

Single-Center, Double-Blind, Randomized, Placebo-Controlled, Study of the Efficacy and Safety of a Cream Formulation for Improving Facial Wrinkles and Skin Quality

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ABSTRACT

Introduction: Several therapeutic modalities from topicals to chemical peels and energy-based devices are available to improve skin quality and reduce the appearance of wrinkles in the face and neck area.
Objective: The objective of this single-center, double blinded, placebo-controlled study was to evaluate the safety and efficacy of Nimni Cream by Hydropeptide® on skin quality and wrinkles.
Methods: 20 patients were randomized in a 3:1 ratio to use either Nimni Cream by Hydropeptide or placebo starting with twice a week application and increasing to daily for 8 weeks. Patient and investigator assessments were conducted on week 4 and 8.
Results: At week 8, blinded and treating investigator assessments showed a statistically significant improvement in global aesthetic improvement scale assessments in the active group for the face, but not the neck area. There was also a trend towards improvement in Fitzpatrick Wrinkle Scale scores in the active, but not placebo group, at both time-points, for the face and neck, but the results were not statistically significant. The majority of patients were satisfied with the results and no adverse effects were reported.
Conclusion: Nimni Cream by Hydropeptide is safe and effective for improving skin quality in the face and can be considered a satisfactory therapeutic option adjuvant to aesthetic procedures.

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INTRODUCTION

Over time, extrinsic and intrinsic factors indiscriminately contribute to aging of the skin. Excess exposure to UV, lifestyle choices such as smoking and alcohol, genetics, concomitant medical conditions, all together influence and aggravate the rate of degradation of skin quality.[1-3] Age-dependent collagen/elastin break down, loss of hyaluronic acid (HA), epidermal thinning together with a decrease in the amount of water held in the epidermis leads to fine lines, discoloration, dullness, textural changes and wrinkles.[4,5]

Conversely, several therapeutic modalities have been developed over time to prevent and reverse the signs of aging primarily in the facial area, but also in the neck, as it has been recognized as an extension of the facial skin that greatly impacts the overall appearance of an individual. [6]. From sunscreens to sophisticated energy-based devices such as intense-pulsed-light, fractional lasers, new generation peels, there is a plethora of cosmetic solutions for improving skin quality and reducing wrinkles. Admittedly however, the use of a topical that can have these benefits would be preferred and embraced by patients as the cost-effectiveness compared to other modalities, and ease of use would reign [7-9].

Over the past decade, topical anti-aging compounds have increased in number, variety, and efficacy in tackling signs of facial and neck aging. Nimni Cream by Hydropeptide® is a patented formulation created by Dr. Marcel Nimni for topical application designed to enhance collagen and proteoglycan synthesis comprising in the skin. The product ingredients include an antioxidant compound selected from the group consisting of lipoic acid, bioflavonoids, constituents of ginkgo, and isoflavones, soluble in an organic penetrant, and in a quantity sufficient to enhance collagen synthesis in the skin [10,11]. Nimni cream also contains a mixture of essential amino acids comprising: isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, histidine, and arginine in a topical pharmaceutically acceptable carrier. This proprietary combination of ingredients crosses the skin barrier by a patented trans-phase delivery system. In in vitro studies, the product was shown to increase deposition of collagen in the dermis and thicken the epidermal layer of rat skin.[12] Moreover, when tested in human volunteers the product was well tolerated and led to results similar to the in vitro findings.

The objective of this preliminary study was to evaluate the efficacy of Nimni Cream by Hydropeptide on skin quality of healthy

candidates with moderate to severe facial wrinkles and folds. As skin quality is multifactorial assessments included live investigator ratings, patient questionnaires and ratings of standardized photographs by a qualified evaluator not in involved in patient treatment and blinded to photographic time points. The tolerability, and safety of Nimni Cream by Hydropeptide was also evaluated.

METHODS

Patients

20 subjects were enrolled in the study. All subjects provided written informed consent prior to receiving any study-related procedures. Patients were screened according to the inclusion/exclusion criteria of the study and participant eligibility was determined. Eligible subjects were healthy females (30-70 years of age, Fitzpatrick photo skin types I-IV), with moderate to severe fine lines, wrinkles, and overall skin quality as determined by the investigator. Subjects were required to avoid sun-exposure in the treated areas, and not have any procedures affecting facial wrinkles or skin quality (ex. microdermabrasion, peels, acne treatments, filler, botulinum toxin, radiofrequency, laser, IPL, ultrasound, etc) for the duration of the study. Patients that had cosmetic treatments (botulinum toxin, fillers, peels, lasers, dermabrasion) within 3 months of the baseline visit were excluded. Subjects with dermatologic conditions including acne, rosacea, eczema, psoriasis, actinic keratosis, severe sun damage, scars, or a history of keloids were also excluded from the study.

Study Design

This was a single-center, double-blind, randomized, placebo-controlled, study conducted in accordance with the principles of the Declaration of Helsinki, current GCP guidelines, and IRB approval. A total of 20 patients were randomized in a 3:1 ratio to use either Nimni Cream by Hydropeptide or placebo as instructed by protocol. Treatment consisted of topical application to facial and neck skin at increasing frequency beginning with application two times per week before bed and increasing to once daily application by week 8 based on tolerability. All subjects were also provided with an identical regimen of homecare products (Facial Cleanser (am/pm), Sunscreen (am), and Moisturizer (PRN)). Live efficacy assessments were conducted at weeks 4 and 8 by both subject and investigator, with a blinded investigator assessment completed at week 8 using subject photos collected at baseline. Visual assessments of the face were conducted on all subjects grading for fine lines, wrinkles, mottled pigmentation, pore size, clarity/radiance, laxity, and overall global photodamage at each visit by a live qualified investigator. Safety and tolerability assessments included an evaluation of erythema, peeling, dryness, and roughness by both subject and investigator. Subject assessment (patient reported outcomes or PROs) of product attributes and impression of efficacy were also collected at each visit. Standardized photos were taken at in office visits occurring at baseline (D0), week 4, and 8. The primary endpoint was defined as the degree of improvement in skin quality rated by a blinded, trained evaluator using standardized photographs, as well as live evaluations by the treating investigator and the patient reported outcome assessments. Secondary endpoints included the positive investigator and patient satisfaction assessed with quartile scales, the efficacy for the correction of moderate to severe facial wrinkles and folds with Validated Assessment Scales (VAS), the

FIGURE 1. Visual assessment of skin quality and photodamage scale.

Visual Assessment of Skin Quality & Photodamage

Scale	Severity	Fine Lines	Wrinkles	Mottled Pigmentation	Pore Size	Clarity/ Radiance	Laxity	Smoothness	Overall Global Photodamage
0	None	o	o	o	o	o	o	o	o
0.5	Mild	o	o	o	o	o	o	o	o
1		o	o	o	o	o	o	o	o
1.5		o	o	o	o	o	o	o	o
2		o	o	o	o	o	o	o	o
2.5		o	o	o	o	o	o	o	o
3		o	o	o	o	o	o	o	o
3.5	Moderate	o	o	o	o	o	o	o	o
4		o	o	o	o	o	o	o	o
4.5		o	o	o	o	o	o	o	o
5		o	o	o	o	o	o	o	o
5.5		o	o	o	o	o	o	o	o
6		o	o	o	o	o	o	o	o
6.5	Severe	o	o	o	o	o	o	o	o
7		o	o	o	o	o	o	o	o
7.5		o	o	o	o	o	o	o	o
8		o	o	o	o	o	o	o	o
8.5		o	o	o	o	o	o	o	o
9		o	o	o	o	o	o	o	o

local tolerability of application of the study product, and the frequency and duration of adverse events.

Assessments

Investigator Assessments

Throughout the study, efficacy assessments were performed on the treatment areas for each subject by the same Live Treating Investigator at baseline, weeks 4 and 8. The efficacy parameters were Validated Assessment Scales for facial wrinkles (Fitzpatrick Wrinkle Scale), Global Aesthetic Improvement Scale (GAIS) and a customized 10-point scale for the assessment of skin quality, Visual Assessment of Skin (VAS) Quality and Photodamage (Figure 1).

Safety

Local (dermal) tolerability examination (of the face and neck separately) was performed at all study visits and will include assessments of stinging/burning (rated by the patient verbally), dryness, scaling, edema, and erythema (rated by the investigator or appropriately trained designee). Local tolerability on the face and neck was rated as none, mild, moderate, or severe.

Standardized Photography

Standardized photographs were taken at 0°, 45°, and 315° angles using the Visia® CR system (Canfield Imaging Systems, Fairfield). For each angle, a set of four different photographs will be taken including non-polarized, cross-polarized and parallel-polarized white light as well as UV light images.

Statistical Analysis

Ordinal variables were analyzed using Wilcoxon test for paired samples. For ratio scaled variables normal distribution was verified by Kolmogorov-Smirnoff test and then analyzed using Student-T test for paired variables or Wilcoxon test. All statistical tests were two-sided and tested in conjunction with a 0.05 nominal significance level. Analyses were carried out using SAS version 9.4 statistical software (Cary, NC).

RESULTS

Population

20 subjects total (2 male and 18 female) with an average age of 54.9 (±7.5) years were enrolled into this study. Two female subjects (1 active and 1 placebo) were lost to follow- up prior to the completion of the study and were not included in the statistical analysis of the results. All female subjects were peri (1) or postmenopausal (17). All but one subject were non-smokers, and all occasionally use alcohol. Patients had skin type I (n=1), skin type II (n=8), skin type III (n=6), and skin type IV (n=5).

Investigator Assessments

No statistically significant differences were found in baseline ratings of investigator visual assessments of skin quality for the face between active and placebo groups for all assessment parameters (fine lines, mottled pigmentation, pore size, clarity/radiance, laxity, and overall global photodamage). Between baseline and week 8, there was an improvement from mild to moderate in Fitzpatrick Wrinkle Scale scores the active group, for face and neck, but not the placebo group. The results however did not reach statistical significance. Statistically significant improvements were noted in the investigator visual assessments of skin quality for the face in the active group, baseline versus week 8, in fine lines, mottled pigmentation, pore size, clarity/radiance, smoothness, and overall global photodamage (Table 1, Figure 2, 3). In the placebo group a statistically significant improvement was noted in mottled pigmentation for facial skin, baseline vs. week 8 (P=0.04). No other factors displayed significant change. When evaluating the neck, statistically significant improvement was noted in the investigator visual assessments of skin quality in the active group, baseline versus week 8, in smoothness (P=0.03). No other factors displayed significant change, and no statistically significant results were noted in the placebo group for neck skin, baseline vs week 8, for investigator visual assessments. Assessments of the face, but not the neck, by both the treating and blinded investigator, demon-

TABLE 1.

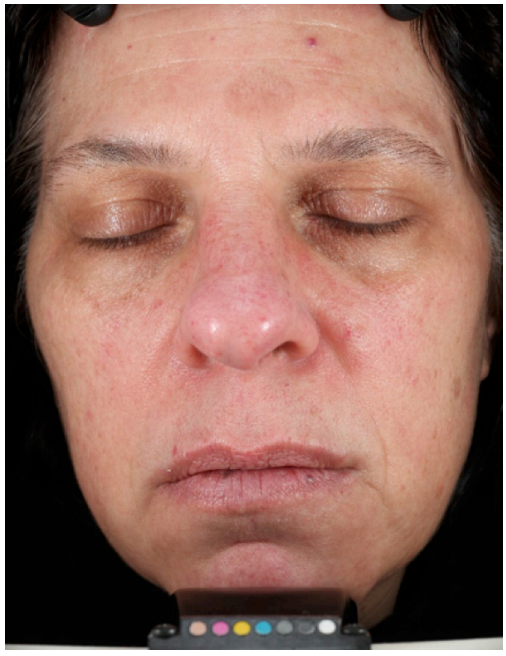
Investigator Visual Assessments of Skin Quality for the Face in the Active Group, Baseline versus Week 8

Visual Assessment	Face		Neck	
	Placebo	Active	Placebo	Active
Fine lines	NS	0.0001	NS	NS
Mottled pigmentation	P=0.04	0.01	NS	NS
Pore size	NS	0.004	NS	NS
Clarity/radiance	NS	0.02	NS	NS
Smoothness	NS	0.006	NS	P=0.03
Overall global photodamage	NS	0.01	NS	NS

NS= non-significant

FIGURE 2. 54-year-old female before (A) and at week 8 (B) of treatment. There is decreased redness, pore size, fine lines, and improved clarity, radiance, pigmentation, and overall photodamage.

(A)



(B)

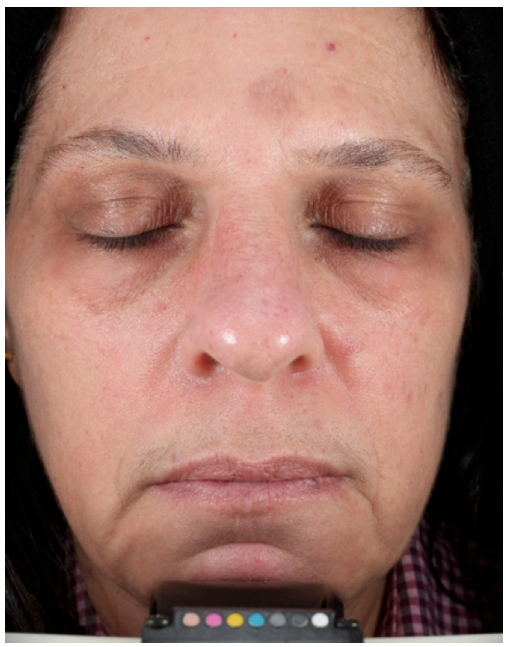
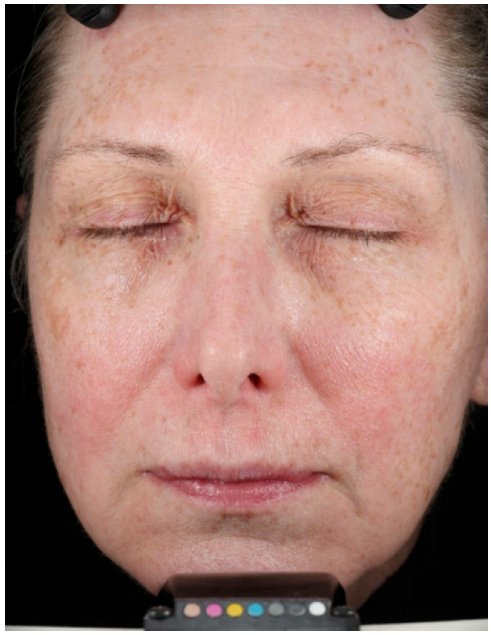
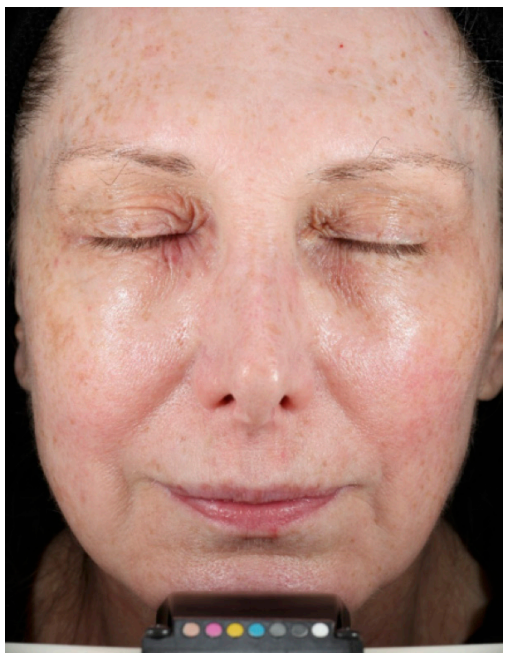


FIGURE 3. 55-year-old female before (A) and at week 8 (B) of treatment. There is decreased redness, pore size, fine lines, and improved clarity, radiance, pigmentation, and overall photodamage.

(A)



(B)



strated statistically significant improvements in GAIS (P=0.03 and P=0.04, respectively; Figure 4, 5). Collectively, investigator assessments for the face showed moderate improvement in 64% of subjects, mild improvement in 27% of subjects and no change in 21% of subjects.

Subject Assessments

All of the subjects included in the study used the tested materials as instructed and reported the product to be easy and convenient to add a daily skincare routine. There was a 1-point increase in subject treatment satisfaction scale rating scores

FIGURE 4. Global aesthetic improvement scale assessment by treating investigator at baseline and 8 week follow up for active and placebo group. Asterisk indicates statistical significance.

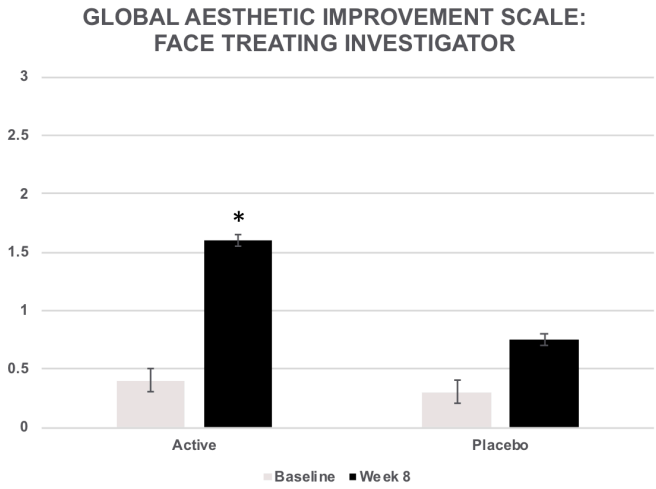
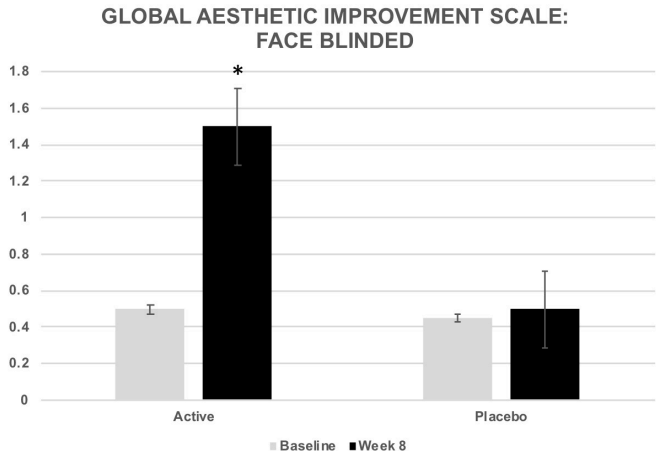


FIGURE 5. Global aesthetic improvement scale assessment by blinded investigator at baseline and 8 week follow up for active and placebo group. Asterisk indicates statistical significance.



between baseline and week 8 in the active group in both face and neck, whereas there was no change in the placebo group. In terms of skin quality, there was statistically significant improvement in subject rated 'Rough Texture' from baseline to week 8 (P=0.01) and 'Dryness' (P=0.02) for the face. No statistically significant changes were found in subject rated skin quality and photodamage assessments of the neck from baseline to week 8. Seventy-one (71%) of subjects were moderately/very satisfied with the product scent, 64% with the product feel, and 71% with the product texture. Over half the subjects (57%) reported that they would consider substituting their current anti-aging skincare with Nimni cream.

Adverse Events and Tolerability

No adverse events or unexpected side effects were observed or reported for any of the subjects. No significant tolerability events were reported by investigator for face or neck (Table 2). Subjects reported minimal tolerability events for face and neck at all time points post baseline (Table 3).

DISCUSSION

New generation topical agents are continuously developed to effectively prevent photoaging, collagen degradation and, stimulate cellular epidermal/dermal remodeling that ultimately improves skin quality. The patented formulation of the study product contains a mixture of peptides, antioxidants designed to stimulate the dermal matrix for collagen and proteoglycan production. In this single-center, double-blind, randomized, placebo-controlled study Hydropeptide Nimni Cream and supporting regimen was shown to be significantly effective in improving signs of aging and skin quality in the face, with no side effects, after two months of treatment. While shown effective in the facial area, there were no significant clinical results observed in the neck area. This can be attributed to several factors; while the neck shares most of the skin physiology wit the face, it has some unique characteristics that can interfere with the efficacy of topical agents. Neck skin is inherently drier, due to the sparse sebaceous gland density, and thinner making it more susceptible to aging.[13] It is possible that a longer duration of application and potentially an increased amount of product would be required in order to observe clinically significant results in this area, compared to the parameters used for the face.

Moreover, Fitzpatrick Wrinkle Scale scores were improved in the active group compared to placebo, in the face and neck, albeit not significantly. While the product can have a clinical effect on skin quality rather rapidly (4-8 weeks of application), the study timeframe was too abbreviated to allow a realistic evaluation of the treatment effect on the appearance of wrinkles. With the exception of dermal fillers that can immediately volumize the face, and have a dramatic effect on wrinkles, most other anti-wrinkle approaches (energy-based devices, chemical peels), can clinically affect the appearance of lines and wrinkles after a minimum of twelve weeks. Subject satisfaction was also high as the product was easy to use with no adverse effects or tolerability issues reported.

TABLE 2.

Investigator Reported Tolerability Events		
	Week 4	Week 8
Face- Dryness	1-mild	1-mild
Face- Erythema	2-mild	1-mild / 1-moderate
Neck- Dryness	1-mild	2-mild
Neck- Erythema	1-mild	1-moderate
Neck- Scaling	1-mild	none

TABLE 3.

Subject Reported Tolerability Events				
	Week 2	Week 4	Week 6	Week 8
Face- Stinging/Burning	1-mild	None	2-mild	1-mild
Neck- Stinging/Burning	2-mild	None	1 – mild / 1-moderate	2-mild

Overall, despite the study limitations that include small number of subjects and short time of follow-up, the product demonstrated a good clinical efficacy and safety profile in improving facial skin quality. To this end, a larger scale study is underway, with more subjects and longer follow-up, to assess more clinical endpoints and evaluate the full effect of the topical on rhytides and fine lines.

Thus, in the context of a general skincare program that includes sunscreen, fillers, neurotoxins, and energy-based devices, Hydropeptide® Nimni Cream can be used daily for preventing, fighting signs of aging and improving skin quality in the face.

DISCLOSURES

Neil Sadick MD, Krista Bohnert BS, and Monica Serra received a research grant by Hydropeptide. Neal Kitchen PhD is Chief Operating Officer at HydroPeptide.

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