doi:10.36849/JDD.8162

Effect of Topical Human Platelet Extract (HPE) for Facial Skin Rejuvenation: A Histological Study of Collagen and Elastin

Saranya P. Wyles MD PhD,[a] Sydney L. Proffer MD MS,[a] Patricia Farris MD,[b] Lindsey Randall BS,[c] Matthew L. Hillestad PhD,[d] Mary P. Lupo MD,[e] Atta Behfar MD PhD[d]

[a]Department of Dermatology, Mayo Clinic, Rochester, MN
[b]P.K. Farris MD, Metairie, LA
[c]Graduate School of Biomedical Sciences, Mayo Clinic, Rochester, MN
[d]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN
[e]Lupo Center for Aesthetic and General Dermatology, New Orleans, LA

ABSTRACT

Background: Regenerative aesthetics has garnered significant attention. In this toolkit, exosomes are small extracellular vesicles derived from various sources such as platelets.

Objective: To characterize the cosmetic effect and tolerability of topical human platelet-derived extract (HPE), Intense Serum (Rion Aesthetics, Inc., Rochester, MN), on facial skin rejuvenation after 12 weeks of twice daily use without any confounding aesthetic procedures.

Materials and Methods: This prospective, single-arm, non-randomized, evaluator-blinded clinical study evaluated subjects at baseline and 12 weeks using participant questionnaires and photo-documentation with Canfield VISIA-CR 3D PRIMOS. The histological evaluation included Masson's Trichrome for collagen and Verhoeff-Van Gieson staining for elastin. Electron microscopy characterized collagen bundle thickness.

Results: Fifty-six participants (mean age: 54 years old) were enrolled. Following topical HPE use, 87.3% of subjects reported improvement in facial skin aging including sustained pigment reduction and improvement in luminosity and color evenness at 12 weeks ($P \leq 0.001$). Histology revealed a significant increase in collagen fibril thickness at 12 weeks ($P \leq 0.0001$). No serious adverse effects.

Conclusion: This study demonstrates improvement in facial skin health after topical HPE use, supported by collagen and elastin formation in the dermis. The product is well-tolerated, and participants were satisfied with the overall cosmetic outcome.

J Drugs Dermatol. 2024;23(9):735-740. doi:10.36849/JDD.8162

INTRODUCTION

Men and women alike suffer from premature skin photoaging due to free radicals[1] and environmental toxicities, such as ultraviolet (UV) radiation to exposed areas, including the face, neck, hands, and decolletage. In 2020, nearly 1 million Americans sought minimally invasive laser skin resurfacing procedures to ameliorate these problems.[2] The holy grail of aesthetic dermatology is a non-invasive therapy that can reverse the aging process, turning back the hands of time. A desirable treatment is a topical anti-aging product that can be used by consumers in the privacy of their homes to address multiple skincare problems, such as large pores, fine lines, wrinkles, loss of luminosity, redness, and dark spots. Such a product should be easy to incorporate into a daily skincare routine to maximize consumer compliance.

One of the latest developments in aesthetic regenerative medicine is using exosomes as an ingredient in commercial skin treatment products. Exosomes are nano-sized extracellular cargos found in a variety of body fluids.[3] They are secreted by most cells to communicate with each other.[1] Exosomes have a stable lipid bilayer structure carrying diverse biomolecules, including proteins, nucleic acids, and lipids, based on their cellular origin.[4] The cellular origin of exosomes affects their content and ability to act on recipient cells. Exosomes also have low immunogenicity along with high hemocompatibility.[5] Exosomes trigger several effects considered beneficial for skin tissue regeneration, including (1) angiogenesis, (2) collagen synthesis, and (3) regulation of inflammation.[6] Exosomes from platelets are of particular interest due to their high propensity for skin healing.

Platelet-derived exosomes can be suspended in carrier gels for topical cosmetic application to address skin problems related to aging and environmental damage in a single cosmetic product. Platelet-derived extract (HPE) Intense Serum (Rion Aesthetics, Inc., Rochester, MN) is a leukocyte-depleted allogeneic product derived from US-sourced, pooled, apheresed platelets produced with consistent batch quality, purity, and effect. HPE is an off-the-shelf regenerative cosmetic product for skin rejuvenation that has demonstrated induction to normalized skin health at 4 to 6 weeks, with improved clinical measures of facial photodamage and cutaneous aging.[7] This clinical and histological study examines evidence-based outcomes for facial skin rejuvenation utilizing HPE, without any other confounding procedure, in a topical cosmetic application after 12 weeks of continuous twice-daily use.

MATERIALS AND METHODS

This prospective, single-arm, open-label, evaluator-blinded study of the safety and tolerability of topical HPE was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, Code of Federal Regulations, and the Declaration of Helsinki. The study was approved by the Mayo Clinic IRB (Rochester, MN). All subjects gave informed consent before any study procedures were performed. This study has been discussed with the US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research. Future studies evaluating medical indications and/or skin health parameters will be pursued under the FDA Investigational New Drug (IND) application.

The target population for inclusion was males and females over 40 years old with mild to moderate global facial wrinkles and lines based on a modified Griffiths 10-point scale.[8] The study aimed to recruit all Fitzpatrick Skin Phototypes. Subjects who met all inclusion criteria and no exclusion criteria were enrolled (Table 1).

The study participants followed a standardized skincare regimen for the 12-week study period. The skincare regimen included twice daily applications of (plated) Intense Serum

TABLE 1.

Inclusion and Exclusion Criteria	
Inclusion	**Exclusion**
Adult males and females ages 40 to 85 years	Pregnant or nursing, or planning on becoming pregnant during the study.
Persons of childbearing potential must have a negative pregnancy test prior to receiving the study product and will agree to use adequate contraception (hormonal or barrier method or abstinence) from the time of screening to a period of 2 years until discontinuation of treatment	Subjects who have had an antiaging or aesthetic treatment prior to the study: Botox or Botox-like products, peelings, plastic surgery, resurfacing with Laser, IPL, threats, radiofrequency treatments, hyaluronic acid treatment, Plasma-Rich Platelets treatment, or any other specific treatments prone to change the skin aspect during the last 6 months.
Mild-to-moderate global face wrinkles and mild-to-moderate global fine lines based on a modified Griffiths' 10-point scale.	Individuals with a history of any dermatological disease or condition, including but not limited to active atopic dermatitis, psoriasis, eczema, active seasonal allergies, collagen diseases, or skin cancer involving the treated sites within the past 6 months.
Fully understanding of the requirements of the study and willingness to comply with the treatment plan, including laboratory tests, diagnostic imaging, and follow-up visits and assessments.	Cutaneous marks on the experimental area which could interfere with the assessment of skin reactions (pigmentation problems, scar elements, over-developed pilosity, ephelides, and nevi in too great quantity, sunburn, beauty spots, freckles, etc.)
Volunteer willingness to discontinue any other anti-aging topical or parenteral treatments for the duration of the study.	Participants with asymmetric photodamage on dorsal hands due to environmental exposures (i.e., golfing) and/or other skin lesions including burns or scars resulting in significant skin surface variability between dorsal hands.
All skin phototypes ≥ grade I of Fitzpatrick's classification.	Eczematous reaction still visible, scar, or pigmentary sequelae of previous tests on the experimental area.
	Allergy to colophony or nickel. Allergy or reactivity to drugs, food or cosmetic products previously observed, including perfumes or cologne products, or Skin hyper-reactivity.
	Forecast of intensive sun, tanning bed use or UV phototherapy during the test period.
	Treatment with Vitamin A acid or its derivatives within 3 months before the beginning of the study.
	Treatment with topical corticosteroids on the experimental area within 16 days before the study.

(active ingredient HPE) to the entire face and decolletage. The regimen included using skin-neutral products (cleanser and light lotion) from Vanicream™ (Rochester, MN). Vanicream™ products are free from preservatives, fragrances, and other common allergens.

Subjects underwent clinical evaluations at week 0 (baseline), week 6, and week 12, which included standardized (Canfield VISIA CR Gen 5 with 3D PRIMOS) white light and polarized imaging for textural and topographical information. Parameters assessed included wrinkle fractional area, erythema fractional area, brown spot fractional area, luminosity score, and color evenness. 3D fringe projections were utilized to evaluate static wrinkles and measure the difference in fractional area between time points. Red/brown processing (RBX) was employed to measure changes in hemoglobin and melanin distributions. For the erythema fractional area, the RBX cross-polarized image was transformed into red pixels that correlated with hemoglobin absorption/distribution. Brown spots, color evenness, and color intensity (luminosity) were measured by assessing overall variation in color values, specifically pixel variation, across defined cosmetic subunits and how rapidly those colors change spatially within them. Participants also responded to cosmetic improvement questionnaires and subject satisfaction surveys at 6 and 12 weeks.

Primary and Secondary Endpoints

The primary endpoints included evaluation of the tolerability of the topical HPE product, including the nature, incidence, and severity of adverse events, as well as the change in photoaging scores from baseline to 12 weeks using the Canfield VISIA system to assess wrinkle count, depth, and volume by full-aligned facial images. Secondary endpoints include patient perception of cosmetic improvement and subject satisfaction in addition to histological analysis for collagen and elastin.

Histological Analysis

Standard 5 mm punch biopsies were obtained from the left upper inner arm skin at baseline (n=20 subjects) and right upper inner arm skin at 12 weeks following twice daily topical HPE application (n=20 subjects). Skin biopsy cross-sections for collagen and elastin were performed according to standard Masson's Trichrome (MT; Millipore Sigma, HT15) and modified Verhoeff Van Gieson (VVG; Millipore Sigma, HT25A) kit instructions, respectively. Papillary and reticular dermal layers were exclusively analyzed using Image-Pro Plus v10.0 software (Media Cybernetics, Rockville, MD) with self-trained algorithms designed to distinguish collagen (blue) vs non-collagen, and elastin (black) vs non-elastin, respectively. Human skin biopsies were also evaluated with scanning electron microscopy (SEM) and transmission electron microscopy (TEM) using the Mayo Clinic Electron Microscope Core Facility.

Statistical Analysis

For each VISIA-CR endpoint, an average of mean percentile change from baseline was calculated across anatomic regions (Forehead, Left and Right Cheek, and Left and Right Perioral zone) to obtain a single measurement per timepoint (baseline vs 12 weeks). Summary statistics and quantiles were calculated per timepoint, with means and 95% confidence intervals. Statistical significance was determined as $P \leq 0.05$. Graphical analysis and paired, two-tailed, Student's t-test were utilized, as appropriate (GraphPad Software Inc, San Diego, CA).

RESULTS

Fifty-six participants, 8 males and 48 females aged 40 to 80 years old with a mean age of 54 ± 11 years old, with mild-to-moderate wrinkles and lines, were enrolled in the study conducted at a single-center in the Mayo Clinic (Rochester, MN). Nine subjects included were Fitzpatrick III or higher.

FIGURE 1. Representative images of forehead rhytids in a 48-year-old female (A) and periocular rhytids in a 61-year-old female (B) at baseline and 12 weeks following twice daily topical HPE application.

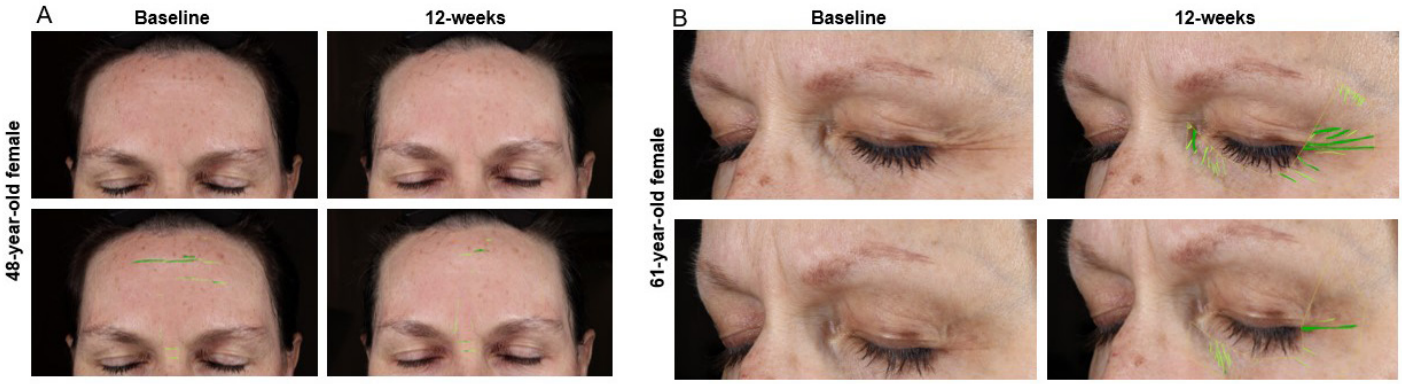
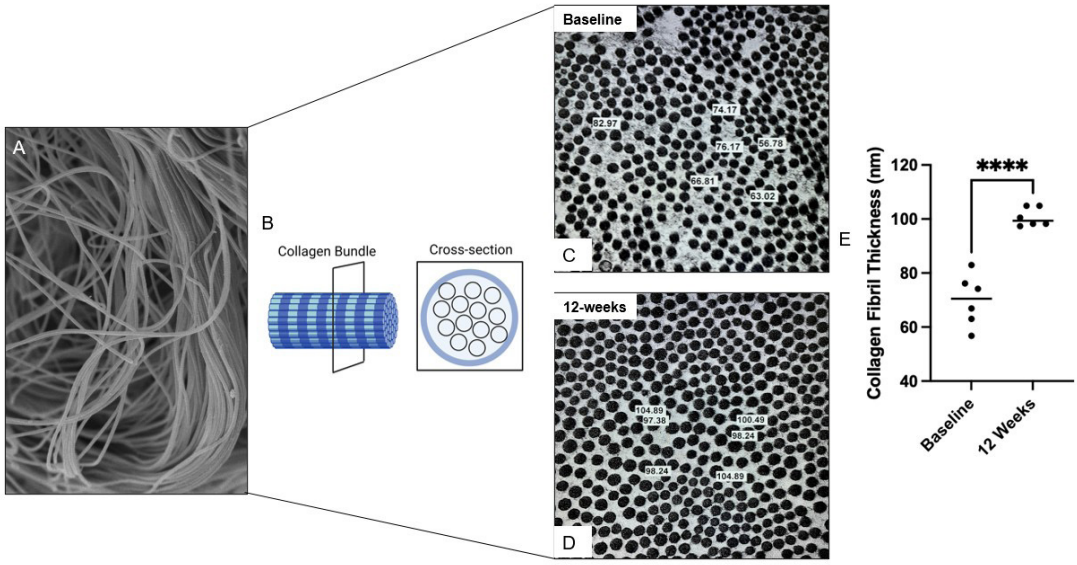


FIGURE 2. Scanning electron microscopy (SEM) of skin collagen fibrils in human reticular dermis (A) and associated cross-sectional analysis on transmission electron microscopy (TEM) (B) TEM images at baseline from the left upper inner arm (C) and 12 weeks from the right upper inner arm following topical HPE application (D), showed a mean uniform collagen thickness improvement of 30.70 ± 11.26 nm (E) nm=nanometer.



****=*P*-value=0.

VISIA-CR analysis evaluated skin health parameters, including wrinkles, erythema, luminosity, color evenness, and pigmentation (brown spots) at baseline, week 6, and week 12.

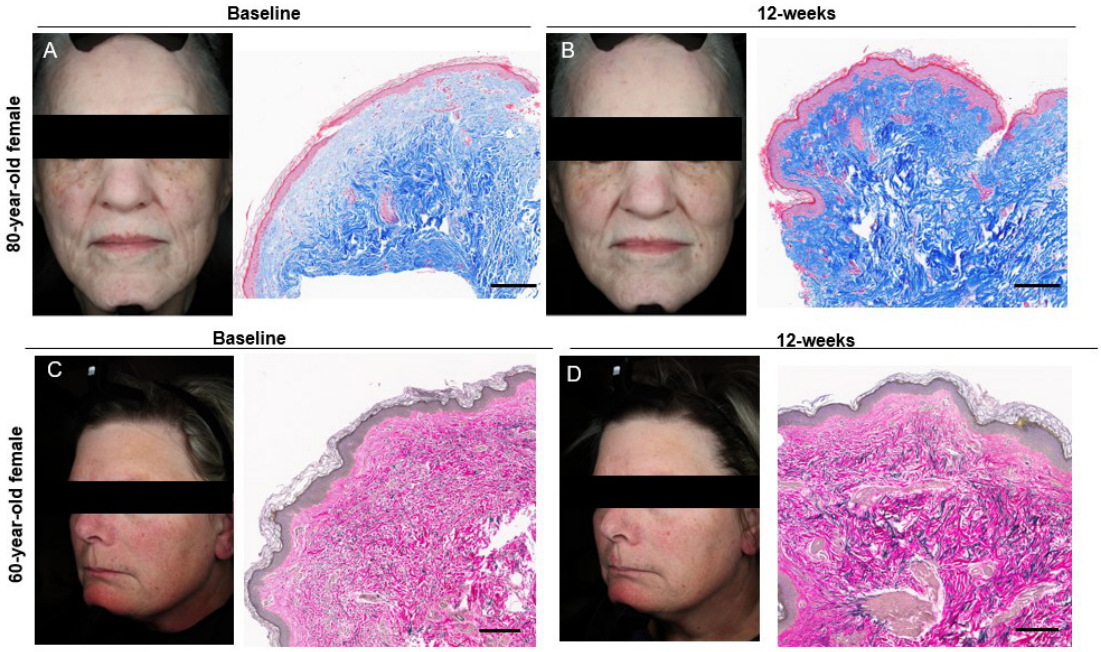
For erythema and brown spot analysis, study participants had sustained improvement at week 12. There were 36% (n=20 of 55) subjects who experienced at least a mean 10% improvement over baseline for the brown-spot fractional area over baseline at 12 weeks. VISIA-CR RBX imaging reported brown spot fractional area averages ranging from 0.0132 to 0.1626 across the entire face. For persons with the most pigment damage at baseline (above 75th percentile at baseline, ≥0.1264), subjects had an average mean improvement (pigment reduction) of -6.3% at week 6 (*P*=0.133), and -13.4% at week 12 (*P*=0.0045). This mimicked findings across the entire cohort, which continued to demonstrate sustained mean pigment reduction at week 12 (*P*<0.0001). At week 12, 42% (n=21 of 50) subjects had at least a mean 50% improvement over baseline for redness, while 28% (n=14 of 50) subjects had at least 75% improvement over baseline. VISIA-CR RBX analysis for erythema fractional area (or redness) showed baseline erythema ranged from 0 to 4.96 pixels. Persons who had higher baseline starting redness (>75th quartile, or 0.845) had significant mean redness or erythema fractional area improvement by 79.7% at week 6 (*P*=0.0393) which continued to be seen at week 12 (87.4%).

For color intensity (luminosity) and color evenness, VISIA-CR white and polarized light were used to analyze each participant. The threshold of participants with the lowest color intensity at baseline was 60.69 (25th percentile; range 42.46 to 71.11). At 12 weeks, 51% (n=28 of 55) saw at least a 5% mean improvement in color intensity. At 12 weeks, 22% (n=12 of 55) subjects saw a 10% mean improvement from baseline in color evenness, while 38% (n=21 of 55) saw at least 5% mean improvement. Persons who had the lowest baseline starting luminosity (<25th quartile) improved by 12.2% at week 12 (*P*=0.0014).

Canfield 3D fringe topography technology analyzed wrinkle fractional area across all subjects and cosmetic facial units. At 12 weeks, 20% (n=11 of 55) of subjects saw at least 10% mean improvement over baseline for the wrinkle fractional area, while 38% (n=21 of 55) saw at least 5% mean improvement over baseline. A 48-year-old female subject with improvement in forehead wrinkles (Figure 1A) and a 61-year-old female subject with improvement in periorbital wrinkles (Figure 1B) are shown.

Regarding overall cosmetic improvement assessed by patient questionnaires, 87.3% patients at week 12 had an improvement compared with 69% (n=39 of 56) subjects at week 6. The majority (90.9%) of participants noticed an improvement in skin texture at week 12, compared with 76.8% (n=43 of 56) subjects at week 6. There were 85.5% of subjects who noticed an improvement in wrinkles at week 12 compared to 73.2% (n=41 of 56) at week 6. 94.6% of subjects noticed improvement in wrinkles at week 12 compared with 73.2% (n=41 of 56) at week 6. There were 67.3% subjects noticed improvement in redness at week 12 compared with 55.4% at week 6. No serious adverse events were reported. Dry skin was reported in 16.3% (n=9 of 55). No participants experienced pain, irritation, or swelling when using the product.

FIGURE 3. Representative image of an 80-year-old female and associated collagen analysis using Masson's Trichrome (MT) at baseline from the left upper inner arm (A) and 12 weeks from the right upper inner arm (B) following topical HPE application. Representative image of a 60-year-old female and associated elastin analysis using Verhoeff-Van Gieson (VVG) at baseline from the left upper inner arm (C) and 12 weeks from the right upper inner arm (D) following topical HPE application.



Ultra-histological evaluation was conducted using scanning electron microscopy (Figure 2A) and cross-sectional collagen bundle thickness analyzed with transmission electron microscopy (TEM; Figure 2B). TEM analysis revealed that collagen bundle thickness 69.98 ± 9.56 nm at baseline (Figure 2C) increased to 100.69 ± 3.41 nm at 12-weeks (Figure 2D). Mean difference showed a statistically significant improvement in uniform collagen thickness of 30.70 ± 11.26 nm ($P \leq 0.0001$).

Additional histological studies were performed using Masson's Trichrome (MT) for collagen analysis and Verhoeff Van Gieson (VVG) for elastin analysis. An 80-year-old female subject experienced collagen improvement from baseline (Figure 3A) to week 12 (Figure 3B), notable in the papillary dermis. A 60-year-old female subject experienced elastin improvement from baseline (Figure 3C) to 12 weeks (Figure 3D), notable in the reticular dermis.

DISCUSSION

By 2030, 20% of all Americans will be older than 65 years, making cutaneous studies of photoaging and skin rejuvenation topics of increasing public interest.[9] The rise in aging population parallels the incidence of dermatologic conditions, with more than 27 million visits to dermatologists each year, most in older adults. Skin rejuvenation strategies aim to restore the youthful appearance and vitality of the skin. Basic science research has elucidated the underlying biological processes involved in skin aging, including collagen degradation, reduced cellular turnover, and impaired antioxidant defense mechanisms. Advanced techniques like laser therapy, radiofrequency, and microneedling utilize controlled energy to induce collagen remodeling and promote skin rejuvenation. Other therapies target the molecular pathways involved in collagen or elastin synthesis and cell renewal by topical delivery of chemical compounds, such as antioxidants, retinoids, and peptides. But these may lack tolerability associated with newer compounds such as platelet-derived extracellular vesicles.

Exosomes are small extracellular vesicles that play a crucial role in intercellular communication and are gaining significant attention in the field of biomedical research.[10] These vesicles, stabilized in a lipid bilayer ranging in size from 30 to 150 nanometers, transfer bioactive molecules triggering diverse physiological processes.[3,5,11] Ongoing research is focused on unraveling the mechanisms of exosome biogenesis, cargo sorting, role in various diseases, and their potential use as biomarkers, drug delivery vehicles and regenerative therapeutic agents.[12–14]

No study to date has assessed the effect of topical human platelet extract (HPE) with platelet-exosome technology on skin rejuvenation after 12 weeks. This study examines the safety and effectiveness of topical HPE on skin health and aging with demonstrable long-lasting effects on increased luminosity,

color evenness, and pigment reduction at week 12. It is well-known that growth factors released from dense granules of platelets promote platelet aggregation, wound healing, and fibrin formation.[15] Among these factors are platelet derived growth factor (PDGF), transforming growth factor beta (TGFβ), and vascular endothelial growth factor (VEGF).[16] As platelets are first responders in the wound healing cascade, release of these mediators might explain why initial reductions in redness/erythema fractional area are noted at week 6,[7] but does not lead to long-lasting reduction in redness across all study subjects. Comparatively, sustained improvement in overall pigmentation, or brown spot fractional area, was noted in our cohort across all Fitzpatrick types, cosmetic subunits, and subjects at week 12. This may occur due to the initial release of anti-inflammatory mediators like interleukin-10 (IL-10), which help mitigate inflammation and reduce post-inflammatory hyperpigmentation in various skin types.[17] Increased cellular turnover by mediators released from platelet exosomes may also help explain why pigmented areas gradually fade to reveal increased luminosity and color evenness scores. TGFβ and basic fibroblast growth factor (bFGF) have also been shown to inhibit melanocyte activity and melanin production by downregulating the expression of enzymes involved in melanin synthesis, such as tyrosinase, leading to decreases in pigmentation, for an overall improvement in luminosity and color evenness.[18] Improved collagen remodeling and structure/organization is another hypothesized mechanism of platelets, further stabilized by exosomes which can contribute to faster skin recovery, resulting in improved overall skin evenness, luminosity, and radiance while using this product. This was further evident in collagen and elastin histological and ultrastructural improvement.

Indeed, the rise in the aging population and associated dermatologic conditions warrant further studies focusing on skin rejuvenation and photoaging. Platelet-derived exosomes, small vesicles involved in intercellular communication and tissue repair, show promise in regenerative aesthetics. This study demonstrates the beneficial effect of topical HPE to improve skin appearance at the clinical and histological levels. Future studies would evaluate a control vehicle in all subjects, a larger cohort of patients, and alternative analysis such as colorimeter or dermato spectrophotometry to better examine the response of pigmentation in higher Fitzpatrick phototypes.

Strengths and Limitations

This is a prospective, single-arm, evaluator-blinded study that tests a novel category of topical skin care with topical HPE, a platelet-derived extracellular vesicle technology. This study solely evaluated the cosmetic and histological impact of HPE, eliminating the confounding effect of paired energy or device-based interventions. Future studies can involve subject randomization, and additional placebo-controlled study design to reduce bias.

CONCLUSION

Topical skin-directed therapies utilizing antioxidants, retinoids, and peptides have shown promise in enhancing collagen and elastin synthesis, in tandem with improving skin texture and tone. Emerging research on platelet-derived extracellular vesicles presents a new and intriguing avenue for skin rejuvenation. Exosomes, with their distinct role in intercellular communication and tissue repair, have the potential to serve as agents in regenerative aesthetics. This study demonstrates the promising and safe effects of topical HPE on skin aging, including increased luminosity, improved color evenness, and pigment reduction. Release of growth factors and mediators from platelets, including PDGF, TGFβ, VEGF, IL-10, and bFGF, among other regenerative signals, may contribute to these observed improvements. Further investigation into the long-term effects of platelet-derived exosomes is warranted as they hold potential as a novel regenerative approach in skin rejuvenation.

DISCLOSURES

Dr Wyles is a consultant for Rion Aesthetics, LLC. Dr Behfar and Mayo Clinic have an ownership interest in Rion, Inc. and Rion Aesthetics, LLC.

REFERENCES

1. Pinnell SR. Cutaneous photodamage, oxidative stress, and topical antioxidant protection. *J Am Acad Dermatol.* 2003;48(1):1-19; quiz 20-22. doi:10.1067/mjd.2003.16
2. 2020 Plastic Surgery Statistics Report. *PLASTIC SURGERY.* Published online 2020. https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-full-report-2020.pdf
3. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science.* 2020;367(6478):eaau6977. doi:10.1126/science.aau6977
4. Xiong M, Zhang Q, Hu W, et al. The novel mechanisms and applications of exosomes in dermatology and cutaneous medical aesthetics. *Pharmacol Res.* 2021;166:105490. doi:10.1016/j.phrs.2021.105490
5. Yang GH, Lee YB, Kang D, et al. Overcome the barriers of the skin: exosome therapy. *Biomater Res.* 2021;25(1):22. doi:10.1186/s40824-021-00224-8
6. Chiu HJ, Sun CK, Tsai SJ, et al. A nationwide study of the risks of major mental disorders among the offspring of parents with rheumatoid arthritis. *Sci Rep.* 2022;12:4962. doi:10.1038/s41598-022-08834-5
7. Proffer SL, Paradise CR, DeGrazia E, et al. Efficacy and tolerability of topical platelet exosomes for skin rejuvenation: six-week results. *Aesthet Surg J.* 2022;42(10):1185-1193. doi:10.1093/asj/sjac149
8. Nguyen TQ, Zahr AS, Kononov T, et al. A randomized, double-blind, placebo-controlled clinical study investigating the efficacy and tolerability of a peptide serum targeting expression lines. *J Clin Aesthet Dermatol.* 2021;14(5):14-21.
9. U.S. Census Bureau QuickFacts: United States. Available at: https://www.census.gov/quickfacts/fact/table/US/PST045222. Accessed May 13, 2023.
10. 10.Vyas KS, Kaufman J, Munavalli GS, et al Exosomes: the latest in regenerative aesthetics. *Regen Med.* 2023;18(2):181-194. doi:10.2217/rme-2022-0134
11. Chernoff G. The utilization of human placental mesenchymal stem cell derived exosomes in aging skin: an investigational pilot study. *J Surg.* 2021:6:1388. DOI: 10.29011/2575-9760.001388.
12. 12.Heydari R, Koohi F, Rasouli M, et al. Exosomes as rheumatoid arthritis diagnostic biomarkers and therapeutic agents. *Vaccines (Basel).* 2023;11(3):687. doi:10.3390/vaccines11030687
13. 13.Kimiz-Gebologlu I, Oncel SS. Exosomes: Large-scale production, isolation, drug loading efficiency, and biodistribution and uptake. *J Control Release.* 2022;347:533-543. doi:10.1016/j.jconrel.2022.05.027
14. 14.Kim HY, Kwon S, Um W, et al. Functional extracellular vesicles for regenerative medicine. *Small.* 2022;18(36):e2106569. doi:10.1002/smll.202106569
15. 15.Rendu F, Brohard-Bohn B. The platelet release reaction: granules' constituents, secretion, and functions. *Platelets.* 2001;12(5):261-273. doi:10.1080/09537100120068170
16. 16.Shi A, Li J, Qiu X, et al. TGF-β loaded exosome enhances ischemic wound healing in vitro and in vivo. *Theranostics.* 2021;11(13):6616-6631. doi:10.7150/thno.57701
17. 17.Pochini ADC, Antonioli E, Bucci DZ, et al. Analysis of cytokine profile and growth factors in platelet-rich plasma obtained by open systems and commercial columns. *Einstein (São Paulo).* 2016;14(3):391-397. doi:10.1590/S1679-45082016AO3548
18. 18.Kim DS, Park SH, Park KC. Transforming growth factor-beta1 decreases melanin synthesis via delayed extracellular signal-regulated kinase activation. *Int J Biochem Cell Biol.* 2004;36(8):1482-1491. doi:10.1016/j.biocel.2003.10.023

AUTHOR CORRESPONDENCE

Saranya Wyles MD PhD
E-mail:..... Wyles.Saranya@Mayo.edu