Clinical Evaluation of the Human Tyrosinase Inhibitor Thiamidol (isobutylamido thiazolyl resorcinol) in Prevention of UVB-induced Hyperpigmentation

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Abstract

Background: Thiamidol (isobutylamido thiazolyl resorcinol) has been identified as a potent human tyrosinase inhibitor. A formulation containing Thiamidol has recently shown promising efficacy for the treatment of some hyperpigmentation conditions.

Objectives: This study aimed to evaluate the efficacy and safety of a Thiamidol-based formulation in the prevention of ultraviolet (UV)-induced hyperpigmentation.

Materials and Methods: We performed a randomized, single-blinded, pilot study in healthy participants, N=30. One arm was randomly assigned to receive a Thiamidol-based formulation for three weeks. Three hyperpigmented spots were induced by UVB irradiation on both arms after 3 weeks of Thiamidol application. Outcome evaluations included measuring mean lightness index (*L) obtained by colorimeter, hyperpigmentation scores by visual analog scale (VAS), and adverse effects.

Results: Both experimental sides showed no significant difference in terms of skin lightening after Thiamidol application. However, the Thiamidol-treated sides showed a statistically significant lower mean lightness index compared to control after an induction with UVB. In addition, the Thiamidol-treated sides had an earlier improvement and resumed normal skin color after 3 weeks post-UVB induction. A clinical evaluation by a blinded non-treating physician and subjects was more favorable on the Thiamidol-treated side than the control side ($P < .05$). No significant side effect was noted.

Conclusions: Thiamidol is an effective agent in the prevention of pigmentary change from UVB irradiation and may serve as a promising agent for preventing other hyperpigmentation conditions.

Materials and Methods

Patients

The study was conducted with approval of the Mahidol University Institutional Review Board for Ethics in Human Research (Protocol number MURA2019/1055). Healthy volunteers with age equal or older than 18 years were enrolled into the study. We excluded subjects with serious underlying conditions, pregnancy or breastfeeding, active skin diseases on experimental sites, history of photosensitive disorders, concomitant use of topical medications or those who had previously undergone laser treatment on experimental sites. Subjects with serious side effects from UV irradiation or inability to comply with the study protocol were also excluded from the study.

Study Design

This was a randomized, single-blinded pilot study. The study was conducted at an outpatient clinic of the university-based hospital (Ramathibodi Hospital, Mahidol University, Bangkok, Thailand). Written informed consent was taken from each subject before enrollment. The demographic data including gender, Fitzpatrick skin type, and current medications were obtained at first visit. The inner aspect of the upper arm of each subject was randomly selected to apply 0.15% Thiamidol-containing serum product (Beiersdorf AG, Germany). After 3 weeks of application, both inner arms were induced for three hyperpigmentary spots on each side using local broadband UVB (DuaLight™, TheraLight Inc). The energy used to induce hyperpigmentation was based on subjects' skin types. Subjects with Fitzpatrick skin type II, III, and IV would receive energy at 210, 270, and 300 mJ/cm^2, respectively. UVB was delivered through a hand piece with a square-shaped tip measuring 2 × 2 cm. Subjects were instructed to avoid sunlight, concomitant use of any topical medications, lotion, whitening cream, and vigorous rubbing on the experimental sites during the study period. Follow-up was appointed every week for 4 times after UVB irradiation.

Outcome Evaluation

Lightness index was measured on each experimental site with a colorimeter (DSM II ColoriMeter, Cortex Technology, Denmark) at every visit. Each experimental site was measured repeatedly three times to calculate the mean lightness index. Comparisons of mean lightness on each visit and its baseline were performed. Standard digital photographs were taken at baseline and on each visit. Subjects graded the hyperpigmentation score from 0 to 10 using the visual analog scale (VAS). Zero was for no visible hyperpigmentation, and 10 was for maximal darkness. One blinded non-treating physician assessed the randomized digital images from experimental sites and scored the degree of hyperpigmentation using the VAS. Adverse events were recorded on every visit during the study period.

Statistical Analyses

All data were statistically analyzed using STATA version 14.0 (Stata Corp). Categorical variables were expressed as numbers (percentages). Continuous variables were presented as mean ± standard deviation or median (range). Paired t test or Wilcoxon signed-rank test was used to compare the continuous data as appropriate. Mixed linear model was used to test continuous variables between Thiamidol-treated side and control side on each visit.

Results

TABLE 1. Summary of Subject Demographics.

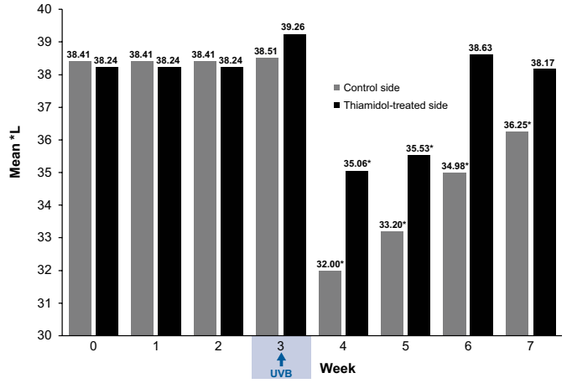
Subject characteristics (n=30)	Data
Mean age, years (± SD)	34.77 (± 9.6)
Sex, n (%)	
Female	29 (96.7)
Male	1 (3.3)
Skin type, n (%)	
III	21 (70)
IV	9 (30)

TABLE 2. Comparison of Mean Lightness Index (*L). Mean lightness index (*L) between control and Thiamidol-treated side at each visit.

		Mean lightness index (*L)		
Visit	Week	Control (Mean ± SD)	Thiamidol-treated side (Mean ± SD)	P-value
1	0	38.41 ± 4.23	38.24 ± 4.69	.833
2*	3	39.02 ± 5.68	39.26 ± 5.17	.775
3	4	32 ± 4.86	35.06 ± 5.07	<.001**
4	5	33.2 ± 4.33	35.53 ± 5	.004**
5	6	34.98 ± 4.17	38.63 ± 10.21	<.001**
6	7	36.25 ± 4.38	38.17 ± 5.01	.018**

*Prior to the UVB irradiation.
**Statistically significant difference.

FIGURE 1. Mean Lightness Index Over Time. Mean lightness index (*L) of Thiamidol-treated side and control side comparing to baseline at each visit.



*Significant difference compared with baseline, P < .05.

TABLE 3. Comparison of Hyperpigmentation Scores (0-10) Evaluated by Subjects and Blinded Physician.

Visit	Week	Control, median VAS (range)	Thiamidol-treated side, median VAS (range)	P-value
Physician evaluation				
3	4	7.6 (2-9.1)	4.8 (0.3-7.8)	<.001*
6	7	6.1 (1.3-8.8)	3.1 (0.1-7.6)	<.001*
Subjects evaluation				
3	4	6.6 (1.3-10)	3.6 (0-10)	<.001*
6	7	4.3 (0.1-9.3)	2.1 (0-8.7)	.004*

*Statistically significant difference.

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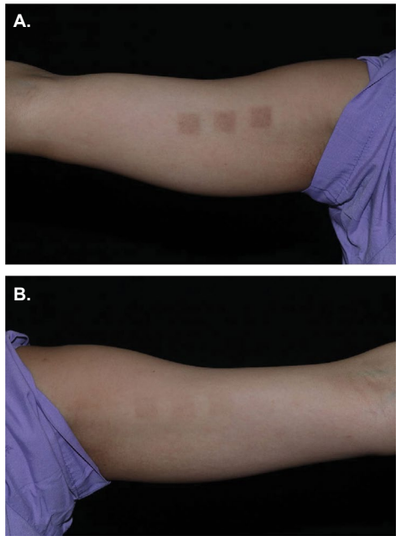
FIGURE 2. Reduction of UV-induced Hyperpigmentation in Thiamidol-treated Subject. Representative pictures of inner upper arms of patient taken at Week 1 after UVB irradiation; A, Control; B, Thiamidol-treated side.



Summary and Conclusions

- Ultraviolet radiation is a major etiological factor affecting hyperpigmentation, mediated by the induction of melanin overproduction
- Tyrosinase is a rate-limiting enzyme for melanogenesis; therefore, inhibition of tyrosinase activity remains a benchmark of hyperpigmentation therapy
- Recently, Thiamidol (isobutylamido thiazolyl resorcinol) has been identified as an effective inhibitor of human tyrosinase
- We found that the application of Thiamidol-containing products for 3 weeks prior to UV irradiation reduced the induction of hyperpigmentation in subjects
- This study demonstrates that Thiamidol has a potential role in the inhibition of UVB-induced hyperpigmentation; thus, Thiamidol-based products should be considered as part of a daily hyperpigmentation regimen

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