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Research Article

Hyaluronic Acid Dissolving Microneedles and Nonablative Fractional Laser for Infraorbital Wrinkles: A Prospective, Randomized, Split-Face Study

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Background. Recently, hyaluronic acid dissolving microneedles (HA-DMNs) have been widely used in antiwrinkle research studies. However, the comparison of HA-DMNs with nonablative fractional laser (NAFL), which is regarded as the gold standard in the treatment of facial wrinkles, is still lacking. *Objective*. The purpose was to compare the therapeutic effects and adverse effects of HA-DMNs and NAFL on infraorbital wrinkles. *Methods*. A prospective, randomized, split-face trial was performed with HA-DMNs on one side and NAFL on the other. The wrinkle numbers, photo-numeric scores, and VISIA assessment scores were compared at baseline and 2, 4, 8, and 12 weeks post-treatment. Reflectance confocal microscopy (RCM) was used to monitor collagen fibers. Adverse effects and subjects' satisfaction scores were evaluated using scales. *Results*. The final analysis included 28 patients. The wrinkle numbers and photo-numeric scores decreased on both the HA-DMNs side and the NAFL side in week-2, 4, 8, and 12. The VISIA scores decreased on the HA-DMNs side in week-8 and on the NAFL side in week-2. There were no significant differences in these indexes between the two sides. The RCM images demonstrated a similar increase in collagen density on the two sides. Burning, erythema, edema, and crust scores were higher on the NAFL side than on the HA-DMNs side. There was no significant difference in the subjects' satisfaction scores of the two sides. *Conclusion*. HA-DMNs are effective treatment options for infraorbital rejuvenation. From the change of wrinkle numbers and scores, HA-DMNs provided comparable efficacy as NAFL in an observation period of 12 weeks. Meanwhile, HA-DMNs offered a more favorable adverse effect profile than NAFL therapy. Mild but persistent pain, erythema, and edema during the HA-DMNs therapy are noteworthy and require improvement.

1. Introduction

Skin rejuvenation has been a topic of discussion and of great interest throughout the world for many years. Facial wrinkles, especially infraorbital wrinkles, are known as one of the most prominent features of skin aging. Genetic factors, ultraviolet exposure, and repeated facial expressions aggravate the formation of infraorbital wrinkles. With considerations of aesthetics, there is an increasing demand for effective, safe, and rapid cosmetic treatments for individuals with infraorbital wrinkles.

Nonablative fractional laser (NAFL) targets water, generating microscopic thermal zones in the dermis, which results in collagen remodeling [1]. As one of the most important treatments for photoaged skin, it has been widely used in dermatology and has proven to be effective in improving wrinkles with minimal side effects [2–7]. NAFL stimulates the production of collagen and elastin without damaging the superficial layer of the skin, providing greater comfort and less downtime compared to ablative fractional laser [3]. However, NAFL treatment requires sophisticated, expensive, dedicated instrumentation, and highly

professional doctors. Dissolving microneedles are micro-sized needles made of biodegradable polymers, which can dissolve and release the active ingredients following skin insertion [8]. Hyaluronic acid is a natural water-soluble polymer with excellent biocompatibility and is the major component of the dissolving microneedles [9]. The use of hyaluronic acid dissolving microneedles (HA-DMNs) for the treatment of periorbital wrinkles has surged in the last few years [10–12]. This new approach has become popular with individuals who live a fast-paced life these days due to the reduction in pain, home use, and reduced downtime.

None of the previous studies has compared the two techniques. The objective of this study was to compare the therapeutic efficacy and side effects of HA-DMNs and NAFL on infraorbital wrinkles.

2. Materials and Methods

2.1. Statement of Ethics. The study protocol was in line with the Helsinki Declaration of 1975 and approved by the Shanghai Skin Disease Hospital Research Ethics Committee. The trial was registered (NCT04989361) at Clinical-Trials.gov. Informed consent was given by all patients.

2.2. Patients. This prospective, randomized, split-face trial was carried out in an outpatient clinic at Shanghai Skin Disease Hospital. Subjects aged 18 to 65 were enrolled. Exclusion criteria include the following: (i) known allergy to the substance under test or related ingredients; (ii) women who are pregnant or breastfeeding; (iii) patients with other cutaneous conditions likely to influence the assessment of the treatment area or have received corticosteroid or retinoic acid therapy within one month before enrollment; (iv) enrolled in any clinical trial (as subjects) within one month before enrollment; and (v) associated with severe systemic or psychiatric disorders that may interfere with assessment.

2.3. Treatment. Subjects' bilateral infraorbital regions were divided into HA-DMNs and NAFL sides by random number tables. On the HA-DMNs side, the HA-DMNs patches (consisted of pyramidal microneedles with a height, base, and tip-to-tip distance of 350 μm, 300 $*$ 200 μm, and 500 μm, respectively ,Taizhou Weikai Biotechnology Co., Ltd.) were applied in three phases. The first phase consisted of one patch per day for 20 days. In the second phase, one patch was given once every two days for 20 days. In the third phase, one patch was used every three days, and the duration was 21 days. After routine cleaning, the subjects were instructed to apply and press the patches in the infraorbital area and remove them after one hour each time. One session of NAFL therapy (1565 nm, 200 spots/cm^2, 45 mJ/cm^2, ResurFX, Lumenis Inc., USA) was conducted on the NAFL side. Before the treatment, the subjects were topically anesthetized using anesthesia cream for one hour. Then, iodophor and saline are used to disinfect the affected area. Subjects were informed to avoid water and any cosmetic products within 24 hours immediately following NAFL treatment.

All subjects were requested to avoid sun exposure and only use basal skin-care products during the whole study. Follow-up was performed at 2, 4, 8, and 12 weeks after the end of the treatment on each side, respectively.

2.4. Assessment of Efficacy. Digital photographs of the face were obtained by the VISIA® Skin Analysis System (Canfield Imaging Systems, Fairfield, NJ, USA), and the treated area was assessed using reflectance confocal microscopy (RCM) before treatment and at each follow-up visit. The water content of the treated skin area was measured using the Corneometer® CM825 (CK Electronic GmbH, Cologne, Germany) each time after 30 minutes at constant temperature and humidity.

The number of infraorbital wrinkles was counted, and the severity of infraorbital wrinkles was rated according to the VISIA photos on a scale (Skin Aging Atlas: Volume 2, Asian type) by two senior dermatologists in the blind. The number of wrinkles, photo-numeric scores, VISIA assessment scores, skin water content, and RCM images were compared between the two sides at baseline and after the treatment.

2.5. Assessment of Adverse Effects and Subjects' Satisfaction. Procedural pain was evaluated on a 10-point numerical scale (NRS: 0 = no pain and 10 = worst pain). Pruritus, burning, erythema, edema, desquamation, and crust were evaluated through visual comparison from baseline at each visit, using a 4-grade scale (0 = absent; 1 = mild; 2 = moderate; and 3 = severe). The highest scores experienced during treatment were used as the endpoint of the assessment.

Subjects' satisfaction was measured on each side with a self-made satisfaction questionnaire (1 = unsatisfied, 2 = somewhat satisfied, 3 = mostly satisfied, and 4 = very satisfied).

2.6. Statistical Analysis. Missing data for one subject that was lost during follow-up were imputed using last observation carried forward (LOCF). The data were analyzed using the Social Sciences Statistical Package, version 26.0 (SPSS Inc.). The number of infraorbital wrinkles and skin water content were compared with the paired sample t-test. The Wilcoxon signed-rank test was used to compare photo-numeric scores, VISIA assessment scores, adverse effects, and subjective satisfaction scores. The difference was considered to be statistically significant when P value was less than 0.05. The data were given in the form of mean ± SD or median (P25, P75).

3. Results

3.1. Study Cohort. A total of 61 subjects with Fitzpatrick III or IV skin types were enrolled in this study, and 27 of them completed the whole trial (Figure 1). None of them had antiaging therapy, including botulinum toxin and hyaluronic acid injections, three months before the study. Data collected for 28 subjects were included in the final analysis,

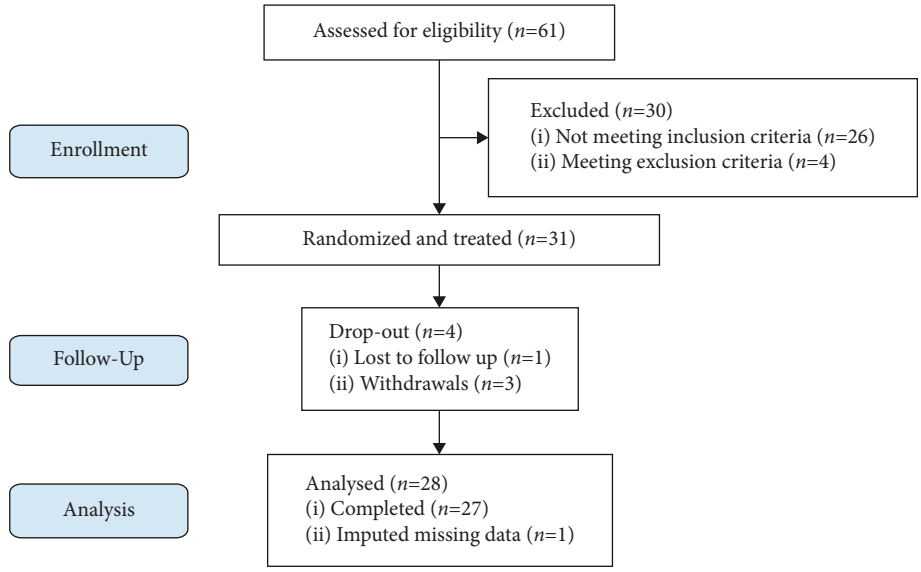

Figure 1: Flowchart of the study.

which consisted of 25 females and 3 males aged from 23 to 65 years. No significant difference was found between the two sides at the baseline.

3.2. Efficacy. The number of wrinkles, photo-numeric scores, and VISIA assessment scores are presented in Figure 2. A marked decrease in the number of wrinkles is observed at week-2, week-4, week-8, and week-12 follow-ups compared to the baseline on both the HA-DMNs side (22.36 ± 7.55 for baseline, 19.82 ± 6.81, 19.54 ± 7.24, 19.11 ± 6.72, and 19.00 ± 6.43 for follow-ups, respectively) and the NAFL side (22.89 ± 8.33 for baseline, 20.96 ± 7.82, 19.43 ± 6.63, 19.50 ± 7.59, and 19.67 ± 7.69 for follow-ups, respectively). However, there was no significant difference between the two sides during the whole period (Figure 2(a)). The wrinkle number decreased with the use of microneedle patches (20.68 ± 7.33, 20.04 ± 6.92, and 19.75 ± 7.36 for days 14, 28, and 56, respectively , Figure 2(b)). The photo-numeric scores of both sides were reduced from the fourth week after treatment (3.00 (2.00, 3.00), 3.00 (2.00, 3.38), 2.75 (2.00, 3.00), and 2.50 (2.00, 3.00) for baseline, week-4, 8, and 12 on the HA-DMNs side, and 3.00 (2.00, 3.50), 2.75 (2.00, 3.00), 2.50 (2.00, 3.00), and 2.50 (2.00, 3.00), respectively on the NAFL side). No significant difference in photo-numeric scores was manifested between the two sides (Figure 2(c)). VISIA assessment scores on the HA-DMNs side decreased significantly at the week-8 follow-up (15.05 (10.95, 24.37) vs. 24.03 (14.66, 30.15), $P < 0.05$) while a significant score decrease was indicated on the NAFL side at the week-4 follow-up (18.77 (11.47, 25.09) vs. 19.41 (14.32, 27.84), $P < 0.05$) (Figure 2(d)).

There was a decline in the water content on the HA-DMNs side at week-8 (62.91 ± 13.73 vs. 71.73 ± 12.93, $P < 0.05$) and at week-12 (58.56 ± 12.40 vs. 71.73 ± 12.93, $P < 0.05$). Moreover, the water content on the NAFL side decreased at week-12 follow-up (62.47 ± 13.93 vs. 70.25 ± 14.19, $P < 0.05$). Photographs obtained by the VISIA system at baseline and after the therapy are shown in Figure 3. Wrinkles identified by VISIA decreased at week-4 and week-8 on the two sides. A slight increase of the identified wrinkles can be observed at week-12 on the HA-DMNs side, while it is still reduced on the NAFL side. RCM images before and after the treatment are demonstrated in Figure 4. Increased density of collagen fiber can be found on either side at week-4 and week-8 following the therapy.

3.3. Adverse Effects and Subjects' Satisfaction. Scores, proportions, and durations are shown in Table 1. Procedural pain was approximately equal on the HA-DMNs side and the NAFL side. The NAFL side showed higher scores in burning, erythema, edema, and crust than the HA-DMNs side. The scores of itching and desquamation were not significantly different. The typical changes of erythema and edema on both sides are shown in Figure 5. Marked erythema with well-defined borders appeared right after the NAFL therapy and vanished after fourteen days. The erythema on the side of the HA-DMNs became gradually more pronounced with the continuous application of microneedle patches. There was no statistically significant difference in subjects' satisfaction scores between the two sides (3.00 (2.00, 4.00) vs. 3.00 (2.75, 3.25), $P = 0.33$) (Figure 6).

4. Discussion

Various techniques have been exploited for infraorbital rejuvenation, including typical products, chemical peels, botulinum toxin, dermal filler injections, lasers, and surgical options. NAFL has been developed since the advent of fractional photo thermolysis and ablative lasers. Numerous studies have confirmed the efficacy and safety of NAFL in infraorbital rejuvenation [5, 13, 14]. HA-DMNs were proposed during the same period and advanced rapidly in the last decade. As the most common type, HA-DMNs with

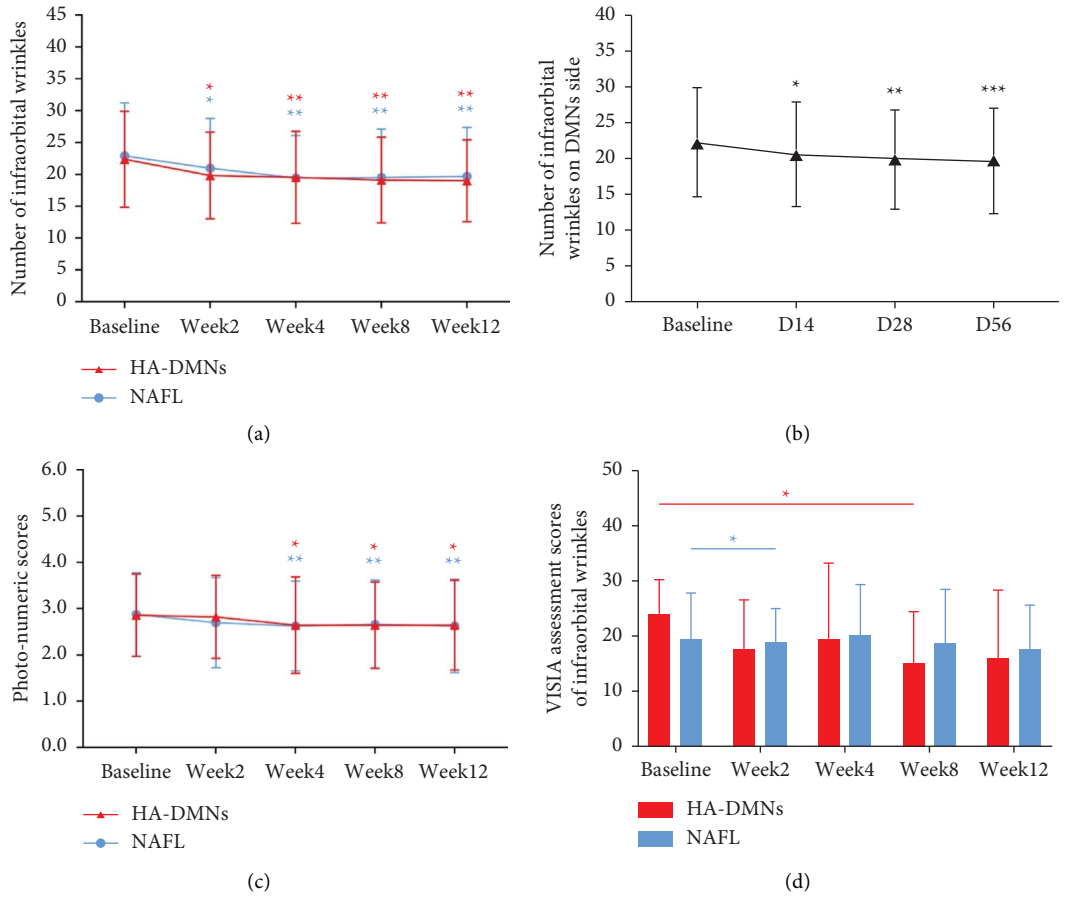

Figure 2: (a) The change of wrinkles numbers on HA-DMNs side (red) and NAFL side (blue) after therapy. (b) The change of wrinkle numbers on HA-DMNs side during the therapy. (c) The photo-numeric scores on two sides. (d) VISIA assessment scores on two sides. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.005$ compared to the baseline.

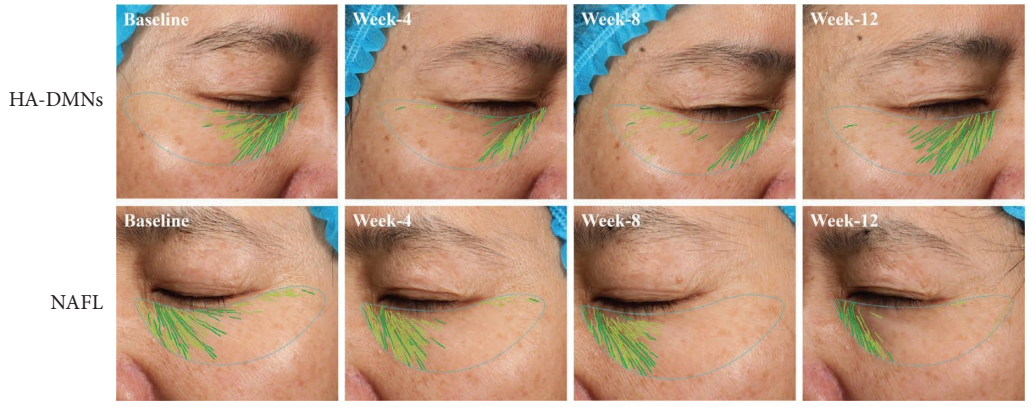

Figure 3: VISIA images of HA-DMNs side and NAFL side, respectively, before and after therapy. The green lines represent wrinkles identified by VISIA system.

hyaluronic acid were found efficacious and tolerable in infraorbital wrinkles and crow's feet wrinkles [10–12].

In this perspective split-face study, we compared the treatment effects and adverse reactions of NAFL and HA-DMNs on infraorbital wrinkles. The wrinkle numbers, photo-numeric scores, and VISIA assessment scores presented similar improvements after treatments on both sides. RCM images were consistent with clinical observations, as the density of collagen fibers in the treated skin area increased obviously after the therapy (Figure 4). The wrinkle numbers decreased significantly on day-14 during HA-DMNs therapy, providing a similar onset time to NAFL under 2-week visit intervals. A previous study revealed that NAFL can be effective for up to six months [4]. We are

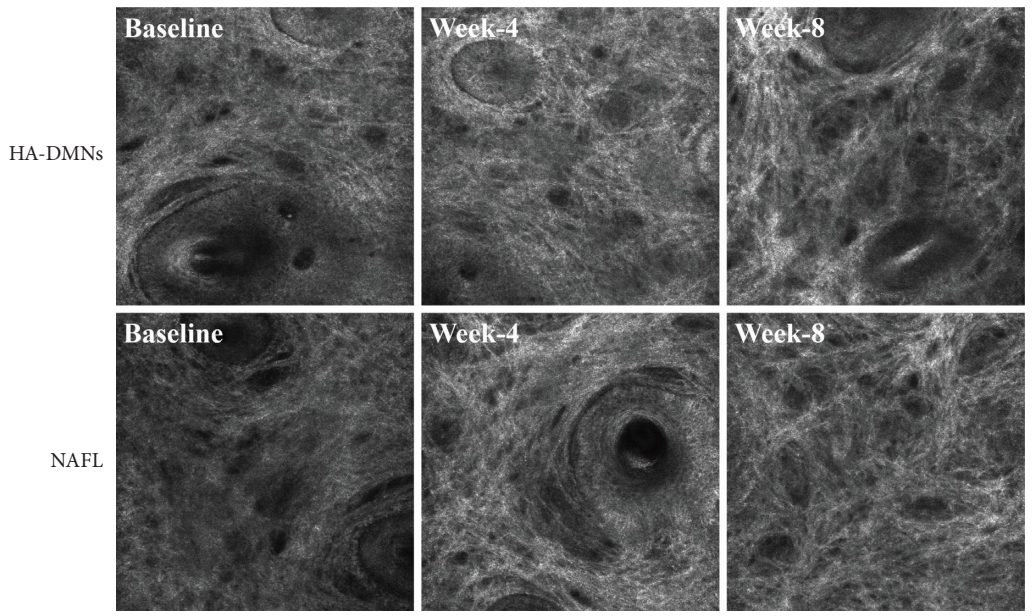

Figure 4: Reflectance confocal microscopy images of HA-DMNs side and NAFL side, respectively, before and after therapy.

Table 1: Scores, proportions, and durations of adverse effects on two sides.

Adverse effect	Scores			Proportion (%)		Duration	
	HA-DMNs	NAFL	*P* value	HA-DMNs	NAFL	HA-DMNs	NAFL
Pain	1.5 (0.0, 2.8)	1.5 (0.3, 2.0)	0.88	60.71	75.00	2–10 min	1–24 h
Pruritus	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	>0.99	14.29	10.71	12–72 h	48 h
Burning	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.01	7.14	42.86	5–12 min	12–24 h
Erythema	0.0 (0.0, 1.0)	1.0 (1.0, 1.0)	<0.01	35.71	100.00	12–48 h	8–72 h
Edema	0.0 (0.0, 0.8)	1.0 (1.0, 1.0)	<0.01	25.00	82.14	12–72 h	12–72 h
Desquamation	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.50	0.00	7.14	—	1–24 h
Crust	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	<0.01	0.00	39.29	—	1–10 d

The scores are shown as median (p25, p75). HA-DMNs: hyaluronic acid dissolving microneedles. NAFL: nonablative fractional laser. Duration on HA-DMNs side refers to the duration of different adverse effects with each use.

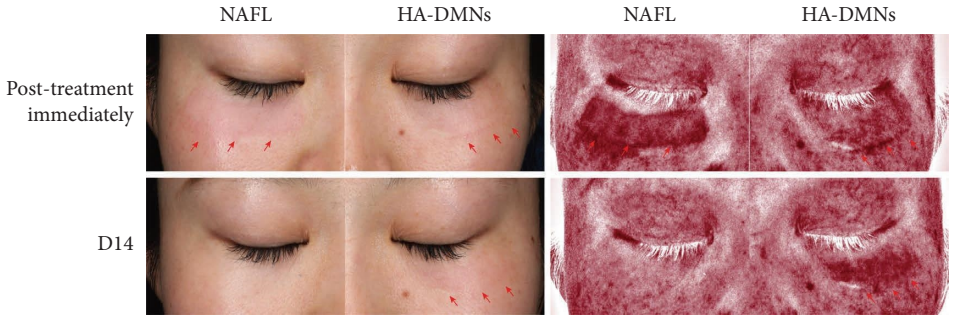

Figure 5: Normal and red area of VISIA images of HA-DMNs side and NAFL side taken immediately after the therapy and after fourteen days. The red arrays indicate the erythema.

inclined to believe that NAFL provided longer anti-wrinkle effects than HA-DMNs, though no such distinction was evident in our data. As demonstrated in Figure 3, infraorbital wrinkles on the NAFL side were improved continuously up to the last follow-up, which was 12 weeks after treatment, while wrinkles got a slight rebound on the HA-DMNs side. Skin water content showed a decrease at week-8 on the HA-DMNs side and at week-12 follow-up on both sides. We speculate that this change was correlated with different environmental humidity due to seasonal variation, as the trial began in July and mostly ended in December.

Overall, the adverse effects were more serious on the NAFL side. Mild to moderate pain was scored by 75% of subjects on the NAFL side, which gradually subsided in 24 hours. Similar pain was evaluated by 60.71% of subjects on the HA-DMN side in the first phase, and it vanished after

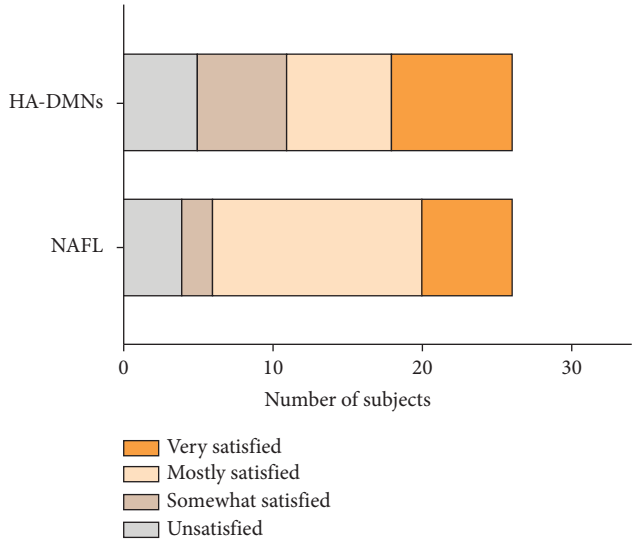

Figure 6: Subjects' satisfaction scores on HA-DMNs side and NAFL side with no significant difference.

2–10 minutes every time. The proportion and the scores of burning sensation, erythema, and edema were all higher on the NAFL side. 100% of subjects showed erythema, and 82.14% showed edema in particular, which resolved in 3 days. After NAFL therapy, 7.14% of subjects reported desquamation and 39.29% of subjects reported crust in the treated area, while no desquamation or crust was reported during and after HA-DMNs therapy. These findings are in line with previous studies [4, 13]. However, it is noteworthy that three subjects reported sustained pain, erythema, and edema during the entire HA-DMNs treatment period, despite the mild severity. One of them chose "unsatisfied" for HA-DMNs because of this "unpleasant experience." The side effects of HA-DMNs were slighter than the NAFL in this study but seem more prevalent than in existing studies.

Treatment protocols for HA-DMNs vary, lacking a unified standard [11, 12, 15]. The price of a single HA-DMNs patch varies from 2.22 to 15.55 $ on the market in China. Thus, the treatment cost of HA-DMNs may vary considerably. It cost 82.14 to 575.35 $ for 37 HA-DMNs patches with a session of 61 days in this study. The cost of a single NAFL was 148.28 to 593.13 $, which was similar to the HA-DMNs side.

Individuals who seek aesthetic treatments aspire to improve their self-esteem and, consequently, their life quality. HA-DMNs are undoubtedly an attractive option, especially for those living a modern, fast-paced life. Hyaluronic acid provides powerful moisture retention capacity, thus leading to an increase in skin elasticity and volume [16]. Microscopic mechanical stretching of fillers and damage caused by microneedle penetration stimulate the production of more hyaluronic acid and collagen synthesis in particular [17, 18]. On these foundations, the addition of more components like ascorbic acid or niacinamide brings broader skin texture and color improvement for HA-DMNs [19, 20]. Shorter intervals of observation are needed to further compare treatment velocities between HA-DMNs and NAFL. More comprehensive assessments of skin barrier function and skin elasticity, like ultrasonography, warrant further investigation. The mechanism of HA-DMNs still needs exploration.

5. Conclusion

HA-DMNs are effective treatment options for infraorbital rejuvenation. From the change of wrinkle numbers and scores, HA-DMNs provided comparable efficacy as NAFL in an observation period of 12 weeks. Meanwhile, HA-DMNs offered a more favorable adverse effect profile than NAFL therapy. However, mild but persistent pain, erythema, and edema merit further improvement since they may affect the willingness to use HA-DMNs. Further investigations to assess more skin physiological indicators and explore the exact molecular mechanisms of HA-DMNs are warranted.

Data Availability

The data supporting the findings of this study available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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