TOPICAL TIMOLOL EYE DROP SOLUTION FOR THE TREATMENT OF FISSURES IN PATIENTS WITH HAND DERMATITIS

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ABSTRACT

Background

Some patients with chronic hand dermatitis may complain of painful and itchy fissures; in some cases, the fissures are reluctant to conventional therapies of hand dermatitis.

Objectives

To evaluate the efficacy and safety of topical timolol eye drop 0.05% solution for the treatment of fissures in patients with hand dermatitis.

Patients and Methods

In this therapeutic trial, twenty-two cases with chronic hand dermatitis whose hand fissures are unresponsive to conventional therapies are treated with a single daily application of topical timolol eye drop 0.05% solution on the fissures for three weeks; those with complete disappearance of the fissures and symptoms are regarded as complete response, those with a decrease in size and number of fissures with partial or no improvement of symptoms are regarded as a partial response, and those with no change in size and number of fissures with no improvement in symptoms are regarded as no response, search of any side effect done.

Results

The age of the patients ranged from 16-39 years, and the majority were females. Eleven patients (50%) showed complete response, eight patients (36.4%) had a partial response, and three patients (13.6%) had no response. Patients with a single fissure had a statistically significant better response than those with multiple fissures. No, local or systemic side effects were recorded.

Conclusion

Topical timolol solution is an effective and safe choice for treating fissures in patients with hand dermatitis.

Keywords: *Timolol eye drop solution, Hand dermatitis, fissures.*

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INTRODUCTION

Hand eczema, or dermatitis of the hand, is an inflammatory condition of the skin of the hands; the prevalence in the general population was up to 14% [1]. Clinical manifestations include erythema, odema, scaling, hyperkeratosis, vesiculation, fissuring, papules and plaques [2]. Chronic hand eczema refers to the eczematous process involving the hands that last more than three months or relapses twice or more per year despite adequate treatment and treatment adherence [3]. The etiologies are complicated and involve interaction among both extrinsic, including irritants and contact allergens, and intrinsic factors, such as predilection to atopy or filaggren gene mutation [4].

Since chronic hand eczema is refractory to the treatments, various treatment options have been studied to demonstrate their responses. Along with moisturizers and skin protection, potent topical steroids, tacrolimus and in refractory cases, systemic immunosuppressive agents, acitretin, and psoraline plus ultraviolet light A (PUVA) are beneficial. However, fissures and erosions are resistant to therapy and troublesome to patients due to associated pain and discomfort [5].

Beta-adrenergic receptors are present on cells in multiple organ systems, including the skin. Within the skin, receptors are present on keratinocytes, fibroblasts, and melanocytes, and they may have a role in the pathophysiology of dermatologic conditions, including atopic eczema, psoriasis, and vitiligo [6]. Beta-adrenergic blockade by topical timolol maleate has been proposed as a therapeutic agent for non-healing wounds of various etiologies with good outcomes [7]; it also accelerates the recovery of the barrier function of the damaged skin [8].

Beta 2-adrenergic receptors (B2AR) play a role in cutaneous homeostasis; B2AR antagonists, e.g. timolol, increase ERK (extracellular signal-regulated kinases) phosphorylation, keratinocyte migration and thus accelerate skin wound re-epithelialization. In acute partial-thickness donor site wounds, B2AR antagonists have been reported to promote wound healing. One potential mechanism is via keratinocyte migration, which occurs by the facilitation of chemotaxis, the polarization of cells, and activation of extracellular signal-related kinases essential in the signalling of promigratory pathways. The B2AR activation inhibits keratinocyte migration by activating the serine/threonine phosphatase 2A, which down-regulates phosphorylation of extracellular signal-related kinases necessary for migration. Therefore, B2AR antagonists prevent the phosphorylation of phosphatase 2A and have the downstream effect of extracellular signal-related kinase promotion, including a promigratory pathway in keratinocytes [9].

Keratinocyte migration also occurs by galvanotaxis, in which cells migrate in response to electric stimuli. For example, keratinocytes can be stimulated to migrate by forming electrical poles and applying electrical fields [9]. The B2AR antagonists improve the ability of keratinocytes to respond to such migratory cues. In contrast, the B2AR agonists decrease keratinocytes' ability to respond, further implicating the use of topical timolol for recalcitrant wounds [10].

The aim of this study is evaluate the efficacy and safety of timolol eye drop 0.05% solution for the treatment of fissures in patients with hand dermatitis

MATERIALS AND METHODS

A therapeutic trial was conducted in a private dermatology clinic in Sulaimani city-Iraq, from January 2021 to July 2021, in which topical timolol eye drop 0.05% solution was used to manage fissures in patients with chronic hand dermatitis. Twenty-two patients have chronic hand dermatitis with fissures that do not respond to conventional therapies for hand dermatitis of either sex or at any age.

- Patients meeting the following criteria are excluded from the study:

- Patients used topical or systemic therapy for their hand dermatitis during the last six weeks before participating in this study.

- Patients with bronchial asthma or severe chronic obstructive pulmonary disease because timolol has the potential risk of triggering bronchoconstriction.

- Patients with known heart diseases may worsen by timolol like heart block.

- History of hypersensitivity to timolol.

- Pregnant and lactating females.

Each patient's history was taken regarding age, sex, occupation, duration of the disease and the main symptoms (pain or itching).

Close examination of the hands was performed for the clinical diagnosis of their dermatitis, and the number, size and site of the fissures were recorded.

Patients are instructed to put 1-2 drops of timolol solution on the centre of the fissures at night for three weeks; photographs of the fissures are taken before starting the treatments and after three weeks.

Response to therapy is measured as follows:

-Complete response (complete re-epithelialization and disappearance of the fissures with the complete improvement of the symptoms).

-Partial response (decrease in the size and number of the fissures and no or partial improvement of symptoms, but not complete disappearance).

-No response (neither decrease in size nor number of the fissures and no improvement of symptoms).

Any local or systemic side effects were recorded.

The informed concept is taken from any patient.

Statistical analysis

Data entered into Microsoft Excel in which coding & clearing of data were done, then transferred into SPSS program version 22 (statistical package of social science) in which two approaches were used for statistical analysis (descriptive approach & analytical approach); the descriptive approach was used for finding frequencies, percentages, means and standard deviation & constructing charts and figures; while the analytical approach was used for finding associations and P-vales by using Chi-square test, t-test &ANOVA Table. A p-value ≤ 0.05 is regarded as a statistically significant association between variables.

RESULTS

Demographic criteria

Participants' mean age/ year was 26.95 ± 6.67, the minimum age was 16 years, and while maximum age was 39 years. Fifteen cases were females, and seven were males, regarding occupation; eleven cases were homemakers, five cases were workers, four were students, and two were teachers, Table 1.

Clinically

The duration of the disease ranged from 8 months to 2 years. Most patients had more than one fissure, and only six cases had a single fissure. The most common site for the fissures was fingers, two cases had fissures on the sides of the palms only, and five patients had fissures on both palms and fingers. The majority complained of pain and itching; five cases complained only from pain, and three only pruritus. The size of the fissures was not more than a few millimetres, Table 2.

Response

After three weeks of topical timolol solution use:

-Eleven patients had a complete response.

-Eight patients had a partial response, of whom five cases had both decreases in number and size of the lesions with partial improvement of symptoms. In contrast, three cases only decreased the size of the lesions with partial improvement of the symptoms.

-Three patients had no response (Table 3) and (Figures 1 and 2).

Patients with a single fissure had a statistically significantly better response than those with multiple fissures (P value=0.01). However, there was no significant difference in response regarding gender, occupation or site of fissures, Table 4.

Side effects

None of the patients had local or systemic side effects.

Table 1. Socio-demographic characteristics of patients.

Socio-demographic characters		Frequency	Percentage
Gender	Male	7	31.8
	Female	15	68.2
Occupation	Housewife	11	50.0
	Student	4	18.2
	Teacher	2	9.1
	Worker	5	22.7
Total		**22**	**100.0**

Table 2. Frequency & percentage of clinical characteristics of the patients.

Variables		Frequency	Percentage
Number of fissure	Multiple	16	72.7
	Single	6	27.3
Site of fissure	Finger	15	68.2
	Palm & Finger	5	22.7
	Palm	2	9.1
Symptoms	Pain & Pruritus	14	63.6
	Pain	5	22.7
	Pruritus	3	13.7
Total		**22**	**100.0**

Table 3. Response of the cases with fissures to topical timolol solution.

Response	Frequency	Percentage
Complete	11	50.0
Partial	8	36.4
No	3	13.6
Total	**22**	**100.0**

Figure 1. Complete response of fissures to 3 weeks use of topical timolol solution.

Figure 2. Partial response of fissures to 3 weeks use of topical timolol solution.

Table 4. Association between some variables & response to the treatment.

Variables	Responses (no. & %)			Total	P-value
	Complete	Partial	No		
Gender:					
Male	4 (36.4)	2 (25.0)	1 (33.3)	7 (31.8)	0.87
Female	7 (63.6)	6 (75.0)	2 (66.7)	15 (68.2)	
Symptom:					
Pain	2 (18.2)	2 (25.0)	1 (33.3)	5 (22.7)	
Pruritus	2 (18.2)	1 (12.5)	0 (0.0)	3 (13.6)	0.93
Pain and Pruritus	7 (63.6)	5 (62.5)	2 (66.7)	14 (63.6)	
Fissure number:					
Single	6 (54.5)	0 (0.0)	0 (0.0)	6 (27.3)	0.01
Multiple	5 (45.5)	8 (100.0)	3 (100.0)	16 (72.7)	
Fissure site:					
Finger	9 (81.8)	5 (62.5)	1 (33.3)	15 (68.2)	
Palm	0 (0.0)	1 (12.5)	1 (33.3)	2 (9.1)	0.38
Palm&Finger	2 (18.2)	2 (25.0)	1 (33.3)	5 (22.7)	
Occupation:					
Student	3 (27.3)	1 (12.5)	0 (0.0)	4 (18.2)	
Housewife	4 (36.4)	5 (62.5)	2 (66.7)	11 (50.0)	
Worker	2 (18.2)	2 (25.0)	1 (33.3)	5 (22.7)	0.639
Teacher	2 (18.2)	0 (0.0)	0 (0.0)	2 (9.1)	
Total	**11 (100.0)**	**8 (100.0)**	**3 (100.0)**	**22(100.00)**	

DISCUSSION

Twenty-two patients enrolled in this therapeutic trial, and their mean age was 26.95 ± 6.67; this finding is compatible with Fathil's study [11], which showed that most of the cases were in the age group of 20-29 years. This may represent the age of maximum physical activity and exposure to irritant chemicals. In addition, females outnumbered males by about two folds; this result was similar to the result of Mollerup's study [12] showed that hand eczema is twice as frequent in women as in men partly because of diverse exposure patients.

In this study, we took those patients who had fissures due to chronic hand eczema, the majority with multiple fissures complaining of pain and itching and failure to respond to topical and systemic therapies used for hand dermatitis; Pawar described the use of topical timolol in 0.5% ophthalmic solution in a 45-year-old man with chronic persistent hand eczema. The patient's fissures and erosions do not respond to prior topical clobetasol propionate, topical tacrolimus, or oral methotrexate. At one week of follow-up, erosions and fissures had healed significantly. The patient was instructed to continue therapy for one month, during which there was no recurrence of fissures or erosions [13].

Based on this result and the excellent results of using topical timolol for recalcitrant wounds conducted by Liza R. Braun [14] and his colleagues on five cases who had recalcitrant wounds (chronic venous leg ulcer, pressure ulcer, traumatic refractory wound and mixed origin of sickle cell and venous leg ulcer), we decided to conduct this study, using topical timolol for fissures in patients with hand dermatitis.

After three weeks of daily application of topical timolol solution on the fissures, eleven patients had a complete response (complete disappearance of the fissures and symptoms), eight patients had a partial response, of whom five cases had both decreases in number and size of the lesions with partial improvement of symptoms while three cases had only decrease in size of the lesions with partial improvement of the symptoms and unfortunately three patients had no any response. We think that these good fissures' response to timolol solution may be due to the timolol's ability to increase extracellular signal-regulated kinases phosphorylation which promotes keratinocyte migration and thus accelerates skin wound re-epithelialization [9], together with the recovery of the barrier function of the damaged skin [8].

We found that there was no significant association between response to treatment with the site of fissures, sex of patients and their occupation; on the other hand, all patients with single fissure had a complete response, while half of the patients with multiple fissures had a partial response, 5 cases complete response and 3 cases had no any response, so those with single fissure better responded, which may be due to compliance of patients by applying the medication on all the fissures.

The drug was well-tolerated, and any local or systemic side effects were not recorded.

In conclusion, Topical timolol solution is an effective and safe mode of treatment for fissures in patients with hand dermatitis, especially for those with a single fissure.

Ethical Clearance

Ethical clearance and approval of the study are ascertained by the author. All ethical issues and data collection followed the World Medical Association Declaration of Helsinki 2013 for ethical issues involving researchers involving humans, and informed consent was obtained from all patients. Data and privacy of patients were kept confidentially.

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