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Intermittent Therapy for Melasma in Asian Patients with Combined Topical Agents (Retinoic Acid, Hydroquinone and Hydrocortisone): Clinical and Histological Studies

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Abstract

Melasma is a common problem in Asians, but treatments have not been satisfactory. In the present study, we evaluated the efficacy of a new formula containing 0.1% tretinoin, 5% hydroquinone, and 1% hydrocortisone (RHQ) in Korean patients with melasma. Twenty-five Korean females with therapy recalcitrant melasma applied RHQ on their faces for 4 months and were evaluated before and 4 weeks after treatment clinically and histologically. They were also evaluated clinically 4 months after treatment. To minimize unavoidable side effects (erythema or peeling), we applied RHQ twice a week instead of the usual daily application. However, we obtained clinical and histological results comparable to other reports from white populations. Statistically significant depigmentation in clinical and histological studies and increased subepidermal collagen synthesis were observed in this study. These effects were seen as early as 4 weeks after treatment with RHQ. We used mMASI scoring, a modified version of the original MASI, to quantify the effects of RHQ more objectively and easily.

Key words: melanosis; tretinoin; hydroquinone; Asian

Introduction

Melasma occurs more commonly in Asian females, who comprise of one-third of all the women in the world, than in Caucasians (1). Treatments have not been satisfactory, even though many kinds of depigmenting agents have been tried, including tretinoin (0.025~0.1%), hydroquinone (2~5%), and other therapeutic agents such as glycolic acid, lactic acid, and trichloroacetic acid (2). Combination or monotherapy with tretinoin (TR) and hydroquinone (HQ) are still commonly used as a treatment regimen and are also used before and after laser treatment or peeling. Even though the therapeutic effects of TR and HQ in white and black populations is well known, their effects on Asian populations remains controversial (3–6). Tadaki reports that application of a mixture containing 0.1% TR and 0.1% hydrocortisone for 6 months was not effective in treating melasma, but rather enhanced the tone of the pigmentation (7).

The purpose of this study was to evaluate the efficacy of a new formula containing 0.1% tretinoin, 5% hydroquinone and 1% hydrocortisone (RHQ) in Korean patients with melasma. We also examined the histological alterations after treatment with RHQ in Asian skin, because our patients experienced depigmentation, improved skin surface texture and color, and effacement of fine wrinkles.

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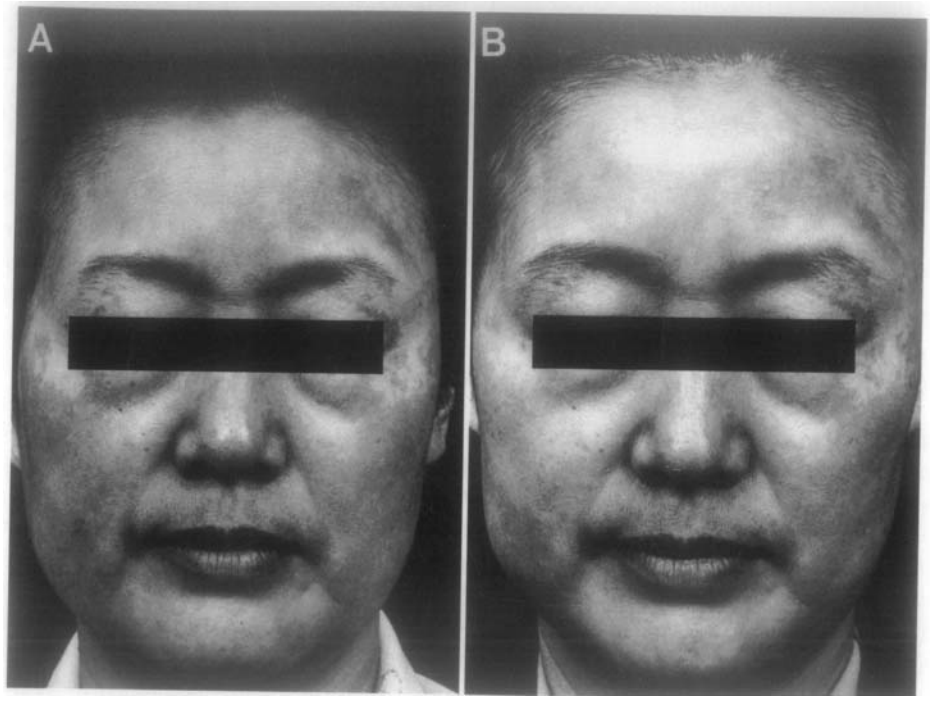

Fig. 1. Subject #1 (F, 48) in pretest. Note the symmetrically-distributed severe melasma at baseline (A) and the almost complete clearing of melasma with notable peeling only on the RHQ-treated right cheek. The vehicle-treated left side showed persistent melasma (B).

Fig. 2. Site selected for mMASI calculation. The superior boundary is the junction between the lower eyelid and cheek extending to the temporal hair line. The lateral boundary is the inferior temporal hair line down to the preauricular skin crease. The inferior boundary is just below the jawline. The medial boundary is the nasolabial crease, between the lower lip and cheek.

Materials and Methods

Pretest: Seven Korean patients aged 38 to 49 years (mean age 43 ± 1.6 years) with melasma were treated with RHQ on the right side of the face and with vehicle cream (only the active ingredients removed) on the left side to ascertain the therapeutic effects of RHQ. They applied RHQ and vehicle twice a week for 4 weeks.

Subjects for main study: Twenty-five Korean females aged 37 to 59 (mean age 44 ± 1.2 years) with therapy-resistant melasma volunteered for this 4-month topical RHQ study. Patients with a history of systemic illness and nursing or pregnant women were excluded. All patients signed informed consent forms, approved by the institutional review board of the Ajou University Hospital.

Methods: The patients were instructed to apply about 0.3 g of RHQ on the melasma lesions in the evening twice a week. All patients were advised to apply a sunscreen cream (SPF 15 or more) and 0.3%-alum solution to relieve RHQ-induced burning sensation or sensation of erythema. This study began in January of 1997 and

Table 1. Melasma in Korean skin: Baseline characteristics and mMASI scores before and after treatment (n=25)

Subjects				Melasma**				mMASI score***		
No.	Name	S/Age	ST*	Cli.	Wood	D	Bx	Baseline	4wks (n=25)	4m. (n=21)
#1	HOK	F/43	IV	CF	ep	8yr	ep	40 (100%)	35 (88%)	20 (50%)
#2	NSK	F/46	IV	CF	ep	11yr	ep	20 (100%)	20 (100%)	12 (60%)
#3	SRK	F/57	IV	M	m	7yr	m	10 (100%)	10 (100%)	1 (100%)
#4	YNK	F/40	IV	M	m	3yr	m	10 (100%)	12 (120%)	dropped out
#5	JWK	F/38	IV	CF	ep	10yr	ep	18 (100%)	12 (67%)	dropped out
#6	JNK	F/40	IV	M	ep	4yr	ep	6 (100%)	6 (100%)	6 (100%)
#7	JCK	F/45	III	M	ep	3yr	ep	1 (100%)	1 (100%)	1 (100%)
#8	JYK	F/39	IV	M	ep	8yr	ep	14 (100%)	12 (86%)	5 (36%)
#9	HJK	F/37	III	CF	ep	3yr	ep	28 (100%)	28 (100%)	6 (22%)
#10	SRP	F/49	IV	M	m	6yr	m	12 (100%)	12 (100%)	8 (67%)
#11	SBP	F/40	IV	M	m	8yr	m	12 (100%)	12 (100%)	8 (67%)
#12	YJP	F/41	IV	M	ep	3yr	ep	24 (100%)	20 (83%)	24 (100%)
#13	SBS	F/59	IV	M	m	18yr	m	6 (100%)	6 (100%)	6 (100%)
#14	MSS	F/43	IV	CF	ep	12yr	ep	28 (100%)	12 (43%)	20 (71%)
#15	MSH	F/40	IV	CF	ep	12yr	ep	30 (100%)	24 (80%)	15 (50%)
#16	BOL	F/39	IV	M	ep	7yr	ep	2 (100%)	1 (50%)	dropped out
#17	OJL	F/41	IV	M	ep	7yr	ep	15 (100%)	8 (53%)	6 (40%)
#18	JSL	F/42	IV	M	m	2yr	m	6 (100%)	6 (100%)	6 (100%)
#19	TSC	F/44	IV	M	ep	6yr	ep	10 (100%)	3 (30%)	2 (20%)
#20	YHJ	F/53	III	M	m	7yr	m	10 (100%)	10 (100%)	3 (30%)
#21	ESJ	F/41	IV	M	m	10yr	m	4 (100%)	2 (50%)	2 (50%)
#22	JJC	F/58	III	M	m	13yr	m	1 (100%)	1 (100%)	1 (100%)
#23	JHH	F/44	III	M	ep	11yr	ep	14 (100%)	8 (57%)	0 (0%)
#24	YKW	F/44	III	M	m	12yr	m	2 (100%)	0 (0%)	0 (0%)
#25	JRH	F/42	IV	M	ep	8yr	ep	9 (100%)	9 (100%)	dropped out
	Mean	44				8yr		100%	80%	60%
	±S.E.	±1.2				±0.8			±5.8	±7.5

*ST: Skin type classified according to reference 21.

**Melasma: Clinical type (Cli.) of melasma was assigned as centrofacial (CF), malar (M) and mandibular (MN), Wood's light (W) and skin biopsy (Bx) was used to determine melasma type as epidermal (ep), dermal (d) or mixed (m). D: Duration of melasma

***mMASI indicates our modification of the original Melasma Area and Severity Index[8]

was finished before June of 1997 to prevent any possible natural shift in the severity of melasma due to strong sunlight in the summer months. All patients were evaluated by two dermatologists before treatment, and 4 weeks and 4 months after treatment. Wood's light was used to determine the melasma type as epidermal, dermal, or mixed. The severity of melasma was scored at baseline, 4 weeks, and 4 months after treatment using a modified version of the Melasma-Area and Severity Index (MASI) developed by Kimbrough-Green et al. (8). Original MASI scores counted the whole face, while our modification (modified MASI, mMASI) counted a confined portion of the right malar area demarcated as described below (Fig. 2). Briefly, mMASI was calculated based on the involved area (A, 0~6), darkness of the pigment (D, 0~4), and homogenicity (H, 0~4). Therefore, mMASI=(D + H) × A.

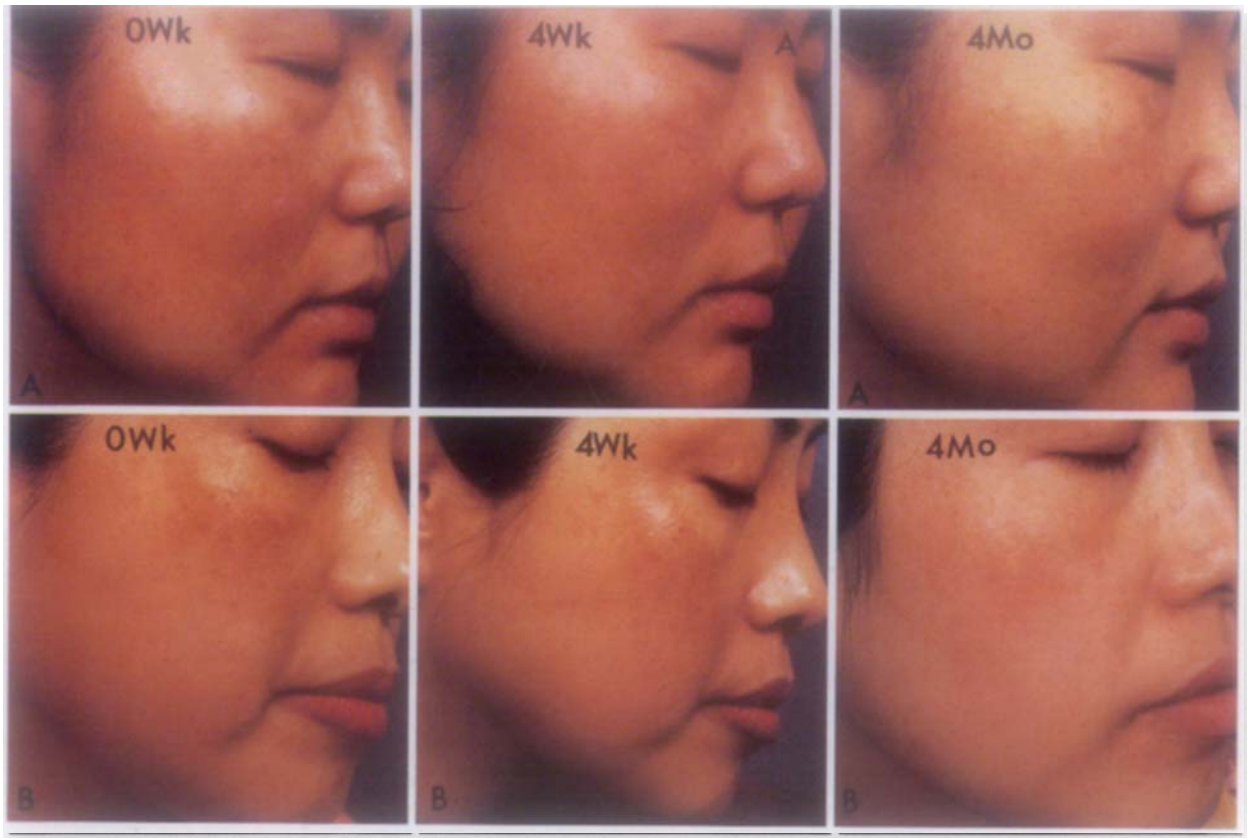

Fig. 3. Clinical photographs of responses of melasma to RHQ cream. (A) A 43-year-old woman (Subject #1): Left, severe melasma at baseline (wk 0); center, after 4 weeks; right, after 4 months of treatment. The mMASI score decreased from 40 (baseline) to 20 (4 months). Melasma of the right cheek has clearly improved at the end of treatment. (B) A 37-year-old woman (Subject #9): Left, severe melasma at baseline (wk 0); center, after 4 weeks: right, after 4 months of treatment. The mMASI score decreased from 28 (baseline) to 6 (4 months). Melasma of the right cheek has virtually disappeared at the end of treatment.

Table 2. Melasma in Korean skin: Histologic results after 4 weeks of topical 0.1% tretinoin, 5% hydroquinone and 1% hydrocortisone therapy (n=24)

Variable	Baseline	after 4 weeks	% change	p-value
Pigment in corneum*	1.7±0.13	1.3±0.12	−24%	p=0.009+
Pigment in epidermis*	1.8±0.12	1.3±0.12	−28%	p=0.001+
Pigment in dermis*	0.45±0.13	0.43±0.13	−4%	p=0.183
Pigment in basal layer*	3.2±0.16	1.1±0.09	−66%	p<0.001+
Stratum corneum compaction*	0.2±0.08	1.4±0.17	+578%	p<0.001+
Thickness of stratum granulosum	2.3±0.14 layers	4.8±0.13 layers	+109%	p<0.001+
Epidermal thickness	61.5±3.59 μm	69.2±4.69 μm	+13%	p=0.087
Thickness of papillary dermis*	0.5±0.13	3.6±0.12	+620%	p<0.001+

*All measurements represent mean±SE and except for epidermal thickness and thickness of stratum granulosum are based on a semiquantitative scale of 0 (none) through 4 (maximum).

Epidermal thickness measured from the top of the granular layer to the epidermal basement membrane

+statistically significant

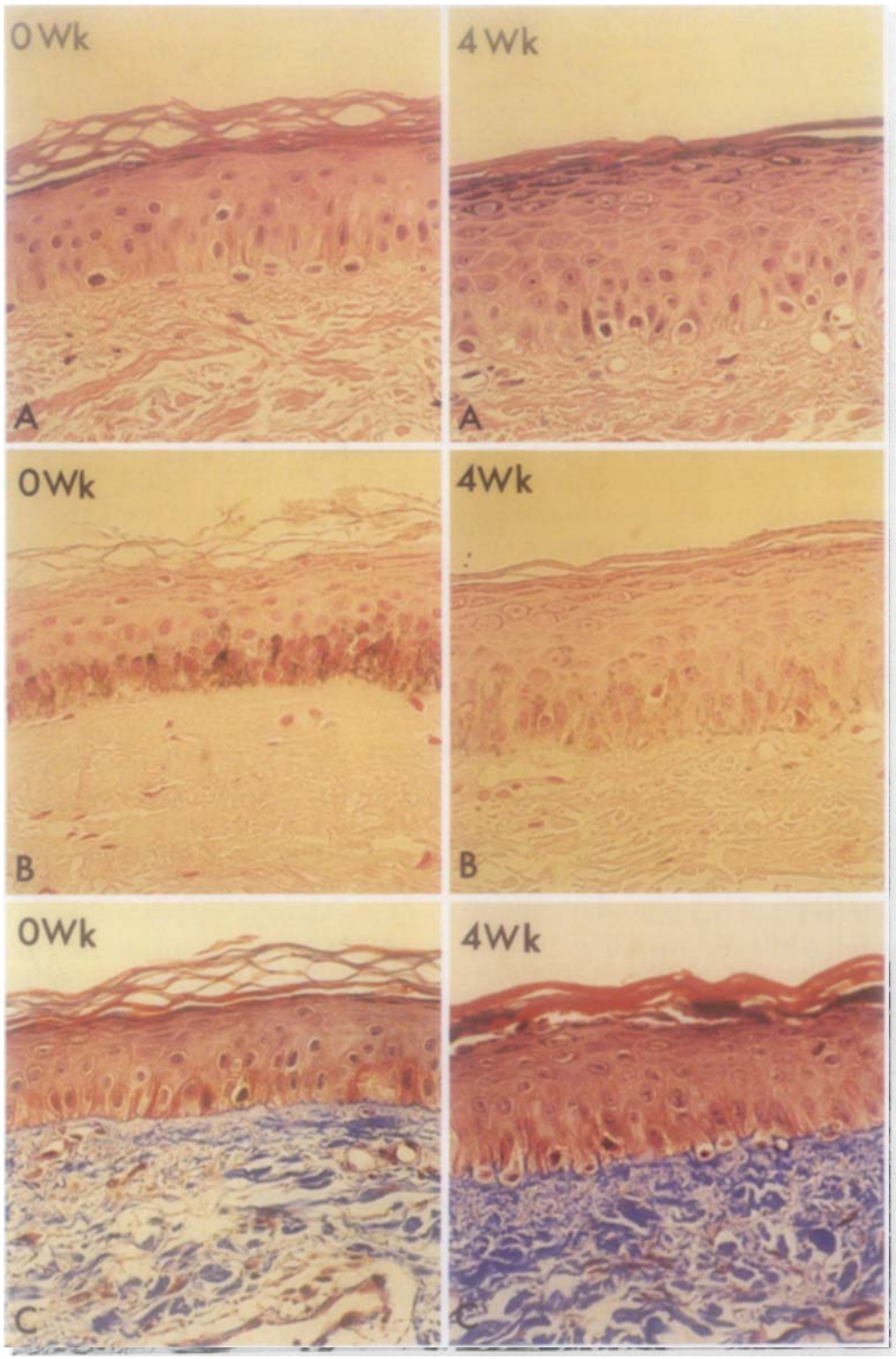

Fig. 4. Photomicrographs of biopsy specimen from Subject #9. (A) Baseline (H&E, ×200) and after 4 weeks of treatment with RHQ (H&E, ×200). Note the thickening of stratum granulosum and compaction of stratum corneum after treatment. (B) Baseline (Fontana-Masson, ×200) and after 4 weeks of treatment with RHQ (Fontana-Masson, ×200). Note the decreased pigmentation in the stratum basale after treatment. (C) Baseline (Masson-Trichrom, ×200) and after 4 weeks of treatment with RHQ (Masson-Trichrom, ×200). Note the formation of new collagen in the subepidermal region after treatment.

The mMASI range was from 0 (minimum) through 48 (maximum).

Photography: A right oblique view of each patient was taken using standardized positioning and lighting at baseline, 4 weeks and 4 months after beginning the therapy. A Nikon F90X camera with an AF Micro Nikkor lens, two Alcar Super A120 flashes, and two 5×2 ft umbrellas at a 45-degree angle were used against a gray unlit background.

Histopathologic studies: At baseline and 4 weeks after treatment, a 2mm punch biopsy was taken under local anaesthesia from the designated area within the same patch of melasma in 24 patients. The 4 week-treatment biopsy was taken far enough away from the baseline biopsy site to avoid potential scar tissue. Specimens were fixed in 10% neutral-buffered formalin, processed in paraffin, sectioned, and stained with hematoxylin and eosin, Fontana-Masson, and Masson-Trichrome for light microscope examination. All specimens were evaluated by a micrometer on the eyepiece of a microscope for thickness of epidermis. Other various histologic parameters of each specimen were evaluated based on a semiquantitative scale of 0 (none) through 4 (maximum). Sections were reviewed by two dermatologists.

Statistical methods: A paired t-test was used to compare mMASI scores and scores of histological findings before and after treatment.

Results

Pretest: Four of seven patients showed definite improvement of melasma after 4 weeks of treatment. Three patients did not show any recognizable differences between RHQ-treated and vehicle-treated control sites. After 4 weeks of treatment, the average mMASI score of the right face (RHQ applied) decreased by 48% ($p<0.01$), from 100% at baseline to 52%, compared with a 0% decrease in the left face (vehicle applied). One representative case with dramatic improvement is shown in Figure 1.

Patient demographics: Of 25 women who were enrolled, 21 completed the entire 4-month study period. Of the 4 patients who dropped out of the study after 4 weeks, two quit because of moderate irritation and the other two because of personal problems. For patient demographics, see Table 1.

Clinical results: The initial mMASI scores in each patient differed according to the severity and area of melasma. We unified the different individual mMASI scores in the beginning of the study as 100%. As early as 4 weeks after treatment, three (12%) of 25 had a definite improvement of more than 50% of the mMASI score, 5 patients (20%) between 30 and 50%, and 4 patients (16%) between 10 and 29%. There was no pigmentary change in 12 patients (48%), and worsening of melasma was observed in only one. After 4 months, 10 patients (52%) had improvement of more than 50% with a continuously decreasing tendency, 4 patients (19%) between 30 and 49%, and 6 patients (29%) showed no improvement. After 4 weeks of treatment, the average mMASI score of the right face (RHQ applied) decreased from 100% at baseline to 80% ($P=0.002$), and it decreased from 100% to 60% after 4 months ($p<0.001$), as clearly shown in Table 1. Representative cases are shown in Figure 3. There was no difference between skin type III and skin type IV from the aspect of clinical improvement. Other factors such as the clinical type of melasma (classified as centrofacial, malar and mandibular) had no specific correlation with the clinical depigmentation effects. But the location of pigmentation diagnosed by Wood's lamp and skin biopsy showed that it was not easy to remove dermal pigmentation with this RHQ therapy. The modified MASI score decreased by 21% on average in 9 women with dermal type melasma after 4-month-therapy, whereas a decrease of 46% was shown in 12 women with the epidermal type.

Histological analysis: Four weeks of RHQ therapy resulted a 28% decrease in epidermal pigmentation; dermal pigment decreased by 4% (baseline 0.45/after 4 weeks 0.43). Detailed measurements are shown in Table 2. RHQ effects also included the compaction of stratum corneum (578%), thick-

Table 3. Effect of tretinoin, hydroquinone, and/or steroids on melasma

Tretinoin	HQ	Steroid	Subjects	Results	Application methods
1975, Kligman & Willis[9]					
0.1%	5%	0.1% dexa	White; n=16	improved (87.5%) in 5–7 weeks	twice daily
1979, Gano & Garcia[6]					
0.05%	2%	0.1% beta	Mexican-American, Caucasian, n=20	improved (65~95%) in 10 weeks	daily sequential triple therapy
1986, Pathak et al.[5]					
0.1%	5%	—	Hispanics, n=20	improved (66%) in 3 months	twice daily
1993, Tadaki et al.[7]					
0.1%	—	0.1% HC	Japanese, n=8	no effect in 6 months	every night
1993, Griffiths et al.[22]					
0.1%	—	—	Caucasian, n=19	improved (68%) in 40 weeks	every night
1994, Kimbrough-Green et al.[8]					
0.1%	—	—	Black, n=15	improved (73%)	every night
1998, Kang & Chun (present study)					
0.1%	5%	1% HC	Korean, n=25	improved (40%) in 4 months	twice a week

HQ: hydroquinone, dexa: dexamethasone, beta: betamethasone valerate, HC: hydrocortisone

ening of granular layers (109%), and increase in epidermal thickness by 13%. The most prominent histological change after RHQ therapy was the formation of young collagen subepidermally. The Masson-Trichrome staining showed a 620% increase in the amount of collagen (before/4 weeks treatment=0.5/3.6) (Table 2, Fig. 4).

Adverse reactions: Cutaneous reactions were the only side effects noted throughout the study and consisted of erythema, peeling and burning. This was experienced in 18 of 25 patients receiving RHQ. The side effects were ameliorated by cold compression with 0.3% alum solution. Two patients dropped out of the study at 4 weeks as a result of these side effects. No side effects such as ochronosis were observed.

Discussion

RHQ effect compared with other reports: In the present study, RHQ cream induced good results in clearing melasma. Compared to Kligman's formula (0.1% tretinoin, 5% hydroquinone, and 0.1% dexamethasone) (9), the RHQ used in this study differed only in its steroid component; we used 1% hydrocortisone instead of 0.1% dexamethasone. Varying results have been reported with retinoic acid (tretinoin), hydroquinone or steroids in combination or alone for melasma treatment in the last three decades (10). Our results are largely consistent with the non-oriental reports listed in Table 3.

Our cure rate (40%) after 4 months seemed to be a little bit lower than the improvement rate ranging from 65% to 88% in other repors. However, we were able to notice a remarkable improvement as early as 4 weeks after beginning the treatment (20% reduction of mMASI score, p=0.002); the response time of improvement in other studies was longer (10 weeks to 10 months).

Table 4. Histological effects of tretinoin, hydroquinone and/or steroids on melasma

Tretinoin	HQ	Steroid	Subjects	Results	Application
1975, Kligman & Willis[9]				after 2–3 months	
0.1%	5%	0.1% dexa	White; n=6 depigmented skin	slight acanthosis increased granular layer increased basophilia hypertrophy of basal layer perivascular infiltration after 3 weeks acanthosis, parakeratosis hypertrophy of epi. cells perivascular infiltration	twice daily
1993, Griffiths et al.[22]				40 weeks	
0.1%	—	—	Caucasian, n=19 Melasma	epidermal pig. (–8%) dermal pig. (–18%) st. corneum compaction (+415%) epidermal thickness (+41%)	every night
1994, Kimbrough-Green et al.[8]				40 weeks	
0.1%	—	—	Black, n=15 Melasma	epidermal pig. (–36%) dermal pig. (+6%) st. corneum compaction (+230%) st. granulosum thickness (+348%) epidermal thickness (+30%) melanocyte number (+5%)	every night
1998, Kang & Chun (present study)				4 weeks	
0.1%	5%	1% HC	Korean, n=24 Melasma	epidermal pig. (–28%) basal layer pig. (–66%) dermal pig. (–4%) st. corneum compaction (+578%) st. granulosum thickness (+109%) epidermal thickness (+13%) melanocyte number (+5%) subepidermal collagen (+620%)	twice a week

HQ: hydroquinone, dexa: dexamethasone, beta: betamethasone valerate, HC: hydrocortisone

One difference was that the frequency of application in our study was twice a week, whereas others applied twice a day or once a night. In a Japanese study that also included Oriental females a mixture containing 0.1% tretinoin and 0.1% hydrocortisone lactate was not effective for melasma but rather enhaced the tone of the pigmentation (7). The reason for the contrasting result could be the lack of hydroquinone, which is essential in decreasing pigmentation of melasma. Another explanation could be the non-usage of sun-screens and frequent application once every night. Retinoid dermatitis is an unavoidable side effect during tretinoin therapy. We believed that daily application of topical depigmenting agents on the already irritated site could aggravate the side effects. Therefore, by using an application frequency of twice weekly we were able to minimize the irritation dermatitis, which could be a cause of repigmentation in the future. Cutaneous retinoid reactions of a mild degree occurred in 72% of our pa-

tients compared to 88% in whites (22) and 67% in blacks (8), but they subsided with cold compression except in 2 patients. Ochronosis, another side effect of HQ, could also be prevented by reducing application frequency.

Lastly, there are still many arguments about the application of topical steroids for the treatment of melasma. Kligman & Willis (9) failed to find any beneficial effects resulting from topical corticosteroids alone. Hydrocortisone 0.1% (7), betamethasone 2% (11), dexamethasone 0.1% (9) and clobetasol propionate 0.05% (12) are topical steroids effectively used for depigmentation. Generally, fluorinated steroids are more potent than nonfluorinated steroids, but the risk of local adverse effects such as atrophy, itching, acne, and telangiectasias increases with the use of potent steroids. In cases where steroids are used in addition to peeling or depigmenting agents, less potent steroids such as hydrocortisone should be used to minimize the side effects. Our patients did not show any steroid-induced complications during the therapy.

RHQ effect, histological: Histological features after 4 weeks of treatment with RHQ correlated well with clinical improvement and are listed in Table 4. First, typical retinoid effects such as epidermal hyperplasia with a prominent granular layer and depigmentation were observed as early as 4 weeks after treatment. In other reports, these epidermal changes were most pronounced at 4–6 months and regressed by 12 months (13, 14). These studies used 0.05% tretinoin on photodamaged skin, and the skin biopsy was done 4–6 months after beginning the therapy. Second, appreciable dermal changes, such as thickening of the papillary dermis, were prominent with an increase of 620%; no dermal changes were observed by light microscopy at 6 months in other reports (13, 15). Electronmicroscopic or biochemical study revealed that the thickened subepidermal dermis was a consequence of new collagen formation (15). The role of tretinoin in the stimulation of collagen synthesis *in vivo* has been repeatedly demonstrated. This increase occurs *via* at least two mechanisms: (A) an increase in steady-state levels of mRNA for types I and III procollagen (16); (B) inhibition of collagenase by tretinoin-enhanced fibroblast secretion of tissue inhibitor of metalloproteinases (17). A recent study has clarified that the effects of tretinoin on skin are retinoic-specific, not merely irritant (18). Our histological findings showed no evidence of irritation.

Evaluation methods for melasma treatments: Evaluation as well as treatment of melasma is difficult. Currently, photography is the most commonly used method because it is simple and easy, requiring minimal facilities. However, there are many pitfalls, including problems with reproducing color tones. In this study, we tried to avoid known evaluation problems. Our study design during the pretest was to apply RHQ to the right face and vehicle to the left in each subject. Therefore, the left face (vehicle) served as a perfect negative control for RHQ; the possibilities of individual differences and photographic error could be excluded in assessing the therapeutic effects of RHQ. We tried to quantify RHQ effects to be more objective. Modified MASI scores were calculated independently by two dermatologists; this confined the evaluated area on the right side of the face (Fig. 2). MASI, which was based on a scoring system similar to that devised for psoriasis (19), has been used for the evaluation of melasma (8, 20). MASI includes relevant clinical components in assessing disease severity, such as darkness, homogenicity, and area. It is a reliable score for representing the degree of melasma, and our modification, mMASI, adds simplicity and ease of usage. In this study, we found that mMASI scores correlated well with clinical response.

In conclusion, as shown in both clinical and histological examinations, the therapeutic effect of RHQ treatment was observed much earlier in our study than in other studies previously reported. This was

specifically due to the agent and absolutely not from irritation. Since the agent was applied twice a week, the erythema or irritation due to TR could be reduced. Cold compression was also used, and it contributed to lessening erythema in a short time.

Finally, it has been reported that recurrence after peeling is characteristic of melasma. Therefore, if the RHQ agent is used repeatedly for a duration of 1 month every 6 months, melasma can be treated easily, and the side effects of long-term treatment of TR or/and HQ would be prevented.

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