0	15.0	0.11
	After	17.5	12.5	0.53
Hyperpigmentation	Before	52.5	37.5	0.18
	After	50.0	35.0	0.17
Hypopigmentation	Before	15.0	7.5	0.29
	After	7.5	5.0	0.65
Vesicle	Before	17.5	2.5	0.09
	After	12.5	0	0.02
Scaling	Before	37.5	30.0	0.48
	After	27.5	25.0	0.80
Dryness	Before	77.5	92.5	0.06
	After	37.5	75.0	0.001

Table III. Distribution of the involved region before and after treatment in both groups.

Involved region	Phase	Drug group(%)	Placebo group (%)	Significance
Head	Before	7.5	7.5	–
	After	7.5	7.5	–
Face	Before	35.0	47.5	0.25
	After	22.5	37.5	0.14
Thorax	Before	72.5	75.0	0.80
	After	45.0	65.0	0.24
Back	Before	70.0	72.5	0.80
	After	42.5	65.0	0.04
Upper limb	Before	5.0	7.5	0.64
	After	2.5	2.5	1.000
Groin	Before	75.5	60.0	0.15
	After	70.0	57.5	0.24
Genitalia and perineum	Before	22.5	10.0	0.13
	After	17.5	2.5	0.02
Armpit	Before	70.0	65.0	0.63
	After	57.5	62.5	0.64
Generalised itching	Before	5.0	2.5	0.55
	After	0	2.5	0.31

Table IV. Frequency of pruritus status before and after treatment in both groups.

Pruritus status	Before treatment (% of patients)		After treatment (% of patients)	
	Drug group	Placebo group	Drug group	Placebo group
Mild	22.5	25.0	80.0	20.0
Moderate	75.0	70.0	20.0	72.5
Severe	2.5	5.0	0	7.5
Significance	0.797		0.001	

treatment. After data were collected, statistical analysis was performed using the Statistical Package for Social Sciences version 13.0 (SPSS Inc, Chicago, IL, USA). Student's t-test and chi-square test were used.

RESULTS

The mean age was 44.3 ± 6.3 years in the drug group and 41.1 ± 6.2 years in the placebo group (p = 0.10). In the placebo group, pruritus prevalence before (100% of patients) and after (100% of patients) the treatment were not significantly different, but in the drug group, a significant difference (100% versus 85%) was present (p = 0.02). Burning sensation was reported by 30% of the drug group and 15% of the placebo group (p = 0.11) before treatment, and decreased to 17.5% and 12.5% after treatment (p = 0.53), respectively. Skin dryness was decreased in both groups (in the drug group from 77.5% to 37.5%, and in the placebo group from 92.5% to 75%), with no significant difference before treatment (p = 0.06) and a significant difference after treatment (p = 0.001) (Table II). The frequency of the itching and eczema locations before and after treatment is showed in Table III. 72.5% of the drug group and 75% of the placebo group had lesions in the thoracic region (p = 0.80). The back region was involved in 70% of the drug group and 72.5% of the placebo group (p = 0.80), which decreased to 42.5% and 65%, respectively (p = 0.04) (Table III).

Erythema was observed in 42.5% of the drug group and 77.5% of the placebo group (p = 0.001), which decreased after treatment to 30% and 65%, respectively (p = 0.002). 2.5% of veterans in both groups had no topical drug usage but 2.5% of the drug group and 37.5% of the placebo group were using topical corticosteroids. Usage of other topical medications in the drug and placebo groups was 77.5% and 57.5% topical anti-histamines, and 17.5% and 2.5% of unknown formula, respectively. However four weeks before the beginning of the study, all of the above-mentioned drugs were discontinued in both groups.

We observed a few non-serious complications,

including complaints about the greasy nature of the ointment in 11 veterans of the drug group and seven subjects of the placebo group, intolerable odour in three patients each in both groups, and a burning sensation in the application region in two patients of both groups during the first week of treatment. Median pruritus scores before treatment in the drug and placebo groups were 19 and 21 points, respectively ($p = 0.28$), but the pruritus scores receded to 15 and 20 points, respectively, after treatment ($p < 0.001$). Severity of pruritus after treatment decreased from severe status to mild and moderate status in the drug group. The severity of pruritus calculated by the pruritus score is shown in Table IV.

DISCUSSION

Chronic skin lesions accompanying pruritus are common SM exposure manifestations, which may be concomitant with a burning sensation, blister, scaling, dryness and pigmentation disorders. Since these lesions usually have psychological effects and result in sleep disturbances, they may decrease the quality of life of those afflicted. Carcinogenic effects of cutaneous SM lesions may be important. Although no related malignancy has been reported in Iran, it would be better to begin the treatment during the early stages, to prevent excoriation, scarring and probable cancers. In a study by Tusi et al, the most common skin complaint in 5,668 chemically-injured patients was pruritus, reported in 75.1% of male and 83.5% of female patients, and the most common finding on physical examination was scarring (31.2% and 8.7%, respectively).[13] There are controversies about correlation of findings. In some studies, the authors have claimed significant association,[14,15] but in others, no correlation has been reported.[13] Our results demonstrated a statistically significant correlation between dryness and pruritus ($p < 0.001$). In the current study, the most common complaints accompanying pruritus were dryness (77.5%) and hyperpigmentation (52.5%), and the most commonly-involved regions were the face and head. In a similar survey by Eliasi, a burning sensation was present in 36%, erythema in 34%, blisters in 29.7%, pruritus in 19%, and pigmentation disorders in 16% of patients.[7]

Some studies have evaluated the efficacy of phenol and menthol, in combination or separately, in the treatment of pruritus with different causes, such as contact dermatitis[16,17] and neurotic excoriation.[18] Although the mechanism of action of phenol and menthol is through increasing the sensitivity of cold receptors and increasing the regional blood flow, those are categorised as cooling agents, and a few studies have demonstrated a voltage-dependent block of neuronal and skeletal muscle sodium channels by thymol and menthol.[19] Most of the patients in our study had mild and moderate pruritus, which after treatment with the 1% phenol and 1% menthol combination, showed significant improvement. The subjects with severe pruritus were also downgraded to mild and moderate status. The mentioned improvements, measured by the pruritus score, showed a significant difference of the score in pre-treatment and post-treatment phases, and confirmed the therapeutic effects of the drug in the treatment of pruritus. In conclusion, the 1% phenol and 1% menthol combination has significant therapeutic effects for mustard gas-induced pruritus in chemical warfare-injured veterans, in comparison with a placebo. Therefore, we recommend the use of this drug for treatment of chemical warfare veterans with no contraindication, with the exception of drug hypersensitivity.

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