Efficacy of Topical Timolol Versus Desoximetasone in Chronic Hand Eczema: A Pilot Study

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Abstract

Hand eczema is a common, multifactorial, dermatologic condition. The prognosis is thought to be poor regard to the high possibility to become chronic and relapsing. Topical potent corticosteroid is the mainstay for treatment, but it may cause numerous adverse effects. Timolol, a non-selective beta-adrenergic antagonist, is shown to have the ability to repair the barrier function of the skin. Therefore, this study aims to evaluate the efficacy of topical timolol 0.5% versus desoximetasone 0.25% in the treatment of chronic hand eczema. A total of six volunteers who has bilateral chronic hand eczema is mild to moderate Physician Global Assessment (PGA) severity were collected to participate clinical prospective, randomized, double-blinded, intraindividual, right-left comparative trial for 8 weeks. Topical treatments, timolol 0.5% and desoximetasone 0.25% were randomly assigned to be applied on either left or right hand. The results were interpreted by Hand Eczema Severity Index (HECSI) and digital photograph. After eight weeks of intervention, both timolol and desoximetasone treated sides showed a comparable downtrend in HECSI. No serious adverse effects developed in both interventions. In conclusion, timolol 0.5% showed a promising result for chronic hand eczema treatment. Larger studies are needed to confirm its efficacy.

Keywords**:** *Hand eczema, Beta-adrenergic antagonist, Timolol, Topical corticosteroids, HECSI*

1. Introduction

Hand eczema is a common dermatologic condition in the general population, with a 1-year prevalence of nearly 10% and a lifetime prevalence of 15% (Thyssen, Johansen, Linneberg, & Menné, 2010). Its etiology is multifactorial and can present with various morphology (Coenraads). Chronic hand eczema is defined as an inflammatory process that lasts over three months or relapses two or more times annually (Diepgen, 2012). The study from Thyssen reported mean duration time of hand eczema exceeds ten years and 10% still have hand eczema after 15 years. Even though most of the patients have mild to moderate severity, due to an often relapsing and chronic condition, the long-term prognosis has generally been reported as poor (Meding, Wrangsjö, & Järvholm, 2005).

Apart from lifestyle modification, several treatment modalities are used to treat the disease, including topical treatment, phototherapy, and systemic therapy. Topical corticosteroids are nowadays the mainstay treatment for hand eczema. However, the requirement for long-term application is related to many adverse effects such as telangiectasia, striae, hypertrichosis, acneiform eruption, rosacea, and hypopigmentation (Brazzini & Pimpinelli, 2000). Furthermore, they may inhibit stratum corneum repair and induce skin atrophy, therefore interfering with recovery.

Timolol, a non-selective beta-adrenergic antagonist has been widely used for many years as an ocular topical formulation for the treatment of elevated intraocular pressure and also be used as an off label for several dermatologic conditions, e.g. infantile hemangiomas, chronic wounds (Püttgen et al., 2016; Thomas, Kurien, Jose, Ulahannan, & Varghese, 2017). Previous studies demonstrated that β-AR antagonists can promote skin barrier repairment in a chronic human skin wound-healing model (Pullar, Rizzo, & Isseroff, 2006). Recently, there was an interesting case in the report showing achievement in the treatment of a patient diagnosed with chronic hand eczema who already failed from the treatment of topical clobetasol dipropionate, tacrolimus and oral methotrexate. The patient had an impressive result after being treated with Timolol 0.5% solution for a month (Pawar, 2021).

Therefore, this study aims to compare the efficacy between timolol and desoximetasone for the treatment of chronic hand eczema. As a result, timolol may be an alternative effective and affordable option in the treatment of chronic hand eczema.

2. Objectives

To evaluate the efficacy of topical timolol 0.5%versus desoximetasone 0.25%in the treatment of chronic hand eczema.

3. Materials and Methods

The study design was a clinical prospective, randomized, double-blinded, intraindividual, right-left comparative trial. It was conducted during the period from March to November 2021 at the Department of Dermatology, Benchakitti Park Hospital and Thammasat University Hospital, Thailand. The protocol was approved by the Human Research Ethics Committee of Thammasat University.

3.1 Patient selection

Six participants, aged between 20-65 years old, had been diagnosed with bilateral, chronic hand eczema, which is defined as 'an eczematous process at lasts for more than three months or relapses twice or more often per year, according to ESCD guideline (Diepgen, 2012), were included in the study. Any volunteers who have the following conditions were excluded from the study.

1. Undergoes pregnancy or lactation
2. Has uncontrolled systemic diseases
3. Has any other active skin diseases on the hands such as psoriasis or acute skin infections
4. Use topical medication (immunosuppressant, retinoid, corticosteroids) 2 weeks before study entry
5. Use systemic medication (immunosuppressant, retinoid, corticosteroids) 4 weeks before study entry
6. Phototherapy four weeks before study entry
7. Those who were allergic to ingredients of timolol or desoximetasone

3.2 Study methods

The product of timolol 0.5% solution, Timolol maleate (ALCON-COUVREUR, BELGIUM) (Timolol 5mg/1 mL) and desoximetasone 0.25% cream, Topicorte® (desoximetasone 250 mg in water-miscible fluid base) were repackaged into similar appearance sterile tube and randomly, using computer-generated randomization, assigned to apply on patient's left or right hand. Single-used cotton bud was used to apply each product to avoid cross-contamination. After applying the study products, patients are advised to leave the product dry for at least 5 minutes. All patients had to apply study products twice daily for eight weeks. Other topical products on the treated area were prohibited during the study. HECSI score and digital photograph were assessed at baseline, follow-up period including at the 2nd, 4th, and 8th week.

3.3 Assessments

Hand eczema severity index (HECSI) was performed by a single-blinded investigator to evaluate the clinical outcome of the study. The assessment was done at baseline, 2nd, 4th, and 8th weeks of treatment.

The evaluation includes the severity of six clinical signs in five different areas of the hands and the percentage of extension in each area. The signs are composed of erythema, induration/papulation, vesicles, fissures, scaling, and oedema. Grading the severity into the score of 0=no skin changes; 1=mild; 2=moderate; and 3=severe. The extent of clinical signs in each area is graded into the score of 0=0%; 1=1-25%; 2=26-50%; 3= 51-75%; and 4=76-100%. At last, the total HECSI calculate by the total sum of all clinical sign severity scores in each area multiplied by the extension score. The total score can range from 0 to 360.

In addition, a series of photographs was taken by a standard digital camera (Full-Frame Mirrorless, Sony α7III, Sony Corp., Tokyo, Japan) at baseline and every follow-up visit. Six photographs including the palmar and dorsum side of both left and right hands of each patient were taken at each visit. A Black screen was used as a background.

Any possible adverse events related to treatment were observed and recorded in every follow-up visit. Including burning, stinging, erythema, or scaling. Pulse rate, blood pressure, and heart and lung physical examination were recorded to detect any sign of cardiopulmonary events.

3.4 Statistical analysis

The software package SPSS (IBM SPSS statistic version 26) was used to analyze the data. Qualitative data were reported as numbers and percentages. The comparison of mean HECSI and percentage change from baseline between two independent groups were made with the independent t-test. In addition, the paired t-test was used to compare mean HECSI from baseline to a different point of time in each group. All statistical comparisons were based on a significant level of $p<0.05$.

4. Results

4.1 Study population

A total of 6 patients, three males and three females participated and completed the study. The average age of the participants was 40.83 ±10.07 years with a range from 28 to 59 years. The mean duration of chronic hand eczema was 51.67±41.73 months with a range between 10 and 120 months. Baseline Physician's global assessment (PGA) severity was in equal portion with three of mild and three of moderate severity. Chronic fissure hand eczema, hyperkeratotic palmar eczema, and vesicular hand eczema subtypes were found to be 50.0%, 16.7%, and 33.3%, respectively (Table 4.1).

Table 4.1 Baseline demographic characteristics of patients

	n = 6
Males/ females, n (%)	3/3 (50.0/50.0)
Age (years), mean±SD	40.83 ±10.07 [28-59]
Duration of chronic hand eczema (months), mean±SD	51.67±41.73 [10-120]
Baseline PGA severity (mild/ moderate), n (%)	3/3 (50.0/50.0)
Type of hand eczema, n (%)	
- Chronic fissure	3 (50.0)
- Hyperkeratotic palmar eczema	1 (16.7)
- Recurrent vesicular hand eczema	2 (33.3)
History of atopy (yes/ no), n (%)	2/4 (33.3/66.7)
Hand-washing frequency, n (%)	
- 1-5 times/ day	3 (50.0)
- 6-10 times/ day	3 (50.0)

4.2 Efficacy

The mean HECSI score at the baseline was found to be 21.17±14.36 in the timolol group and 18.33±17.33 in the desoximetasone group. There was no statistically significant difference in the score between both interventions (table 4.2).

Table 4.2 The mean HECSI score at the baseline, 2nd, 4th, and 8th week of interventions

Mean HECSI score	**Timolol 0.5%**	**Desoximetasone 0.25%**	**p-value**
	Mean ± SD	**Mean ± SD**	
Week 0	21.17±14.36	18.33±17.33	0.764
Week 2	19.00±12.18	10.17±6.43	0.157
Week 4	15.50±11.66	9.67±9.22	0.359
Week 8	12.17±6.77	6.33±2.80	0.1951

During the study period using timolol, the HECSI score gradually declined with approximately 7%, 18%, and 37% change after the second, fourth, and eighth week of application, respectively (table 4.3) (figure 2). While desoximetasone group demonstrated a further reduction in the HECSI score compared to the timolol group. Nearly 15% fall in the score was shown within the first two weeks, 28% after four weeks, and around 44% after eight weeks of treatment. There was no statistically significant reduction in the score between different points of time in both interventions (table 4.4) (figure 1).

Table 4.3 Percent change of mean HECSI score from baseline to different points of time

%Change of mean HECSI score from baseline (week 0)	Timolol 0.5%	Desoximetasone 0.25%	p-value
	Mean ± SD	Mean ± SD	
Week 0	Ref.	Ref.	
Week 2	7.18±34.00	14.61±49.44	0.768
Week 4	17.67±52.90	28.46±39.49	0.697
Week 8	36.90±22.48	44.43±30.46	0.363

Table 4.4 P values of HECSI score in a group of timolol 0.5% and desoximetasone 0.25% between different points in time

P values	Timolol 0.5%			Desoximetasone 0.25%		
	Week0-2nd	Week0-4th	Week0-8th	Week0-2nd	Week0-4th	Week0-8th
HECSI score	0.553	0.448	0.086	0.254	0.229	0.108

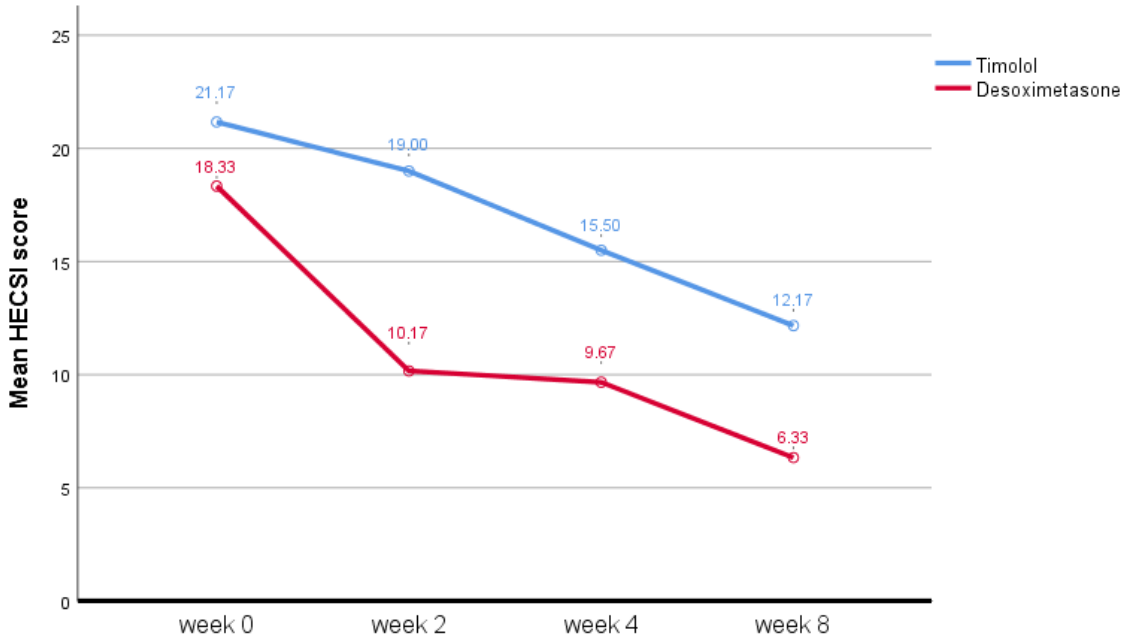

Figure 2 Comparison of mean HECSI score between timolol 0.5% and desoximetasone 0.25% group

4.3 Adverse effects

Dryness was reported by all the patients in Timolol-treated hands, which usually occurs right after applying the solutions, causing more scales to the hand. Whereas in desoximetasone-treated hands, there is no report of any adverse events such as skin atrophy, telangiectasia, or discoloration. There were no serious adverse events reported in both interventions.

5. Discussion

Although hand eczema is not a life-threatening dermatologic condition, it can cause a drastic negative impact on the quality of life of the individual, reported at the same level as those psoriases and asthma Moberg, Alderling, & Meding, 2009) especially when it becomes chronic. Topical potent corticosteroid is the treatment of choice (Diepgen, 2012), but it may cause numerous adverse effects, especially when used in the long term.

Timolol is the 1st generation nonselective beta-adrenergic receptor antagonist. It is commonly used topically for the treatment of open-angle glaucoma. In recent decades, its popularity using as an off-label treatment for dermatologic conditions has been rising. Infantile hemangioma (IH) and other vascular tumors such as pyogenic granuloma, angiofibroma, and Kaposi sarcoma are proposed timolol as an alternative treatment option (Krowchuk et al., 2019; McGinness, Gillam, Yeh, & Mathes, 2018) due to its supposed mechanism of vascular adrenergic receptor blockage. Thereby, inhibiting tumor proliferation and angiogenesis. In addition, it has been increasingly used to treat the chronic wound. The mechanism is by blocking the beta2-adrenergic receptor at the epidermis causing an acceleration of epithelial migration and enhancing re-epithelialization, thus accelerating epidermal barrier repair. Pullar, Manabat-Hidalgo, Bolaji, & Isseroff, 2008; Pullar, Rizzo, & Isseroff, 2006).

There is a case report, published by Manoj Pawar (2021), shows success in the treatment of chronic hand eczema with timolol solution in a chronic hand eczema patient who presented with painful fissures and erosions who have previously been treated with topical clobetasol dipropionate, tacrolimus and oral methotrexate but the erosions and fissures of the hands did not improve. After being treated with timolol 0.5% solution 2-3 drops over lesions at bedtime for a month, the lesions were improved drastically. The mechanism of timolol on the skin can improve skin homeostasis by re-epithelialization. It may also disrupt the pathogenesis of hand eczema hence improving the clinical therapeutic outcome.

This research is the first clinical prospective, randomized, double-blinded, intraindividual, right-left comparative trial provided the comparison of efficacy between topical timolol, a nonselective beta-adrenergic receptor antagonist, and desoximetasone, a potent corticosteroid, in the treatment of chronic hand eczema. Eight weeks of intervention were completed by six volunteers. HECSI score and digital photographs were evaluated at baseline and every follow-up visit including the 2nd, 4th, and 8th week.

In our study, both timolol and desoximetasone treated sides demonstrated a constant downward trend toward hand eczema severity, with no significant difference between the 2 groups at any visit. There was a gradually dropped in HECSI score in the timolol group. Whereas in desoximetasone group, it showed a sharply fell in HECSI score instantly after 2 weeks of intervention. At the end of week 8, the reduction of disease severity was approximately 40% and 44% in the timolol and desoximetasone groups, respectively. However, there was no statistically significant change in the severity score of HECSI from the baseline to eight weeks of treatment. The limitation of this study includes the limited number of volunteers. Also, some factors affecting skin hydration such as the use of cleansers, moisturizers and hand washing have not been recorded. Dryness was reported as a common side effect from the timolol group which was minimal and can be relieved by a combination used with emollients. There was no serious adverse event reported during the study.

Our own data point in the same direction as Pawar's (2021) report. However, a small number of participants is the main limitation of our studies. Therefore, further studies are needed to evaluate the effectiveness of timolol in the treatment of chronic hand eczema.

6. Conclusion

According to the findings of this study, timolol 0.5% showed a promising result for chronic hand eczema treatment. Larger studies must perform to complement its efficacy and adverse effects. Additional follow-up periods may include observing any relapse of the disease after treatment cessation.

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8. References

Brazzini, B., & Pimpinelli, N. (2002). New and established topical corticosteroids in dermatology. *American journal of clinical dermatology*, *3*(1), 47-58.

Diepgen, T. L. (2012). Occupational skin diseases. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*, *10*(5), 297-315. doi:10.1111/j.1610-0387.2012.07890.x

Krowchuk, D. P., Frieden, I. J., Mancini, A. J., Darrow, D. H., Blei, F., Greene, A. K., ... & Whelan, M. A. (2019). Clinical practice guideline for the management of infantile hemangiomas. *Pediatrics*, *143*(1).

McGinness, A., Gillam, A., Yeh, I., & Mathes, E. F. (2018). Topical timolol: An effective treatment option for agminated pyogenic granuloma. *Pediatric dermatology*, *35*(5), e300-e303.

Meding, B., Wrangsjö, K., & Järvholm, B. (2005). Fifteen-year follow-up of hand eczema: persistence and consequences. *British Journal of Dermatology*, *152*(5), 975-980.

Moberg, C., Alderling, M., & Meding, B. (2009). Hand eczema and quality of life: a population-based study. *British Journal of Dermatology*, *161*(2), 397-403.

Pawar, M. (2021). Topical timolol in chronic, recalcitrant fissures and erosions of hand eczema. *Journal of the American Academy of Dermatology*, *84*(3), e125-e126. doi:10.1016/j.jaad.2020.04.070

Pullar, C. E., Manabat-Hidalgo, C. G., Bolaji, R. S., & Isseroff, R. R. (2008). β-Adrenergic receptor modulation of wound repair. *Pharmacological research*, *58*(2), 158-164.

Pullar, C. E., Rizzo, A., & Isseroff, R. R. (2006). β-Adrenergic receptor antagonists accelerate skin wound healing: evidence for a catecholamine synthesis network in the epidermis. *Journal of Biological Chemistry*, *281*(30), 21225-21235. doi:10.1074/jbc.M601007200

Püttgen, K., Lucky, A., Adams, D., Pope, E., McCuaig, C., Powell, J., ... & Frieden, I. (2016). Topical timolol maleate treatment of infantile hemangiomas. *Pediatrics*, *138*(3). doi:10.1542/peds.2016-0355

Thomas, B., Kurien, J. S., Jose, T., Ulahannan, S. E., & Varghese, S. A. (2017). Topical timolol promotes healing of chronic leg ulcer. *Journal of Vascular Surgery: Venous and Lymphatic Disorders*, *5*(6), 844-850. doi:10.1016/j.jvsv.2017.04.019

Thyssen, J. P., Johansen, J. D., Linneberg, A., & Menné, T. (2010). The epidemiology of hand eczema in the general population–prevalence and main findings. *Contact dermatitis*, *62*(2), 75-87. doi:10.1111/j.1600-0536.2009.01669.x