Assessment of three potential retinol-induced skin irritation mitigants through occlusive human patch test using investigator assessments and instrumental measurements in the Chinese population

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Introduction:

Topical retinol is well-known for its activity in improving the appearance of skin photodamage signs, such as fine lines, wrinkles, and pigmentation [1]. Nevertheless, it also causes severe local irritation manifested as mild erythema and stratum corneum peeling of the skin [2]. The erythematous reaction is clinically similar to mild irritant dermatitis, commonly known as 'retinoid dermatitis' [3-5]. Therefore, the erythema index plays a significant role in indicating the intensity of retinol-induced inflammation. Even though many people could benefit from retinol treatment, many could not continue this treatment due to the discomfort, especially for Asian people [1, 6]; thus, trying to mitigate the retinol-induced irritation is necessary. In recent decades, some ingredients are proposed to be capable of attenuating skin irritations and inflammations, such as phytosterol [7, 8], ceramide [9], niacinamide [10, 11], and so forth. Accordingly, the present study was designed to determine whether these three ingredients, phytosterol, ceramide, and niacinamide, have the potential for mitigating retinol-induced irritation. A 5-day occlusive human patch test was developed for assessing retinol-induced inflammation through erythematous reaction, which was proceeded as a short-term screening protocol for the optimized formula. The erythema index was chosen as the retinol-induced irritation indicator since it plays a crucial role in indicating the intensity of retinol-induced inflammation. Therefore, the investigator assessments and instrumental measurements, colorimetric measurements (Colorimeter CL400 a* scale), Mexameter erythema scale (Mexameter MX18 EI), and image analysis (Visia-CR a*), were measured before and after the patch test. Furthermore, the correlations between clinical scores and instrument measurements were studied.

Materials & Methods:

Materials

0.1% retinol skincare cream was employed as the positive control. Three other creams used the same formula compared to the positive control, containing 3% niacinamide, 5% physiologic lipid mixture, and 2% phytosteryl/octyldodecyl lauroyl glutamate (POLG), respectively. Physiologic lipid mixture was mixed with 67% glycerin, 12% octyldodecanol, 10% water, 6% ceramide Ⅲ, 3% hydrogenated lecithin and 2% cholesterol.

Subjects

Eighteen healthy Chinese volunteers, four men and fourteen women, aged 23-40 years (mean±SD, 30.0±4.4).

- free of skin or systemic diseases
- not apply any topical preparations on the test areas within 30 days before the test started
- no moles, scars, and some other blemishes on the test areas
- female subjects not pregnant or breasting feeding
- written informed consent was obtained from all subjects
- approved by the local ethical committee

Occlusive Human Patch Test Protocol

First patch lasted for 48h

- visual gradings after the patch removal for 0.5h
- apply the second test patch (same as the first one) at the identical position

Second patch lasted for 72h

- both visual investigator assessments and instrumental measurements were undergone at all these four time points

Baseline

- collect all the biophysical parameters
- apply the test patch on the volar forearm including one positive control,three test treatments and one blank

0.5h after patch removed | 24h after patch removed | 48h after patch removed | 96h after patch removed

- All the visual gradings were scored under the guidance of the terminology established by the International Contact Dermatitis Research Group (ICDRG) by qualified research experts.

Instrucmental Measurement

- Visia-CR (Canfield, USA)

- Mexameter MX18 MDD (Courage+Khazaka electronic GmbH, Germany),
- Colorimeter CL 400 (Courage+Khazaka electronic GmbH, Germany)

Consumer 4-week In-use Test

Two groups, aged 18-35 years Chinese women, were randomized to use a blindly labeled skincare preparation (either 0.1% retinol+ 2% POLG or 0.1% retinol in identical cream base) for 4 weeks. First two weeks, consumers used the products twice a week in the evening only, in the following two weeks, consumers used the products every night.

Statistics

Each subject with the equation: CII = sum of irritation scores/number of readings Irritation scores (visual grading score) for each treatment combination were graded, ranging from 0 to 4. Individual CIIs were averaged across subjects to obtain an MCII for each treatment. All the comparing statistical analyses, including visual grading scores and Bioengineering parameters, were performed using paired Student's t-test between the data of 0.1% retinol and that of the other four treatments at each time point. P<0.05 was considered significantly different. Correlation between irritation scores and the data of bioengineering parameters was analyzed by Spearman's correlation coefficient (r) at 0.05 significant level.

Results & Discussion:

Visual Grading and Biophysical Parameters

- Expert visual grading scores and biophysical parameters indicated that both PLOG and physiologic lipid mixture cream attenuated the retinol-induced cutaneous erythematous reactions and inflammation effectively
- PLOG provided a more significant benefit than physiologic lipid mixture cream
- Niacinamide did not show an influential positive role in mitigating the retinol-induced irritation

A: 0.1% retinol cream; B: 0.1% retinol + 3% niacinamide cream; C: 0.1% retinol + 5% physiologic lipid mixture cream; D: 0.1% retinol + 2% phytosteryl/octyldodecyl lauroyl glutamate cream; E: blank

Table 1. MCII for each test articles
*** p<0.05 vs 0.1% retinol cream; ** p<0.01 vs 0.1% retinol cream, n=18**

	MCII
A	0.60±0.36
B	0.57±0.41
C	0.41±0.36*
D	0.36±0.35**
E	0.02±0.09**

Table 2. Mean values and standard deviations for MX18 EI values of five different test treatments at different measuring time points
*** p<0.05 vs 0.1% retinol cream; ** p<0.01 vs 0.1% retinol cream, n=18**

	A	B	C	D	E
Baseline	158.80±45.60	162.52±52.23	155.98±44.78	157.85±53.21	155.15±44.97
0.5h	207.43±67.35	206.39±62.89	197.85±53.03	188.20±56.98*	182.33±52.45**
24h	213.04±62.26	226.56±57.93*	200.87±58.26	197.17±50.39*	180.48±54.71**
48h	200.89±58.95	219.89±69.11*	187.24±52.19*	181.50±49.44*	159.19±51.50**
96h	191.19±62.87	199.72±62.06	173.96±51.00	171.44±44.93*	153.28±47.06**

Table 3. Mean values and standard deviations for CL400 a* values of five different test treatments at different measuring time points
*** p<0.05 vs 0.1% retinol cream; ** p<0.01 vs 0.1% retinol cream, n=18**

	A	B	C	D	E
Baseline	5.79±1.07	5.99±0.99	5.78±0.92	6.06±1.17	6.03±1.03
0.5h	7.74±1.88	7.55±1.88	7.27±1.51	7.38±1.54	6.93±1.55**
24h	7.61±1.68	7.85±1.80	7.19±1.54	6.99±1.44**	6.29±1.23**
48h	7.14±1.54	7.60±1.99	6.75±1.45	6.69±1.26*	6.00±1.15**
96h	6.81±2.06	6.87±1.94	6.08±1.34	6.17±1.14	5.71±1.11**

Table 4. Mean values and standard deviations for Visia-CR a* values of five different test treatments at different measuring time points
*** p<0.05 vs 0.1% retinol cream; ** p<0.01 vs 0.1% retinol cream, n=18**

	A	B	C	D	E
Baseline	5.07±1.35	4.97±1.42	4.94±1.33	4.77±1.64	5.07±1.44
0.5h	7.68±2.79	7.35±2.64	6.92±2.02*	6.28±2.44**	6.37±2.28**
24h	7.51±2.55	7.65±2.89	6.76±2.45*	6.19±2.29**	5.60±2.05**
48h	7.03±2.52	7.60±3.42	6.18±2.29*	5.82±2.20**	4.97±1.94**
96h	5.94±2.62	6.91±3.95	5.35±2.12	5.32±2.17	4.61±1.94**

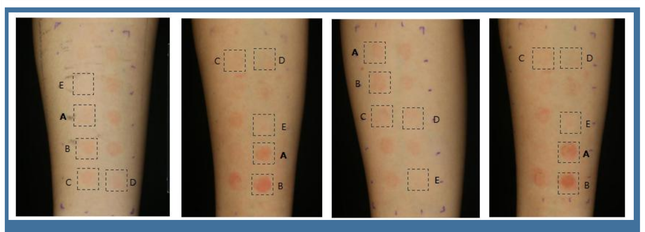

Figure 1. the images of four subjects taken by Visia-CR: the erythematous reaction of five different treatments on retinol induced irritaion

Consumer 4-week In-use Test

- The percentage of the adverse reactions of the 0.1% retinol + 2% PLOG cream was much lower than that of 0.1% retinol cream in all discomfort parameters, especially the pimples/acne parameter.
- 63% (45 out of 72) of consumers who were in the 0.1% retinol + 2% PLOG treatment group persisted in using during the whole test, whereas only 52% (32 out of 62) of consumers in 0.1% retinol cream treatment group persisted.

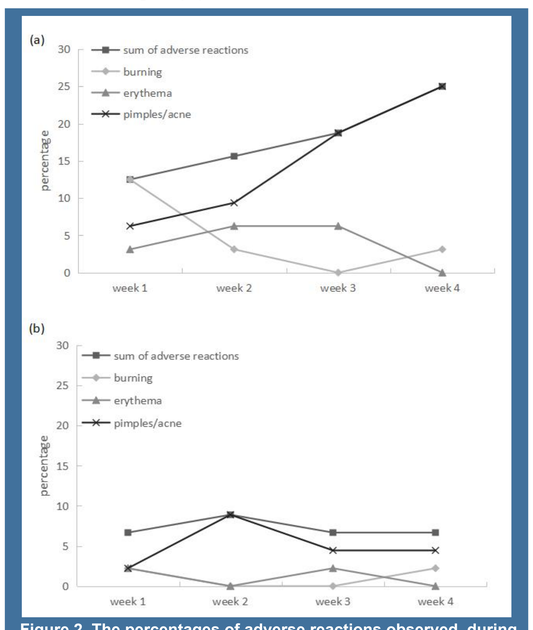

Figure 2. The percentages of adverse reactions observed during 4 weeks
(a) 0.1% retinol cream, n=32; (b) 0.1% retinol + 2% PLOG cream, n=45

Correlation between Visual Gradings and Biophysical Parameters

- Positive correlations between visual grading scales and bioengineering parameters, CL400 a*, Visia-CR a* and MX18 EI, were observed (p<0.01). These correlations indicate that the results of the patch test by visual grading and instrumental measurements are consistent.
- The correlation coefficient of clinical scores and a* values obtained by Visia-CR image analysis method is the highest compared to other instrumental parameters.

Table 5. the values of Correlation coefficient and p-values between visual grading and bioengineering parameters, ** p<0.01

		Visual grading	CL400 a*	MX18 EI	Visia-CR a*	
Correlation Coefficient	Visual grading		0.002	<0.001	<0.001	P-value
	CL400 a*	0.145**		<0.001	<0.001	
	MX18 EI	0.186**	0.800**		<0.001	
	Visia-CR a*	0.477**	0.175**	0.165**		

Conclusions:

In this study, we proceed with occlusive patch tests in assessing the potentials of three treatments in mitigating the retinol-induced irritations. Phytosteryl/octyldodecyl lauroyl glutamate was found to be the most promising mitigant among these three test articles. Meanwhile, the consumer 4-week in-use test also supported that phytosteryl/octyldodecyl lauroyl glutamate treatment was more tolerable than positive control. Retinol and phytosteryl/octyldodecyl lauroyl glutamate used in combination can increase the overall skin benefits, and represent a new advancement in balancing the efficacy and irritation of retinol.

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