

Article

A Multicomponent Bioactive Cosmetic After Radiofrequency Microneedling: Effects on Skin Barrier, Downtime, and Multi-Domain Skin Parameters in a Randomized, Split-Face, Controlled Trial

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Abstract

This prospective, single-center, randomized, split-face controlled trial evaluated whether a multicomponent investigational cosmetic serum (ISCE) applied immediately after radiofrequency microneedling (RF-MN) provides additional benefit over RF-MN alone. In 22 healthy Korean women aged 40–69 years, one hemiface was randomly assigned by a computer-generated sequence to RF-MN plus ISCE and the other to RF-MN alone, in two sessions 3 weeks apart; outcome assessors and statisticians were blinded. Primary endpoints were transepidermal water loss (TEWL) and procedure-induced erythema; secondary endpoints were hydration, elastic recoil, elasticity, density, wrinkles, pores, and pigmentation. Twenty participants were analyzed. TEWL decreased more on the combination side from the first session (between-side difference $-0.50 \text{ g/m}^2\cdot\text{h}$, 95% CI -0.68 to -0.33 ; $p < 0.001$), and the procedure-induced increase in erythema was smaller after the second session (-1.07 A.U. , 95% CI -2.08 to -0.05 ; nominal $p = 0.041$). After the second session, all exploratory secondary endpoints favored the combination side (unadjusted $p < 0.05$). No adverse events occurred. ISCE after RF-MN yielded a greater short-term reduction in TEWL than RF-MN alone, whereas the erythema finding is preliminary and requires confirmation; because no vehicle control was included, the TEWL benefit is attributable to the formulation as a whole. The trial was not registered in a trial registry.

Keywords: multicomponent bioactive cosmetic; epidermal progenitor cell-conditioned medium; split-face trial; skin barrier; elasticity; photoaging; pigmentation; transdermal delivery; radiofrequency microneedling

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1. Introduction

Skin aging proceeds simultaneously along multiple axes—declining barrier function, loss of collagen and elastin, photoaging-related wrinkles and pore enlargement, and pigmentary change—so that a single intervention is rarely sufficient to improve every domain at once [1,2]. Topical formulations alone seldom reach these targets, because most bioactive molecules larger than approximately 500 Da do not cross the intact stratum corneum [3]. This has motivated pairing multi-target topical formulations with a procedure that transiently opens a delivery window while itself stimulating dermal remodeling, albeit at the cost of transient post-procedure downtime [1,2,4–7].

Radiofrequency microneedling (RF-MN) transiently creates microchannels that facilitate transdermal delivery of topically applied agents [8–10], while RF energy delivered through microneedle electrodes induces controlled dermal thermal injury and subsequent wound-healing responses associated with neocollagenesis and dermal remodeling [1,2,4–7]. Although RF-MN transiently disrupts the epidermal barrier, transepidermal water loss has been reported to return to baseline within approximately one week [11], and microneedling has been associated with upregulation of epidermal differentiation markers such as filaggrin [12,13].

In clinical practice, topical products are commonly applied immediately after microneedling-based procedures to support recovery and enhance outcomes; these include hyaluronic acid-based serums, growth factor preparations, stem cell-conditioned media and, more recently, extracellular vesicle (exosome)-containing solutions [14,15]. Several controlled split-face studies have evaluated such adjuncts. Lee et al. reported greater skin rejuvenation when microneedling was combined with human stem cell-conditioned medium than with microneedling and a control solution [16], and El-Domyati et al. observed greater clinical and histological improvement when conditioned medium was combined with skin needling than with needling alone [17]. In a randomized controlled trial, adding a topical growth factor complex to microneedling improved skin texture and hydration more than microneedling with a control serum, although skin tone and melanin improved significantly only in the control group [18]. Park et al. showed that an adipose stem cell-derived exosome-containing solution combined with microneedling produced greater improvement in several aging parameters over 12 weeks than microneedling with a control solution [19]. However, these studies generally tested a single regenerative ingredient after conventional microneedling. Evidence for multicomponent formulations applied after RF-MN, with simultaneous assessment of post-procedure downtime and multiple skin aging domains, remains limited.

Therefore, the aim of this study was to evaluate whether applying a multicomponent investigational cosmetic serum (ISCE), containing ingredients selected to target distinct skin functional axes, immediately after RF-MN provides additional benefit over RF-MN alone. We hypothesized that the combination would improve post-procedure barrier recovery and downtime, as well as structural, photoaging, and pigmentation parameters. To test this hypothesis, we conducted a randomized, split-face, controlled trial with objective instrumental assessment of five skin functional domains.

2. Materials and Methods

2.1. Study Design and Ethics

This study was a prospective, randomized, split-face, controlled, single-center human-applied trial conducted at Human Skin Clinical Trial Center Co., Ltd. (Seoul, Republic of Korea; trial management number HM-P25-0061). The trial was conducted in accordance with the spirit of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines, prioritizing the rights, safety, and welfare of participants, and followed the

institution's Standard Operating Procedures (SOP). The protocol was approved by the Institutional Review Board (IRB approval number HM-IRB-P25-0061; approved on 27 January 2025), and written informed consent was obtained from all participants after a full explanation of the purpose and content of the study. The study period was from 11 February to 27 March 2025. As a cosmetic clinical trial, this study was not subject to mandatory clinical trial registration. The study protocol is available from the corresponding author upon request. This trial is reported in accordance with the CONSORT 2025 statement, with considerations from the CONSORT extension for within-person randomised trials (Table S1).

2.2. Randomization and Blinding

Each participant's face was divided into left and right hemifaces at the midline. Using simple randomization with a computer-generated random sequence, one hemiface was assigned to the combination side (RF-MN + ISCE) and the contralateral hemiface to the control side (RF-MN alone). The allocation sequence was generated and implemented by the study researchers, and the treatment side of each participant was assigned strictly according to this sequence. Outcome assessors and statisticians were blinded to treatment allocation. Because the product was applied to only one hemiface, blinding of the treating investigator and participants was not feasible.

2.3. Participants

Twenty-two participants meeting the inclusion and exclusion criteria were enrolled; 2 were withdrawn because of protocol deviations, leaving 20 participants (mean age 59.15 $\pm$ 7.90 years) in the final analysis.

Inclusion criteria

- Healthy Korean women aged 40–69 years;
- Presence of wrinkles and pigmented spots;
- Free of acute or chronic systemic disease, including skin disorders;
- Provided voluntary written informed consent after a full explanation of the study purpose and procedures;
- Able to be followed up for the duration of the study;

Exclusion criteria

- Pregnant, breastfeeding, or planning pregnancy;
- Psychiatric disorder or infectious skin disease;
- Use of topical steroid-containing products for ≥ 1 month;
- Participation in the same trial within the preceding 6 months;
- Visible skin abnormalities (e.g., moles, acne) at the test site;
- Use of anticoagulant medication;
- Use of whitening/pigmentation-related cosmetics or drugs at the test site within the preceding 3 months;
- Filler, botulinum toxin, thread-lift, or peeling procedures at the test site within the preceding 3 months;
- Use of cosmetics or drugs with the same or similar efficacy at the test site within the preceding 3 months;
- Dermatologic procedures at the test site within the preceding 6 months (e.g., liposuction, laser, ultrasound lipolysis, other skin treatments);
- Employee of the sponsor, or judged by the investigator to be unsuitable for participation.

During the study period, participants were instructed to discontinue use of functional cosmetics and anti-inflammatory, antihistamine, or steroid medications; to

maintain their usual makeup habits; to avoid cosmetic or dermatologic procedures; and to avoid excessive ultraviolet exposure.

2.4. Test Product and Intervention

Radiofrequency microneedling was performed on the entire face twice at a 3-week interval using the SYLFIRM X system (VIOL Medical Co., Ltd., Seongnam, Republic of Korea), which delivers RF energy through non-insulated microneedle electrodes. Immediately after each session, the multicomponent bioactive cosmetic (ISCE; IALL Co., Ltd., Seoul, Republic of Korea), comprising a Component 1 liquid and a Component 2 lyophilized powder, was applied to the combination-side hemiface, while the control-side hemiface received RF-MN alone with no additional topical application. The disclosed ingredient list of the ISCE is presented in Table 1. The quantitative concentrations of the individual active components in the final formulation are proprietary and could not be disclosed by the manufacturer, a limitation that is addressed in the Discussion. The epidermal stem cell-conditioned medium listed in Table 1 corresponds to the conditioned medium of mesenchymal-stem-cell-derived epidermal progenitor cells (EPC-CM), whose secretome and anti-aging activity have been characterized previously [20–22]. Reported concentrations of key secreted factors in this conditioned medium include nidogen-1 at approximately 15,180 pg/mL, thrombospondin at 63.65 pg/mL, TRANCE at 29 pg/mL, and interleukin-15 receptor alpha (IL-15R α) at 19 pg/mL [21,22]. Treatment parameters were standardized across all participants but adjusted according to the facial treatment area. The XE-25 tip was used in PW2 mode at power levels of 4–6, with one pass at a needle depth of 0.3 mm followed by one pass at 0.8 mm.

Table 1. Disclosed ingredient list of the multicomponent bioactive cosmetic (ISCE).

Component	Listed Ingredients
ISCE—Component 1 (liquid)	Sodium hyaluronate, copper tripeptide-1 (GHK-Cu), amino acid complex, vitamin complex
ISCE—Component 2 (lyophilized powder)	Epidermal stem cell-conditioned medium, CHA-hGH/CHA-VEGF, <i>Lactobacillus</i> -derived exosomes

The ISCE was formulated so that each active ingredient targets a distinct skin functional axis (Table 2). Copper tripeptide-1 (GHK-Cu, approximately 340 Da) is an anti-aging peptide whose effects on collagen synthesis, matrix metalloproteinase (MMP) regulation, and antioxidant/anti-inflammatory activity have been summarized in previous reviews [23–25]; a 12-week controlled clinical study in photoaged women aged 50–59 years, described in [25,26], reported improvements in skin elasticity, density, wrinkles, and pigmentation. Epidermal stem cell-conditioned medium is rich in regenerative cytokines and growth factors that promote keratinocyte proliferation and re-epithelialization [20–22]. Growth factor analogues (CHA-hGH/CHA-VEGF) support fibroblast activation, angiogenesis, and extracellular matrix remodeling [14,18,27]. *Lactobacillus*-derived extracellular vesicles have been reported to upregulate barrier proteins such as filaggrin and lorincrin [28], exert anti-inflammatory effects [29–31], and suppress melanogenesis through NF- κ B/MAPK inhibition [30].

Table 2. Active ingredients of the ISCE, their targeted skin functional axes, and reported mechanisms of action.

Ingredient	Target Axis	Primary Mechanism (References)
GHK-Cu (Component 1)	Structure/Anti-inflammatory	Collagen synthesis, MMP regulation, antioxidant/anti-inflammatory [23–26]

Epidermal stem cell-conditioned medium (Component 2)	Regenerative signaling	Defined secretome (TIMP-1/2, TGF- β BP-1/Smad4, SPARC, thrombospondin, nidogen-1) $\rightarrow$ antioxidant defense, type I procollagen, keratinocyte proliferation [20–22]
CHA-hGH/CHA-VEGF (Component 2)	Angiogenesis/ECM	Fibroblast activation, neovascularization, matrix remodeling [14,18,27]
<i>Lactobacillus</i> -derived exosomes (Component 2)	Barrier/Pigmentation	Upregulation of filaggrin/loricrin, anti-inflammatory activity, melanin regulation [28–31]

2.5. Measurement Environment and Evaluation Instruments

All measurements and evaluations were performed in a draft-free, sunlight-free room under controlled environmental conditions (22 ± 2 °C, relative humidity $50 \pm 5\%$) after participants had acclimatized. Post-procedure indicators (barrier: transepidermal water loss [TEWL] and hydration; downtime: erythema and elastic recoil) were measured before treatment, immediately after the first treatment, before the second treatment (3 weeks after the first), and immediately after the second treatment. For these post-procedure measurements (referred to as “immediately after” treatment), both hemifaces were measured simultaneously after a 30-min stabilization period following application of ISCE to the combination side, under the controlled environmental conditions described above. Structure, photoaging, and pigmentation indicators were measured before treatment, 3 weeks after the first treatment, and 3 weeks after the second treatment (Figure 1). All instruments are non-invasive objective measurement devices widely used in dermatologic and cosmetic clinical research [32,33]; instruments and corresponding indicators are summarized in Table 3.

Study timeline and measurement points

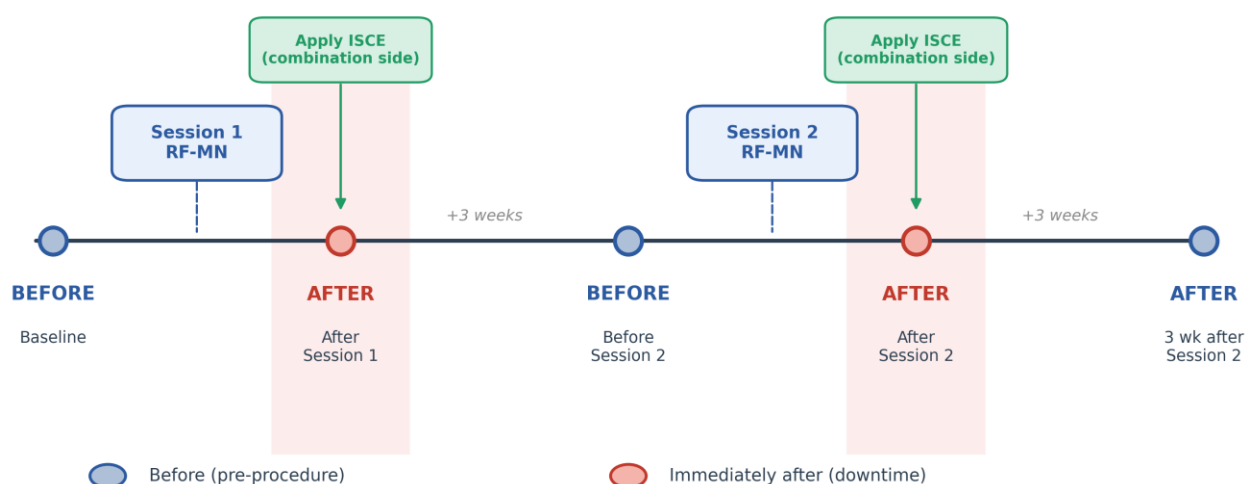


Figure 1. Study timeline. Two RF-MN sessions were performed 3 weeks apart, and ISCE was applied to the combination side immediately after each session. Post-procedure barrier and downtime indicators (TEWL, hydration, erythema, elastic recoil) were measured before and immediately after each session (blue = before, pre-procedure; red/shaded = immediately after the procedure), whereas structure, photoaging, and pigmentation indicators were assessed at baseline, 3 weeks after the first session, and 3 weeks after the second session (final). Each participant’s face was split at the midline into a combination side (RF-MN + ISCE) and a control side (RF-MN alone). Abbreviations: RF-MN, radiofrequency microneedling; ISCE, investigational cosmetic serum (multicomponent bioactive cosmetic); TEWL, transepidermal water loss; wk, weeks.

Table 3. Measurement instruments and principles for each evaluation indicator.

Instrument	Evaluation Indicator	Principle/Measurement Site
Antera 3D (Miravex Ltd., Dublin, Ireland)	Erythema, elastic recoil (depression of volume), periorbital wrinkles (1, 3 mm), pore volume, melanin	Multi-spectral 7-wavelength LED reflectance-based 3D image analysis (cheek/periorbital area)
Corneometer CM 825 (Courage + Khazaka, Cologne, Germany)	Skin hydration (A.U.)	Capacitance method, cheek area
Vapometer (Delfin Technologies, Kuopio, Finland)	Transepidermal water loss (TEWL, g/m ² ·h)	Closed-chamber method, cheek area
Cutometer dual MPA 580 (Courage + Khazaka, Cologne, Germany)	Skin elasticity (superficial 2 mm/deep 8 mm, R2)	Negative-pressure suction and recovery measurement, cheek area
DUB SkinScanner (tpm, Lüneburg, Germany)	Skin density	22 MHz high-resolution ultrasound imaging, cheek area
VISIA-7 (Canfield Scientific, Parsippany, NJ, USA)	Pigmented-spot area (pixels)	Standardized frontal and lateral image capture

2.6. Endpoints

To limit multiplicity, only two primary endpoints were pre-specified: TEWL (barrier) and erythema (downtime). Secondary endpoints were organized by skin functional domain: barrier/hydration (moisture content), downtime (elastic recoil), structural remodeling (elasticity at 2 mm and 8 mm R2, density), photoaging (periorbital wrinkles at 1 mm and 3 mm, pore volume), and pigmentation (melanin, pigmented-spot area). A 13-item satisfaction questionnaire (6-point scale; scores of 4–6 defined as a positive response), investigator-assessed adverse events, and participant self-reports were also collected. Secondary endpoints were regarded as exploratory and supportive. No changes were made to the pre-specified endpoints or methods after the trial commenced; the between-side effect estimates with 95% CIs, the baseline comparability analysis, and the conservative multiplicity interpretation were added post hoc in response to peer review.

2.7. Safety Assessment

Adverse events (persistent or excessive erythema, edema, scaling, pruritus, stinging, burning, tightness, prickling, etc.) were monitored throughout the study period through clinical assessment by the investigating dermatologist and participant self-report. A pre-specified procedure was in place to immediately discontinue product use upon occurrence of an adverse event and to provide dermatologic evaluation and appropriate treatment if symptoms did not resolve.

2.8. Statistical Analysis

As an exploratory split-face study, no formal a priori sample-size calculation was performed; the sample size was determined by feasibility and is consistent with comparable split-face trials of microneedling combined with topical actives [16,17,19]. Because each participant served as her own control, the within-subject split-face design reduces inter-individual variability relative to a parallel-group design of similar size; nevertheless, the study was not powered for specific effect sizes, and its results should be interpreted as preliminary. Statistical analyses were performed using SPSS Statistics 26 (IBM Corp., Armonk, NY, USA) and R (R Foundation for Statistical Computing, Vienna, Austria), with a two-sided significance level of 0.05. Normality was assessed using the Shapiro–Wilk test. Analyses were performed in the per-protocol population of participants who completed the study; data from the two participants who withdrew were

excluded, and no missing data were imputed. Baseline comparability of the two sides was assessed using the paired t-test or the Wilcoxon signed-rank test. Within-side changes from baseline were analyzed using the paired t-test or Wilcoxon signed-rank test (two time points) and repeated-measures ANOVA or the Friedman test followed by Bonferroni-corrected Wilcoxon signed-rank post hoc tests (≥ 3 time points). For between-side comparisons, the paired (within-participant) structure of the split-face design and the repeated measurements were modeled jointly using raw data. When normality was satisfied, repeated-measures ANOVA was used with treatment side and time as within-subject factors, and the between-side p -value for each treatment session corresponds to the session-specific side $\times$ time interaction contrast; otherwise, a generalized estimating equation (GEE) was fitted with the participant as the clustering unit to account for the correlation between the two hemifaces of the same participant and across visits. For the primary endpoints, between-side differences (combination minus control) in the change from the pre-treatment value of each session are additionally reported as mean differences with 95% confidence intervals (CIs), calculated from the paired within-participant differences. Regarding multiplicity, the two primary endpoints were pre-specified to address distinct clinical questions (barrier function and downtime) and were each tested at $\alpha = 0.05$ without adjustment. Secondary endpoints were not adjusted for multiple comparisons and are regarded as exploratory and hypothesis-generating. Percent improvement was calculated as $(\text{post-treatment} - \text{pre-treatment})/\text{pre-treatment} \times 100$, with the sign reversed for parameters in which a decrease indicates improvement, and the relative improvement of the combination side versus the control side was calculated as $(\text{combination} - \text{control})/\text{control} \times 100$. Questionnaire data are reported as frequencies and percentages.

2.9. Use of Generative AI

During the preparation of this manuscript, Claude (Anthropic, San Francisco, CA, USA), accessed via Claude.ai (June–October 2026), was used for language editing and for revising the manuscript text, figures, and references. All statistical analyses were performed by the authors using SPSS Statistics 26 (IBM Corp., Armonk, NY, USA) and R. The authors reviewed and verified all AI-assisted content and take full responsibility for the content of this publication.

3. Results

3.1. Participant Characteristics and Safety

Of the 22 participants enrolled, 2 were withdrawn at the final visit (3 weeks after the second treatment) because of protocol deviations and were excluded from all analyses; the remaining 20 participants (all women; mean age 59.15 ± 7.90 years, range 46–69 years; skin type dry, $n = 18$; normal, $n = 1$; combination, $n = 1$) completed the study and were included in the analysis (Figure 2). Baseline values of all 12 efficacy endpoints did not differ significantly between the combination and control sides (all $p \geq 0.063$). Throughout the study period, no adverse events—including edema, scaling, or pruritus—were observed or reported by either the investigating dermatologist or participant self-report, indicating favorable tolerability of the combination regimen; transient procedure-induced erythema was evaluated as a downtime endpoint rather than recorded as an adverse event.

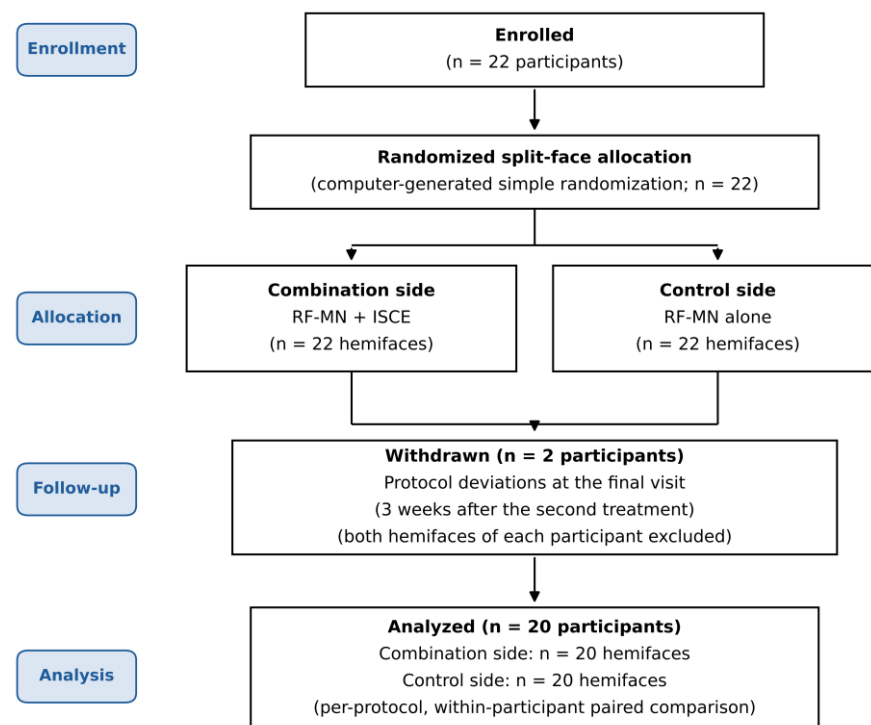


Figure 2. CONSORT flow diagram of participants. In this within-person (split-face) design, both hemifaces of each enrolled participant were randomly allocated, one to RF-MN + ISCE and the other to RF-MN alone; participant withdrawal therefore excluded both hemifaces from the analysis. Abbreviations: RF-MN, radiofrequency microneedling; ISCE, investigational cosmetic serum.

3.2. Primary Endpoints: Barrier and Downtime

TEWL, the barrier indicator, showed a significantly greater decrease on the combination side than the control side from immediately after the first treatment (between-side $p < 0.001$), and this advantage was maintained after the second treatment ($p = 0.031$) (Figure 3B). The between-side mean difference (combination minus control) in TEWL change was $-0.50 \text{ g/m}^2\cdot\text{h}$ (95% CI -0.68 to -0.33) for the first treatment session and $-0.30 \text{ g/m}^2\cdot\text{h}$ (95% CI -0.56 to -0.03) for the second, with negative values indicating a greater decrease on the combination side. Erythema, the downtime indicator, did not differ significantly between sides after the first treatment (between-side difference -0.10 A.U. [95% CI -0.84 to 0.65]; $p = 0.793$). Because erythema was assessed immediately after each session, it reflects procedure-induced downtime rather than a longer-term change in baseline redness. After the second treatment, the procedure-induced increase in erythema was smaller on the combination side, reaching nominal significance (between-side difference -1.07 A.U. [95% CI -2.08 to -0.05]; $p = 0.041$; negative values indicate a smaller increase on the combination side). This difference would not remain significant after a conservative correction for multiplicity (see Limitations) and should therefore be regarded as preliminary, requiring confirmation in larger trials (Figure 3A). In absolute terms, these differences were modest, corresponding to approximately 3% of the pre-treatment mean for TEWL after the first session and 4% for erythema after the second session; for erythema, the mean procedure-induced increase was approximately 46% smaller on the combination side (1.24 vs. 2.30 A.U.). Thus, among the two primary endpoints, the barrier axis showed a significant between-side difference from the first treatment, whereas the downtime axis showed only a nominally significant, preliminary difference after the second treatment.

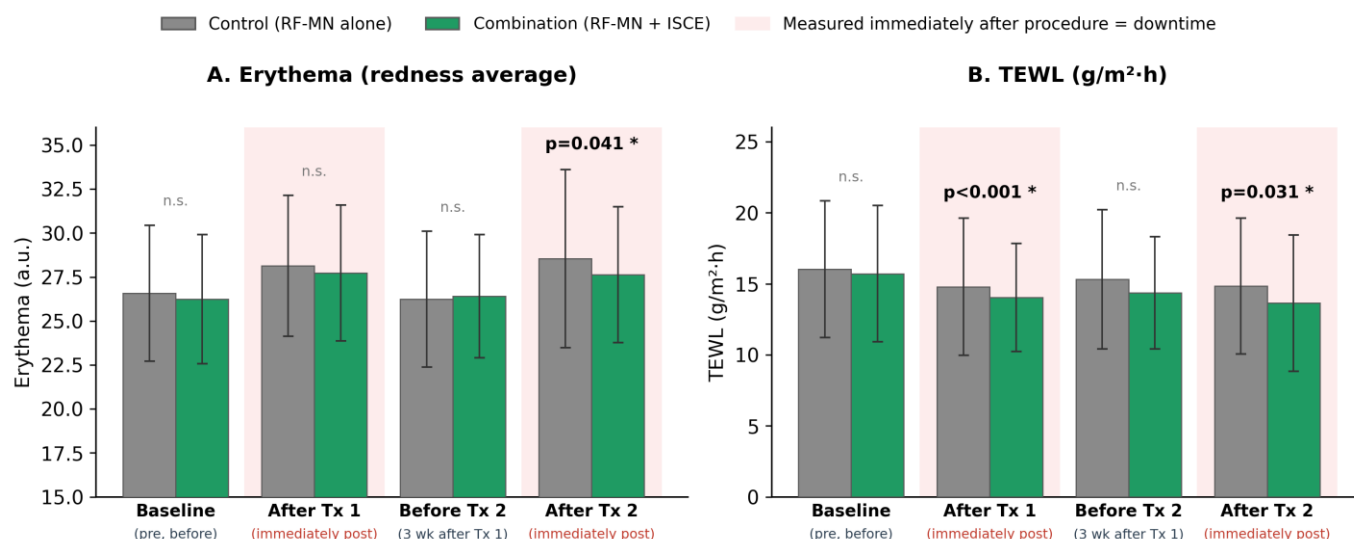


Figure 3. Downtime/barrier indicators (mean $\pm$ SD): (A) erythema and (B) TEWL on the combination side vs. the control side at four timepoints: baseline (pre-treatment), immediately after treatment 1, before treatment 2 (3 weeks after treatment 1), and immediately after treatment 2. Erythema was measured immediately after each procedure and therefore reflects procedure-induced redness (downtime): higher values indicate more redness, so a smaller post-procedure increase on the combination side (observed only after the second treatment; nominal $p = 0.041$, preliminary) denotes less downtime rather than a reduction of baseline redness. Between-side p -values are shown; * $p < 0.05$ (nominal, unadjusted for multiplicity); n.s. = not significant. Abbreviations: RF-MN, radiofrequency microneedling; ISCE, investigational cosmetic serum; TEWL, transepidermal water loss; SD, standard deviation; Tx, treatment; a.u. (A.U.), arbitrary units.

3.3. Exploratory Secondary Endpoints

In exploratory analyses unadjusted for multiplicity, all secondary endpoints improved significantly more on the combination side after the second treatment, and all except elastic recoil ($p = 0.136$) also after the first treatment (Figure 4; Table 4). Hydration improved significantly more after both the first and second treatments ($p < 0.001$ and $p = 0.020$, respectively). The structural remodeling indicators—superficial (2 mm) and deep (8 mm) elasticity and skin density—improved significantly more on the combination side at both time points (all $p < 0.001$), with the relative between-side difference being largest for density. Among the photoaging indicators, coarse wrinkles (3 mm), fine wrinkles (1 mm), and pore volume improved significantly more on the combination side ($p \leq 0.006$, $p \leq 0.034$, and $p \leq 0.044$, respectively), as did the pigmentation indicators melanin ($p \leq 0.028$) and pigmented-spot area ($p \leq 0.005$). Given the number of comparisons and the small sample ($n = 20$), these exploratory results should be interpreted as hypothesis-generating.

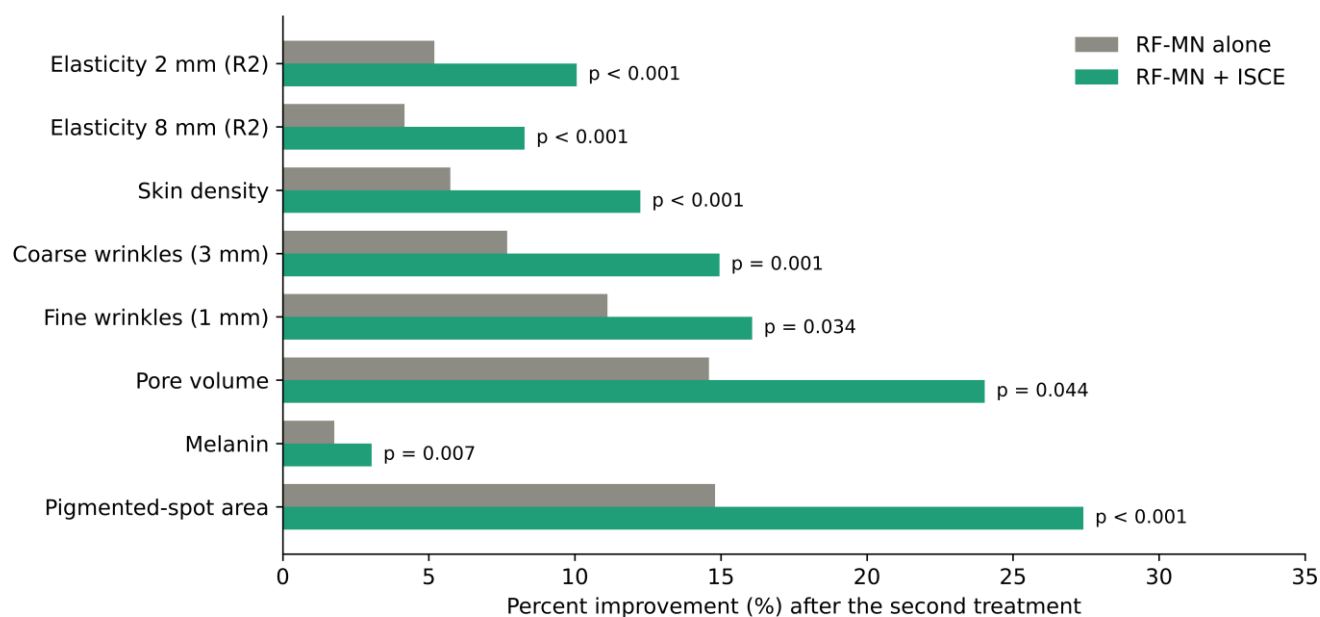


Figure 4. Percent improvement in the structural, photoaging, and pigmentation indicators after the second treatment, combination side vs. control side, with between-side *p*-values (exploratory endpoints; unadjusted for multiplicity). Abbreviations: RF-MN, radiofrequency microneedling; ISCE, investigational cosmetic serum; R2, gross elasticity (Ua/Uf) measured with the Cutometer.

Table 4. Results by skin functional domain: percent improvement on the RF-MN-alone and RF-MN + ISCE sides (after the second treatment), within-side significance on the RF-MN-alone side (from baseline), and between-side *p*-values (treatment 1/treatment 2).

Domain	Indicator	RF-MN Alone	RF-MN + ISCE	Within-Side <i>p</i> (RF-MN Alone) †	Between-Side <i>p</i> (1st/2nd)
Barrier	TEWL	2.91%	5.15%	<0.001	<0.001/0.031
	Skin hydration	5.02%	6.56%	<0.001	<0.001/0.020
Downtime	Erythema	+8.75%	+4.67%	0.008	0.793/0.041
	Elastic recoil (ΔVol)	22.71%	38.65%	<0.001	0.136/<0.001
Structure	Elasticity 2 mm (R2)	5.19%	10.06%	<0.001	<0.001/<0.001
	Elasticity 8 mm (R2)	4.17%	8.28%	<0.001	<0.001/<0.001
	Skin density	5.74%	12.24%	<0.001	<0.001/<0.001
Photoaging	Coarse wrinkles 3 mm	7.68%	14.95%	<0.001	0.006/0.001
	Fine wrinkles 1 mm	11.12%	16.07%	<0.001	0.033/0.034
	Pore volume	14.59%	24.03%	0.001	0.016/0.044
Pigmentation	Melanin	1.76%	3.04%	0.001	0.028/0.007
	Pigmented-spot area	14.80%	27.41%	<0.001	0.005/<0.001

Note: Values in the RF-MN-alone and RF-MN + ISCE columns are percent improvement after the second treatment; between-side *p*-values (treatment 1/treatment 2) compare the two sides. † Within-side *p* denotes the significance of change from baseline on the RF-MN-alone side (paired *t*-test/Wilcoxon signed-rank, or repeated-measures ANOVA/Friedman with post hoc correction); RF-MN alone produced significant within-side changes in every efficacy endpoint (improvement in all except erythema, which increased after each procedure). For erythema (a downtime indicator measured immediately after each session), values denote the post-procedure change in redness; positive values indicate an increase, so a smaller value on the RF-MN + ISCE side reflects less downtime. Secondary endpoints (all indicators other than TEWL and erythema) were exploratory, and their between-side *p*-values are unadjusted for multiplicity. Abbreviations: TEWL,

transepidermal water loss; Δ Vol, depression volume; R2, gross elasticity (U_a/U_f) measured with the Cutometer; RF-MN, radiofrequency microneedling; ISCE, investigational cosmetic serum.

3.4. Subjective Assessment

Across the 13-item satisfaction questionnaire, 95.0–100.0% of participants responded positively overall, with high ratings for overall satisfaction and willingness to repurchase or recommend, indicating high participant acceptability.

4. Discussion

In this randomized, split-face, controlled trial, the side receiving the multicomponent bioactive cosmetic immediately after the procedure showed a greater short-term reduction in TEWL than the control side, together with a nominally significant, preliminary difference in procedure-induced erythema. Exploratory secondary endpoints in the structural, photoaging, and pigmentation domains also favored the combination side. Importantly, this trial was designed as a pragmatic evaluation of the product as it is used in clinical practice, namely applied immediately after RF microneedling, rather than as a mechanistic test of ingredient-specific efficacy. Accordingly, the comparator was the procedure alone, reflecting the practical clinical decision of whether to add the post-procedure serum. Consequently, the between-side differences reflect the effect of the complete topical product—including its vehicle, which may itself provide hydrating or occlusive effects—rather than the effect of its bioactive ingredients alone.

Notably, RF-MN acts as an active therapeutic component by inducing dermal remodeling through controlled RF-mediated thermal stimulation, and it may also facilitate topical delivery. Significant within-side improvements were also observed on the RF-MN-alone control side in all efficacy endpoints except erythema, consistent with the established remodeling effects of RF-MN.

The pattern of between-side differences across multiple domains was derived largely from exploratory secondary endpoints that were not adjusted for multiplicity in a sample of 20 participants. It should therefore be interpreted as hypothesis-generating rather than as evidence of broad multi-domain efficacy. With this caveat, the pattern is consistent with the ingredient-axis design of the formulation (Table 2). It may also reflect enhanced penetration of active ingredients through RF-MN-created microchannels, which has been described in previous delivery studies [8–10]. However, because skin penetration and tissue concentrations of the actives were not measured in this study, enhanced transdermal delivery should be regarded as a plausible mechanism rather than a demonstrated effect.

The temporal pattern of the between-side differences should be interpreted cautiously. The barrier indicators (TEWL, hydration) differed between sides from immediately after the first treatment, whereas the downtime indicators (erythema, elastic recoil) differed only after the second treatment; for erythema, this difference was only nominally significant ($p = 0.041$) and is preliminary. The early barrier effect may partly reflect the hydrating and occlusive properties of the formulation itself. Previous studies and reviews have reported that GHK-Cu suppresses inflammatory mediators and matrix metalloproteinases [23,25]; stem cell-conditioned medium and growth factor analogues promote fibroblast activation, collagen synthesis, and angiogenesis [14,16,27]; and *Lactobacillus*-derived extracellular vesicles have been associated with barrier protein upregulation, anti-inflammatory activity, and suppression of melanogenesis [28–31]. These actions correspond to the domains in which improvement was observed, but the present design cannot determine which component, if any, was responsible for the observed effects.

Among the applied actives, the epidermal progenitor cell-conditioned medium (EPC-CM) is a defined secretome that has been reported to be enriched in extracellular-matrix-protective and pro-regenerative factors, including tissue inhibitors of metalloproteinases, latent TGF- β binding protein-1, and nidogen-1 [20–22]. In cultured human dermal fibroblasts, EPC-CM has also been shown to reduce oxidative stress and restore type I procollagen expression [20]. These reported properties are consistent with the observed pattern of between-side differences; however, because the formulation was tested as a single multicomponent product against an RF-MN-alone control, any specific contribution of EPC-CM remains hypothetical.

These results extend prior split-face studies combining microneedling with a single regenerative ingredient (stem cell-conditioned medium [16] or adipose-derived stem cell exosomes [19]) by showing, with identical procedural exposure on both sides, that a multicomponent cosmetic was associated with a larger short-term decrease in TEWL and, in exploratory analyses, greater improvement in several other aging domains. Clinically, this study suggests that the post-procedure window may be used to apply bioactive ingredients, which may support short-term barrier recovery; potential benefits for downtime and for structural, photoaging, and pigmentation outcomes are suggested only by preliminary or exploratory findings, and whether these benefits persist requires longer follow-up.

This study also has several strengths. First, the split-face design compared the two hemifaces of the same participant, thereby controlling for inter-individual variability. Second, allocation was randomized, and outcome assessors and statisticians were blinded to treatment allocation (although blinding may have been imperfect at the visits immediately after application). Third, downtime indicators immediately after each procedure and structural, photoaging, and pigmentation outcomes up to 3 weeks after the second treatment were captured in the same participants. Fourth, five skin functional domains were quantified using non-invasive objective instruments.

This study has several limitations. First, the sample was small ($n = 20$), no formal sample-size calculation was performed, and many secondary outcomes were assessed at several time points without adjustment for multiplicity. The study may therefore have been underpowered for some outcomes, the effect estimates may be imprecise, and isolated significant findings could have arisen by chance; the secondary results should thus be regarded as exploratory. In addition, the between-side differences in the primary endpoints were modest in absolute terms, and no minimal clinically important differences have been established for these instrumental measures; their clinical relevance should therefore be interpreted with caution. Furthermore, the two primary endpoints were tested without adjustment for multiplicity, and each was assessed at two treatment sessions; under a conservative Bonferroni correction ($\alpha = 0.025$ for two endpoints, or $\alpha = 0.0125$ if both sessions are counted), the TEWL difference after the first session would remain significant, whereas the TEWL difference after the second session ($p = 0.031$) and the erythema difference ($p = 0.041$) would not reach the corrected significance threshold. The erythema finding in particular therefore needs to be confirmed in larger trials. Second, the study was conducted at a single center and enrolled only Korean women aged 40–69 years. Because skin structure, barrier function, pigmentation, and responses to energy-based procedures may differ by ethnicity, sex, and Fitzpatrick skin type, the findings may not be generalizable to other ethnic groups, men, or younger individuals. Third, follow-up ended 3 weeks after the second treatment. This period is short for evaluating dermal remodeling after RF-MN, which may continue for several months after treatment [1,2]; the changes in elasticity and skin density should therefore be interpreted as early responses, and their persistence remains unknown. Fourth, the control side received RF-MN alone without a vehicle formulation. The between-side differences may therefore

partly reflect the topical formulation itself (e.g., hydration or occlusion) rather than its bioactive ingredients, and ingredient-specific effects cannot be isolated. In addition, post-procedure downtime indicators were measured 30 min after the serum had been applied to the combination side only; although both sides were measured simultaneously after stabilization, residual product on the skin surface may still have influenced the erythema, TEWL, and hydration readings, and the visible application may have limited assessor blinding at these visits. Fifth, the quantitative concentrations of the active components in the final formulation could not be disclosed because they are proprietary; only the disclosed ingredient list and published secretome data for the conditioned medium are provided. This limits reproducibility and precluded dose–response analysis. Sixth, skin penetration, tissue concentrations of the actives, and histological changes were not measured, so the proposed delivery-related mechanisms remain inferential. Future studies should include a vehicle-controlled arm, a larger multicenter and multiethnic population with a formal sample-size calculation, longer follow-up (e.g., 3–6 months), and tissue-level evidence (e.g., Masson’s trichrome staining or type I collagen immunohistochemistry) [4,5].

5. Conclusions

In this randomized, split-face trial, applying a multicomponent bioactive cosmetic immediately after RF-MN resulted in a greater short-term reduction in TEWL than RF-MN alone, a difference that was evident from the first session; this first-session difference would remain significant under a conservative Bonferroni correction. The smaller procedure-induced increase in erythema, observed only after the second session, reached only nominal significance; it is therefore preliminary and requires confirmation in larger trials. Exploratory secondary endpoints in the structural, photoaging, and pigmentation domains also favored the combination side; because these analyses were not adjusted for multiplicity and included only 20 participants, they should be regarded as hypothesis-generating. No adverse events were observed. These clinical observations suggest that adjunctive use of the formulation after RF-MN may be beneficial. However, this study did not measure transdermal delivery, did not identify which component was responsible for the observed effects, and did not include a vehicle control. The proposed biological mechanisms therefore remain hypotheses that should be tested in vehicle-controlled studies with longer follow-up.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cosmetics13050277/s1>, Table S1 is based on the CONSORT 2025 statement and the CONSORT extension for within-person randomised trials. References [34,35] are cited in the Supplementary Materials.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Human Skin Clinical Trial Center Co., Ltd. (protocol code HM-IRB-P25-0061 and date of approval 27 January 2025).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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