

Evaluation of the clinical efficacy and safety of Under Eye Cream in the treatment of Under Eye Dark Circles and Pigmentation

Dhanalaxmi, U. R.¹, Pralhad S. Patki²

Abstract

Aim : This study was planned to evaluate the clinical efficacy and safety (short- and long-term) of Under Eye Cream (Batch No. FD/UE/63) in the management of under eye dark circles, pigmentation, wrinkles, and under eye puffiness.

Material and Methods : It was a prospective, open, non-comparative, phase III clinical trial. A total of 50 patients, who were diagnosed as suffering from moderate to severe form of under eye dark circles and pigmentation, were included in the study. A baseline history was obtained in order to determine the patient's eligibility for enrolment in the trial. All the patients were advised to apply and massage the Under Eye Cream into the skin around the eyes twice daily for a period of 6 weeks. All the patients were followed-up for a period of 6 weeks. Clinical assessment of under eye dark circles and pigmentation lesions was done objectively (by doctor) and also subjectively (by patient). The severity of symptoms was evaluated using 0-3 grading scale (0=Nil, 1=Mild, 2=Moderate, 3=Severe). All 50 patients (42 female, 8 male) completed the study. Statistical analysis of all the data obtained at the end of the study was done by using repeated measures of ANOVA by Friedman test followed by Dunnett's Multiple Comparison Posthoc test to find out the level of significance.

Results : There was highly significant reduction in the mean score of under eye dark circles in all patients at the end of the study. Also there was

significant reduction in the mean scores of erythema, scaling, pruritus, puffiness, wrinkles, laxity of skin, and pigmentation. This study observed significant symptomatic and clinical improvement in under eye dark circles and pigmentation in 6 weeks.

Conclusion : The excellent action of Under Eye Cream might have been due to synergistic actions of its ingredients *Bergenia ligulata*, *Cipadessa baccifera*, and oil of *Triticum sativum*. None of the patients exhibited any adverse reactions. Thus, it may be concluded that Under Eye Cream is effective and safe in the management of under eye dark circles and pigmentation.

KEYWORDS : *under eye circles, pigmentation, erythema, wrinkles, under eye puffiness.*

Introduction

Youthful appearance is characterized by non-wrinkled skin, which is hydrated and silky, firm and toned, radiant, smooth, and without any pigmentation. Wrinkles are the main problems leading to under eye puffiness and disfigurement. Facial wrinkling is one of the most striking signs of skin ageing.¹

There are many etiologies to cause this symptom, such as lack of sleep, heredity, and bruising.² The skin around the eyelids (periorbital skin) is the thinnest skin in the body (around 0.5 mm thick compared with 2 mm in other areas). Lack of nutrients in the diet or lack of a balanced diet can

1. M.D., D.D., D.I.P.N.B., Senior Assistant Surgeon, Department of Dermatology, Kilpauk Medical College Hospital, Chennai, India. Bharathi Rajaa Hospital and Research Centre Pvt. Ltd., Department of Dermatology, Madley Road, T. Nagar, Chennai, Tamil Nadu, India.
 2. M.D., Head - Medical Services & Clinical Trials, R&D Center, The Himalaya Drug Company, Bangalore-562 123 (India).
- Corresponding author :** Dr. Pralhad S. Patki, M.D., Head - Medical Services & Clinical Trials, R&D Center, The Himalaya Drug Company, Bangalore-562 123 (India), Ph.: 91 080 2371 4444, Fax: 91 080 2371 4471, E-mail: dr.patki@himalayahealthcare.com

contribute to the discoloration of the area under the eyes. Lack of sleep or excessive tiredness can cause paleness of the skin, which again allows the blood underneath the skin to become more visible and appear more blue or darker.

Dark circles are likely to become more noticeable and permanent with age. This is because as people get older, skin loses collagen and it gets thinner and more translucent. In addition to these, overexposure to sun, changes in fat content and skin collagen, and dehydration may contribute to the process of wrinkling. As the skin ages, water retaining properties are compromised. Dry skin is actually a hallmark of excessive water loss.

Once the skin ages, production of ground substances called glycosaminoglycans (GAGs) also declines. These GAGs are essential because it surrounds collagen, elastin, and cells of the skin. These substances bind water molecules and assist in hydrating skin proteins. GAGs are also known to relax the muscles, which are associated with wrinkling. The puffiness of skin under eye is usually the result of fat accumulating on the lower lids leading to tired and aged appearance. These adipose tissues get hypertrophied due to a severe load of triglycerides in connecting tissues. Free radicals, glycosylation, and inflammatory pigmentation lead to darkening of the eye lids and initiation of dark cells. A number of agents such as isopropyl palmitate, glycerin, pycnogenol, glycosaminoglycans, genistein, silymarin, algisium C, etc. have been used to correct under eye problems.

In the recent past, there has been a tremendous increase in the use of plant-based health products in developing as well as developed countries resulting in an exponential growth of herbal products globally. Herbal medicines have a strong traditional or conceptual base and the potential to be useful as drugs in terms of safety and effectiveness without causing any adverse events. India, with its megabiodiversity and knowledge-rich ancient traditional systems of medicine, viz. Ayurveda, Siddha, Unani, and local health traditions, provides a strong base for the utilization of a large number of plants in general healthcare and alleviation of common ailments.

Ayurveda cited several plants, which are useful in protecting and replenishing skin without any side effects. Himalaya's Under Eye Cream, is a light nourishing cream that protects the delicate skin around the eyes, while reducing puffiness, dark circles and fine lines around the eyes. It contains the extracts of *Bergenia ligulata*, *Cipadessa baccifera* and oil of *Triticum sativum*, which are useful in protecting and replenishing skin without any side effects.

Aim of the Study

This study was planned to evaluate the clinical efficacy and safety (short- and long-term) of "Under Eye Cream" (Batch No. FD/UE/63) in the management of under eye dark circles, pigmentation, wrinkles, and puffiness.

Material and Methods

Study design :

This study was a prospective, open, non-comparative, phase III clinical trial conducted in the Department of Dermatology, Bharathi Rajaa Hospital and Research Centre Pvt. Ltd., Madley Road, T. Nagar, Chennai, Tamil Nadu, India from August 2006 to January 2007. The study protocol, case record forms, regulatory clearance documents, product related information, and informed consent forms were submitted to the "The Institutional Ethics Committee" and were approved by the same.

Inclusion criteria :

A total of 50 patients, who were diagnosed as suffering from moderate to severe form of under eye dark circles and pigmentation, were included in the study.

Exclusion criteria :

Patients with concomitant severe skin infection, history of hypersensitivity to cosmetics, children below 18 years of age, patients with preexisting severe systemic disease necessitating long-term

medication, patients with genetic and endocrinal disorders, and those patients who refused to give informed written consent were excluded from the study. Pregnant and lactating women were also excluded from the study.

Study procedure :

A baseline history was obtained in order to determine the patient's eligibility for enrolment in the trial. The baseline assessment included personal data, a description of symptoms and details of past medical history (family history, history of possible exacerbating factors, etc.). All the patients were advised to apply and massage the "Under Eye Cream" into the skin around the eyes twice daily for a period of 6 weeks. All the patients were asked to adhere to "Under Eye Cream" only as the treatment for under eye dark circles and pigmentation, and no other medicated topical application was allowed.

Follow-up and monitoring :

All the patients were followed-up for a period of 6 weeks and at each weekly follow-up visit, they were asked about the frequency of the application. Clinical assessment of under eye dark circles and pigmentation lesions was done objectively (by doctor) and also subjectively (by patient). The severity of symptoms-eye dark circles, erythema, scaling, pruritus, puffiness, wrinkles, laxity of skin and pigmentation was evaluated using 0-3 grading scale (0=Nil, 1=Mild, 2=Moderate, 3=Severe).

Patients, with the help of linear analogue scale, did the subjective assessment and the extremes of linear analogue scale were predefined as "no improvement" and "total cure".

Participants were photographed at the beginning and at the end of the study. Photographic evaluation was done with the same equipment, lighting and location. At the end of 6th week, the overall performance of the "Under Eye Cream" was evaluated.

Data collected was evaluated statistically by using GraphPad Prism Software, Version 4.01. Adverse effects reported by the subjects were recorded in a data sheet.

Primary and secondary endpoints :

The predefined primary efficacy endpoints were reduction in skin wrinkles. The predefined secondary safety endpoint measures were incidence of adverse events and overall patient compliance to the treatment.

Adverse events :

All the adverse events, either reported by the patients or observed by investigators, were recorded in case record forms with information about severity, date of onset, duration, and action taken regarding the study drug. The relation of adverse events to the study product was predefined as "Unrelated", "Probable" and "Possible".

Patients were allowed to voluntarily withdraw from the study if they experienced serious discomfort during the study or sustained clinical events requiring specific treatment.

Statistical analysis :

Statistical analysis was carried out using repeated measures of ANOVA by Friedman test followed by Dunnett's Multiple Comparison Posthoc test to find out the level of significance. The severity score was expressed as mean \pm SD, and signs and symptoms were evaluated using 0-3 grading scale. The minimum level of significance was fixed at $p < 0.05$. Statistical analysis was carried out using GraphPad Prism software Version 4.01.

Results

None of the patients exhibited any adverse reaction like erythema, edema, pruritus, and urticaria. The Under Eye Cream did not produce any adverse effect on lid margins, eyelashes, sclerae, conjunctivae, pupils and lenses. It did not produce any rise in intraocular pressure. These results indicate safety and significant beneficial effects of Under Eye Cream in subjects with dark circles and wrinkles under the eyes. Overall compliance to the treatment was excellent.

Effect of Under Eye Cream on clinical parameters in the management of dark circles and wrinkles indicate that Under Eye Cream has statistically

significant efficacy in producing anti-wrinkling and soothing effect, and in eradicating dark circles. It also produced antilaxity effect and skin tightening effect. The results and statistical significance for various parameters are shown below (Table 1).

All 50 patients (42 female, 8 male) completed the study. The mean age of patients was 38 years. The history of under eye dark circles and wrinkles ranged from 6 months to 5 years. There was highly significant reduction in the mean score of under eye dark circles in all patients at the end of the study. Also there was significant reduction in the mean scores of erythema, scaling, pruritus, puffiness, wrinkles, laxity of skin, and pigmentation (Table 2).

Photographic evaluation also revealed significant reduction in under eye dark circles, erythema, scaling, puffiness, and wrinkles.

Out of 50 patients with under eye dark circles, 42 (84%) got excellent improvement, 2 (4%) got good improvement, while 3 (6%) got moderate improvement after treatment. Out of 44 patients with erythema, 28

(63.63%) got excellent improvement, 12 (27.27%) got good improvement, while 4 (9.09%) got moderate improvement after treatment. Out of 48 patients with scaling, 13 (27.08%) got excellent improvement, 20(41.66%) got good improvement, while 11 (22.91%) got moderate improvement after treatment. Out of 32 patients with pruritus, 20 (62.5%) got excellent improvement, 6(18.75%) got good improvement, while 5 (15.62%) got moderate improvement after treatment. Out of 30 patients with puffiness, 20 (66.66%) got excellent improvement, and 10(33.33%) got good improvement. Out of 50 patients with wrinkles, 30 (66%) got excellent improvement, 14(28%) got good improvement, while 2 (4%) got moderate improvement after treatment. Out of 46 patients with laxity of skin, 24 (52.17%) got excellent improvement, 13(28.26%) got good improvement, while 4 (8.69%) got moderate improvement after treatment. Out of 50 patients with pigmentation, 41 (82%) got excellent improvement, 3(6%) got good improvement, while 2 (4%) got moderate improvement after treatment (Table 3).

Table 1 : Effect of Under Eye Cream on signs and symptoms

Parameters	Treatment Duration		
	Initial	Day 14	Day 42
Dark circles under the eye	2.14 ± 0.65	1.95 ± 0.80	1.48 ± 0.75 ^a p<0.01
Erythema	0.14 ± 0.30	0.10 ± 0.30	0.00 ± 0.00
Scaling	0.19 ± 0.40	0.14 ± 0.36	0.00 ± 0.00
Pruritus	0.33 ± 0.48	0.29 ± 0.46	0.14 ± 0.36
Puffiness	0.33 ± 0.57	0.29 ± 0.46	0.24 ± 0.44
Wrinkles	1.52 ± 0.75	1.52 ± 0.75	1.43 ± 0.68
Laxity of skin	1.33 ± 0.97	1.33 ± 0.97	1.24 ± 0.77
Pigmentation	2.38 ± 0.50	2.00 ± 0.45	1.38 ± 0.50 ^a p<0.001, ^b p<0.01

Note : Values are mean ± SD.

^a: as compared to initial values;

^b: as compared to day 14 values.

Table 2 : Response to Under Eye Cream

Parameters	No. of patients before treatment	No. of patients improved after treatment			
		Excellent	Good	Moderate	No response
Dark circles under the eye	50	42	2*	3*	3
Erythema	44	28	12*	4	0
Scaling	48	13	20*	11	4
Pruritus	32	20	6*	5	1
Puffiness	30	20	10	0	0
Wrinkles	50	30	14	2	4
Laxity of skin	46	24	13	4	5
Pigmentation	50	41	3*	2	4

* $p < 0.05$ as compared to baseline levels

Table 3 : Improvement in patients after treatment

Parameters	Results in %		
	Excellent	Good	Moderate
Dark circles under the eye	84	4	6
Erythema	63.63	27.27	9.09
Scaling	27.08	41.66	22.91
Pruritus	62.5	18.75	15.62
Puffiness	66.66	33.33	-
Wrinkles	66	28	4
Laxity of skin	52.17	28.26	8.69
Pigmentation	82	6	4

Discussion

Wrinkles are the main problems leading to under eye puffiness and disfigurement. Puffiness under the eyes is usually the result of fat accumulating on the lower lids causing patients to have a tired and aged appearance. Hypertrophy of the adipose tissue is due to an overdose of triglycerides in the adipocytes and an alteration in the connective tissue due to proteolytic enzymes that enable lipid hypertrophy

within the tissues. The increase in the collagenase activity, a major proteolytic enzyme, occurs from normal aging phenomena and UV stimulation resulting in (a) the epidermis becoming thinner from reduced cell proliferation, (b) the alteration of dermis-epidermis junction with disappearance of microvilli resulting in a defective adhesion of the epidermis to the dermis, and (c) degeneration of collagen and elastin is found in the dermis.

The outward manifestations of tissue ageing

primarily involve the two major structural proteins of the body, collagen and elastin. Also inflammatory process creates many of the conditions that contribute to the development of dark circles and puffy eyes such as increased melanin deposition and increased collagenase activity, respectively.

Photoageing by UV involves competing reactions, chain cleavage and crosslinking, the former predominating on long-term exposure. Many molecules forming the extracellular matrix are produced by the keratinocytes of the epidermis and the fibroblasts of the dermis. Deterioration of this matrix plays an important role in the aging phenomenon and implies a progressive diminution in dermal thickness, collagen content, and protein organization. UV exposure stimulates the activity of collagenase as well as free radical formation. Free radicals adversely affect skin lipids, proteins, and DNA that are critical for normal skin function.

This study observed a significant reduction in mean scores of erythema, scaling, pruritus, puffiness, wrinkles, laxity of skin, and pigmentation. Subjective evaluation revealed remarkable improvement.

The excellent action of Under Eye Cream might have been due to synergistic actions of its ingredients. The leaf and root of *Bergenia ligulata* has astringent and spasmolytic activities. The same is used in different disorders like dysuria, splenomegaly, pulmonary infections including cough, menorrhagia, and urinary tract infections. Its nutritive effect is useful in diseases like dizziness, headache, and vertigo.³ The essential oil of the plant shows antibacterial⁴ and anti-microbial activity. Some active ingredients also exhibit anti-inflammatory activity.⁵

The rhizome contains bergenin (a C-glycoside), gallic acid, glucose, mucilage, wax and tannins. Presence of flavonoids is also reported.⁶ It also possesses cytoprotective activity.⁷ The roots of *Cipadessa baccifera* are used for killing tapeworms, whereas the hydro-alcohol extract of aerial parts shows spasmolytic activities.⁸ The essential oil of *Triticum sativum* is rich in tocopherol (Vitamin E) content,⁹ total tocopherol is 1897 mcg/g, alpha tocopherol is 67%. The presence of ergosterol (provitamin D) has been reported. It also contains hemoproteins possessing peroxidase activity.¹⁰ It has cooling and tonic activity.¹¹

Conclusion

This study observed significant symptomatic and clinical improvement in under eye dark circles and pigmentation in 6 weeks. The excellent action of Under Eye Cream might have been due to the synergistic actions of its ingredients. It is also well tolerated by the patients. Therefore, it may be concluded that Under Eye Cream is effective and safe in the management of under eye circles and pigmentation.

References

1. Calder AJ, Yang AW. 2005. Understanding the recognition of facial identity and facial expression. *Nat. Rev. Neurosci.* 2005; 6(8): 641-651.
2. Mayo Clinic Women's Healthsource 2003; 7(6): 8. [PMID 12838159].
3. Khare CP. *Indian Medicinal Plants: An illustrated dictionary.* Springer. 2004: p. 90.
4. Mazhar-ul-Islam, Azhar I, Mazhar F, Usmanghani K, Ahmad A, Gill MA and Shahab-ud-Din. Evaluation of antibacterial activity of *Bergenia ciliata*. *Pak. J. Pharm. Sci.* 2002; 15(2): 21-27.
5. Sinha S, Murugesan T, Maiti K, Gayen JR, Pal M and Saha BP. Evaluation of anti-inflammatory potential of *Bergenia ciliata* Sternb. rhizome extract in rats. *J. Pharm. Pharmacol.* 2001; 53(2): 193-196.
6. Kahre CP. *Encyclopedia of Indian Medicinal Plants.* Springer. 2007: pp. 100-101.
7. Kakub G, Gulfranz M. Cytoprotective effects of *Bergenia ciliata* Sternb. *Phytother. Res.* 2007; 21(12): 1217-12120.
8. Asolkar. Second supplement to Glossary of Indian Medicinal Plants with active principles. Part-I(A-K)(1965-1981). Publications & Information Directorate (CSIR), New Delhi. 1992: pp. 204-205.
9. Leenhardt F, Fardet A, Lyan B, Gueux E, Rock E, Mazur A, Chanliaud E, Demigné C, Rémésy C. Wheat germ supplementation of a low vitamin E diet in rats affords effective antioxidant protection in tissues. *J. Am. Coll. Nutr.* 2008; 27(2): 222-228.
10. Khare CP. *Indian Medicinal Plants: An illustrative Dictionary;* Springer. 2007: p. 676.
11. Chopra RN, Nayar SL, Chopra IC. *Glossary of Indian Medicinal Plants.* National Institute of Science Communication, 4th Re-print. 1996: p. 249.