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A pilot split-scalp study of combined fractional radiofrequency microneedling and 5% topical minoxidil in treating male pattern hair loss

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Summary

Background. Various trials have been conducted on the management of male pattern hair loss (MPHL), but the outcomes often seem to be limited. Adjuvant therapies are urgently needed.

Aim. To evaluate the efficacy and safety of combined fractional radiofrequency microneedling (FRM) and 5% topical minoxidil in the treatment of male pattern hair loss.

Methods. In total, 19 Chinese men were enrolled in this randomized, controlled, split-scalp trial. Participants received monotherapy with 5% topical minoxidil twice daily to one half of the scalp, while on the other half of the scalp the treatment with twice-daily 5% topical minoxidil was combined with five sessions of FRM at 4-week intervals. Mean hair count and hair thickness, global assessment by the investigators, subject self-assessment and adverse effects were assessed.

Results. After 5 months of treatment, mean hair count increased from 44.12 ± 21.58 to 73.14 ± 25.45 on the combined-therapy side and from 46.22 ± 18.77 to 63.21 ± 19.22 on the monotherapy side, while mean hair thickness increased from 53 ± 13 μm to 71 ± 15 μm and from 52 ± 16 μm to 66 ± 14 μm, respectively. Compared with the monotherapy side, the combined-therapy side had a higher degree of improvement in both hair count ($P = 0.01$) and hair thickness ($P = 0.02$).

Conclusions. Combined treatment with fractional radiofrequency microneedle and 5% topical minoxidil could be an effective and safe treatment option for male pattern hair loss.

Introduction

Pattern hair loss, also called androgenetic alopecia (AGA), affects both men (male pattern hair loss; MPHL) and women (female pattern hair loss; FPHL). MPHL is the most common hair loss disorder in men. It is a hereditary androgen-dependent disorder, characterized by nonscarring progressive miniaturization of the hair follicle. MPHL often manifests in a pattern distribution on the parietal or vertex regions of the scalp, with gradual recession of the frontal hairline. The prevalence of MPHL in China was reported to be 21.3%, with an increased incidence of 41.4% in men aged ≥ 70 years.[1]

MPHL affects the quality of life and self-esteem of patients, and their expectation about therapy results is usually unrealistically positive. Despite the high prevalence of MPHL, approved therapeutic options are limited. There are only two drugs approved by the Food and Drug Administration (FDA) for MPHL treatment: minoxidil for topical application and finasteride for oral medication. These two medications are effective to a certain extent, but patients who exhibit a poor

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response to these methods have limited alternative treatment. Surgical hair transplantation is another option, but is expensive and is associated with various adverse effects, owing to its invasive nature.

Energy-based devices have grown in popularity in dermatological and cosmetic applications over the past decade, with increased interest in their potential role in treating hair loss. Paradoxical hair growth after laser treatment with intense pulsed light, diode laser or long-pulse alexandrite laser has been reported, opening a new field of potential study.[2] As the causal relationship of photoinduced hair growth is not yet entirely clear, the correct type of laser wounding for hair regrowth stimulation is still to be satisfactorily determined. Low-level light therapy (LLLT) has been reported to have a stimulatory effect on hair growth,[3,4] which may be explained by biostimulation of light on the outer root sheath kerationocytes and dermal papilla cells.[5] High-energy lasers have also been used for the treatment of alopecia. The 1550 nm fractional erbium–glass laser has been shown to be effective in both MPHL and FPHL.[6,7] Other lasers and light sources such as excimer laser, helium–neon laser, and psoralen plus ultraviolet A light therapy have been tested for hair loss,[8] but the outcomes often seem to be limited. As a result, adjuvant therapies and procedures are in urgent need of proposal and detailed investigation.

Fractional radiofrequency microneedling (FRM) is a recently introduced, minimally invasive techniquie that delivers bipolar radiofrequency (RF) current through insulated microneedles.[9] This technology creates a controlled thermal zone at a selected depth, and can affect deeper tissue compared with light-based devices. The current study was conducted to evaluate the efficacy and safety of combined FRM and 5% topical minoxidil in the treatment of MPHL.

Methods

The study was approved by the Medical Ethics and Human Research Committee of China Medical University. All patients were informed of the risks, benefits and possible complications of the process before enrolment in the study, and written informed consent was obtained from each patient.

Participants

In total, 19 Chinese men with MPHL were enrolled in this study. The clinical characteristics of participants are detailed in Table 1. Exclusion criteria were use of previous systemic or topical treatment that could affect the hair cycle within the past 6 months, hair transplantation on the target areas, presence of hair disorders other than MPHL and presence of any known systemic diseases. Participants were required to maintain the same hair colour, hairstyle and hair length before each treatment and at the subsequent follow-up visit.

Treatment protocols

The study was designed as a single-centre, prospective, randomized, split-scalp study. Using a computer-generated randomization table, participants were randomly assigned to either monotherapy with minoxidil, or combined therapy with minoxidil plus FRM.

Participants were instructed to spray 1 mL (about seven sprays) of 5% minoxidil tincture (Mandi; Wansheng Medication Manufacture Corporation Ltd, China) directly to the whole balding region of the scalp twice a day. This was the only treatment provided for one half of the scalp (monotherapy side).

For the other half of the scalp, FRM was added to the therapy. This was performed five times at 4-week intervals, using an FRM device (BodyTite, Derma Optic & Electronic Ltd, Chongqing, China) with a disposable tip. The treatment tip was 1 cm^2 in size, and contained 49 insulated microneedle electrodes with a diameter of 0.25 mm each. The device delivered 1 MHz of bipolar radiofrequency pulses through the microneedles. The parameters in our study were power of 12 W, microneedle penetrating depth of 1.5 mm and pulse duration of 300 ms. For each treatment, topical lidocaine cream (25 mg prilocaine and 25 mg lidocaine; Beijing Ziguang Medication Manufacture Corporation Ltd, Beijing, China) was applied to the

Table 1 Characteristics of the participants at baseline (all male, $n = 19$).

Characteristic	
Age, years	
Mean ± SD	35.2 ± 6.8
Range	23–45
Duration of hair loss, years	
Mean ± SD	7.3 ± 3.9
Range	1–17
Familial history of hair loss, *n* (%)	9 (47.4)
Hamilton–Norwood scale, *n* (%)	
Type III	6 (31.6)
Type IV	4 (21.1)
Type V	7 (36.8)
Type VI	2 (10.5)

scalp under occlusion for 60 min and wiped off with a moistened gauze pad immediately before the FRM treatment, and the 5% minoxidil tincture was applied right after the FRM treatment. All patients were instructed to avoid shampooing, warm baths and intense physical exercise for 8 h after the FRM treatment.

Efficacy evaluation

Phototrichogram assessment. A phototrichogram system (Dino-Lite; AnMo Electronics, Taiwan) was used to evaluate the number and thickness of hairs. Phototrichogram images were taken at baseline and 5 months by the same investigator (XGX) at the same scalp location (specifically, the intersection points of the horizontal line extending from the tips of the tragus and the vertical line extending from the lateral margin of the lateral canthus). The hair in the target area of 10 mm^2 was clipped to 1 mm in length and cleaned with 75% alcohol.

Global assessment. Photographs were taken with a Nikon camera (D40S; Tokyo, Japan) under controlled light by the same investigator (XGX) in approximately the same position. Three independent investigators (LLB, YJL, YXD), blinded to the treatment, performed the clinical assessment based on the photographs taken at baseline and 5 months. The assessment was measured on a seven-point scale: significantly worsened (−3), moderately worsened (−2), slightly worsened (−1), no change (0), slightly improved (+1), moderately improved (+2), significantly improved (+3). Participants were also asked to give their assessment of the procedure, using the same seven-point scale at 5 months.

Adverse events. During and after the procedure, any adverse events (AEs) related to the treatment, including bleeding, persistent pain, erythema, erosion and broken hair shaft, were recorded. Patients were asked to rate pain according to a visual analogue pain scale (0 meaning no pain and 10 meaning the most severe pain).

Statistical analysis

Statistical analysis was performed using SPSS Statistics (v22; IBM SPSS, Armonk, NY, USA). Results are expressed as mean ± SD. All data were analysed using the paired *t*-test. $P < 0.05$ was considered statistically significant.

Results

Phototrichogram assessment

At baseline, there were no significant differences in hair count ($P > 0.05$) or hair thickness ($P > 0.05$) between the FRM plus minoxidil combined-therapy side and the minoxidil monotherapy side (Table 2). At follow-up 1 month after the final FRM treatment, both sides had significant improvements in hair count ($P < 0.001$) and hair thickness ($P < 0.001$). Mean hair count increased by 66% on the combined-therapy side and 37% on the monotherapy side, while mean hair thickness increased by 34% and 27%, respectively. The combined-therapy side therefore had a higher degree of improvement than the monotherapy side in both mean hair count ($P = 0.01$) and mean hair thickness ($P = 0.02$) (Fig. 1).

Global assessment

Global photographs showed clinical improvement in most participants, with hair regrowth at 5 months on the combined-therapy side in 94.7% (18/19) of participants and on the monotherapy side in 89.5% (17/19) of participants (Table 2). There was a significant difference between the two sides according to the investigator global assessment ($P < 0.001$), with a greater percentage of patients achieving moderate or significant improvement on the combined-therapy side relative to the monotherapy side: 73.7% (14/19) vs. 52.7% (10/19), respectively. Representative photographs are shown in Fig. 2.

There was a statistically significant difference ($P < 0.001$) at 5 months for the subject assessment for both sides, with the percentage of participants who rated the improvement as moderate/significant being 63.1% (12/19) for the combined-therapy side and 47.4% (9/19) for the monotherapy side.

Adverse events

No serious AEs were encountered during the treatment term. Pain during the FRM treatment with was well tolerated by all participants, with an average pain score of 3.63 ± 1.38. Transient pinpoint bleeding was observed during FRM treatment. Mild erythema occurred at the FRM-treated site and resolved within 24 h. No erosion or breakage of hair shaft was noted on the FRM-treated side. Eight participants reported dandruff on the drug-applied area of the scalp.

Table 2 Comparison of clinical efficacy compared between a combined therapy of fractional radiofrequency microneedling and minoxidil and monotherapy with minoxidil alone.

	Combined therapy	Monotherapy	*P*
Mean hair count			
Baseline	44.12 ± 21.58	46.22 ± 18.77	0.29
After 5 months of treatment	73.14 ± 25.45	63.21 ± 19.22	0.01
Mean change from baseline	29.02 ± 17.60	16.99 ± 17.07	< 0.01
Mean hair thickness, μm			
Baseline	53 ± 13	52 ± 16	0.90
After 5 months of treatment	71 ± 15	66 ± 14	0.02
Investigator assessment			
Significant improvement (+3)	8 (42.1)	1 (5.3)	< 0.001
Moderate improvement (+2)	6 (31.6)	9 (47.4)	
Slight improvement (+1)	4 (21.0)	7 (36.8)	
No change (0)	1 (5.3)	2 (10.5)	
Worsened (−1, −2, −3)	0	0	
Subject self-assessment			
Significant improvement (+3)	7 (36.8)	1 (5.3)	< 0.001
Moderate improvement (+2)	5 (26.3)	8 (42.1)	
Slight improvement (+1)	6 (31.6)	8 (42.1)	
No change (0)	1 (5.3)	2 (10.5)	
Worsened (−1, −2, −3)	0	0	

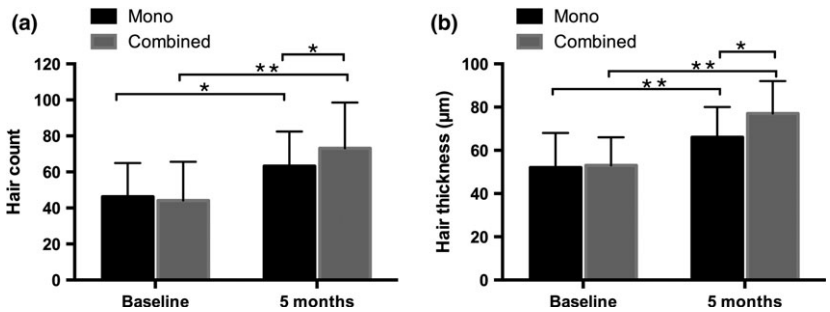

Figure 1 (a) Hair count and (b) hair thickness at baseline and 5 months after monotherapy with minoxidil 5% monotherapy and combined therapy with fractional radiofrequency microneedling and minoxidil 5%. *$P < 0.05$, **$P < 0.01$. The bars on the graph represent standard error.

Discussion

Stimulation of hair follicle growth or acceleration of hair cycling after wounding has been discussed previously, with reports indicating that some hair follicles develop anew after wounding in mice, rabbits and humans.[10–12] Ito *et al.* reported that hair follicles could regenerate *de novo* in genetically normal adult mice after wounding. Following wounding, regenerated hair follicles establish a stem cell population, express known molecular markers of follicle differentiation, produce a hair shaft and progress through all stages of the hair follicle cycle via activation of the Wnt/β-catenin pathway.[10] A wound related to thermal injury can also trigger hair regeneration. Jung *et al.* reported that the 10 600-nm fractional CO_2 laser appeared to be effective for inducing hair regrowth in a murine model,[13] while the nonablative 1550-nm fractional erbium–glass laser was reported to be an effective and safe treatment modality for both MPHL and FPHL.[6,7] A study on a murine model revealed that transient moderate inflammation was associated with anagen induction.[14] Cho *et al.* used both nonablative and ablative lasers, which effectively promoted hair growth.[15] Microneedles have also been reported to induce hair growth in MPHL.[16,17] The FRM device we used produces both mechanical wounds by microneedles and thermal injury by radiofrequency. Therefore, it is hypothesized that it is feasible to use FRM to induce the correct type of injury to stimulate hair growth.

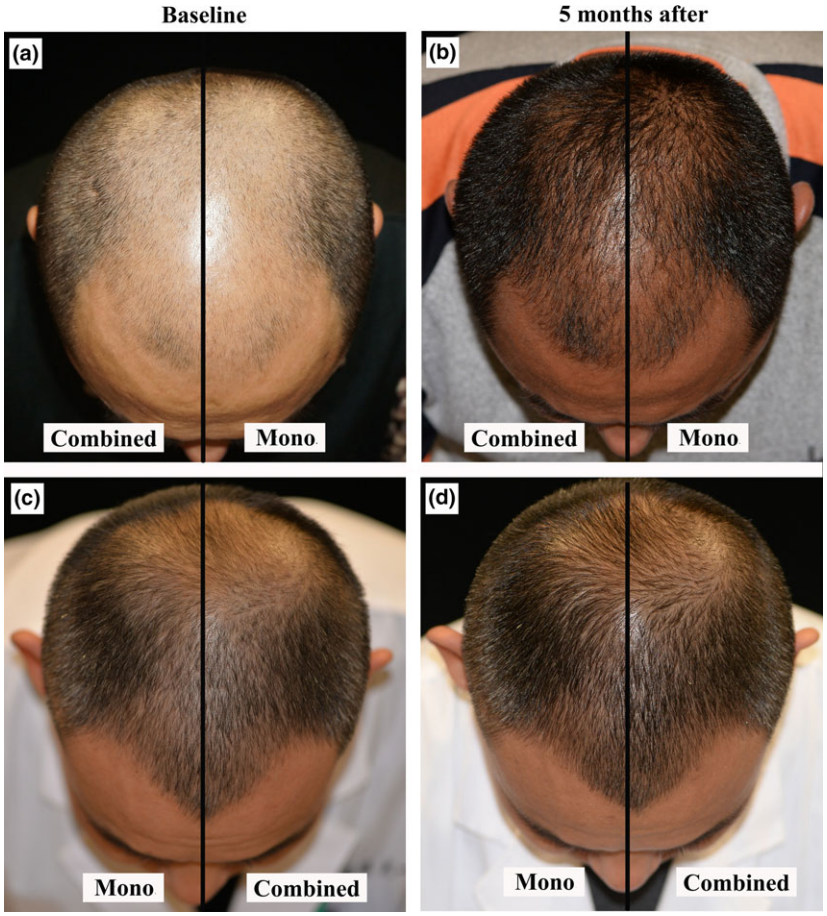

Figure 2 (a,b) Patient 1: 41 years old, Hamilton–Norwood type IV hair loss. (c,d) Patient 2: 2, 45 years old, Hamilton–Norwood type VI hair loss. (a,c) At baseline; (b,d) both patients showed significant improvement in hair growth at 5 months.

FRM has been reported to be a promising technique to treat inflammatory acne, acne scars and for skin rejuvenation.[18–20] The radiofrequency released by the FRM device causes polar molecules to vibrate, and then converts this vibrating energy to thermal energy, generating well-controlled column thermal zones. Each microneedle is insulated except for the tip point, which generates RF energy limited to the top of the tip without thermal damage to the neighbouring epidermis. RF energy delivered to the skin spares adnexal structures and adipose tissue. FRM efficiently releases energy to the scalp without any blockage from the overlying hair, exerting a fractional thermolysis effect onto the target tissue. FRM causes inflammation, which increases blood flow and follicular vascularization. Inflammatory cells (especially macrophages) and cytokines (including interleukins and tumour necrosis factor-α), may have an important role in this process. In addition, FRM might have a direct impact on the dermal papilla or bulge. Zheng *et al.* found that microneedle RF affected terminal hair follicles and coagulated follicular epithelium and perifollicular structures. The treatment might disrupt the structural integrity of hair follicles, depending on the treatment parameters.[21]

Currently, minoxidil is the only topical drug approved by the FDA to treat MPHL. Its possible mechanism involves increasing blood flow to hair follicle, enhancing levels of vascular endothelial growth factor and prostaglandin E2.[22] The fractional themolysis and microchannels induced by FRM might facilitate transdermal delivery of topical minoxidil without causing AEs.[21,23] Minoxidil is reported to be effective in 41–57% of treated patients.[24] In the current study, the side treated with the combined therapy of FRM and minoxidil showed greater efficacy than the side treated with minoxidil monotherapy, in terms of hair density, hair thickness (indicating reversal of the

miniaturization process of MPHL) and slowing of the progression of hair loss. This encouraging result might be partially attributed to the facilitation of high-efficiency transduction of minoxidil.

Conclusion

Despite the positive results of efficacy and controllable AEs in this study, the small sample size limits the study. The optimal parameters and intervals need to be tested in further studies. The mechanism of action of this novel method would be a worthy candidate for future investigation.

What's already known about this topic?

• Although MPHL is a very prevalent condition, the approved therapeutic options are limited.
• Interest is increasing in the potential role of energy-based treatments for hair loss.

What does this study add?

• FRM plus minoxidil gave better results than minoxidil alone.
• FRM combined with topical minoxidil could be a novel treatment for MPHL, with good efficacy and tolerable AEs.

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