Original Article

Fractional Radiofrequency Microneedling Combined With Low-Dose Isotretinoin versus Standard-Dose Isotretinoin in Moderate-to-Severe Acne: A Randomized Controlled Pilot Study

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Abstract

Background Oral Isotretinoin is highly effective for moderate-to-severe acne but is limited by adverse effects and delayed onset of action. Fractional radiofrequency (RF) microneedling may enhance outcomes through targeted sebaceous gland destruction and dermal collagen remodeling.

Objective To compare the efficacy of fractional RF microneedling combined with low-dose Isotretinoin versus standard-dose Isotretinoin monotherapy in moderate to severe acne and assess the impact of body mass index (BMI) on treatment response.

Methods In this randomized controlled pilot study, 40 patients with moderate-to-severe acne (Investigator Global Assessment (IGA 3–4)) were assigned to combination therapy (RF microneedling plus isotretinoin 20 mg/day) or standard Isotretinoin (0.5 mg/kg/day). The primary endpoint was IGA at Week 8.

Results At Week 8, the combination group showed greater improvement (mean IGA 1.55 vs. 2.90; *P*<.0001) and higher responder rates (90% vs. 30%). Lesion reduction was significantly greater with combination therapy. Six-month success rates were similar by intention-to-treat but favored combination therapy per-protocol (100% vs. 75%). All treatment failures occurred in obese patients (BMI ≥30 kg/m²), with lower failure rates in the combination group. No serious adverse events or wound healing complications were observed.

Conclusion Combination therapy with fractional radiofrequency microneedling and low-dose Isotretinoin resulted in faster and greater clinical improvement than standard-dose Isotretinoin monotherapy, with a favorable safety profile. Higher BMI was associated with treatment failure.

Keywords Acne; Combination therapy; Fractional radiofrequency; Low-dose isotretinoin, Obesity.

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Introduction

Acne vulgaris is a common chronic inflammatory disorder of the pilosebaceous unit. Moderate-to-severe disease may produce persistent inflammation and permanent scarring, with substantial psychosocial consequences potentially mediated by neuroendocrine interactions.[1-5] Isotretinoin remains one of the most effective treatments for moderate-to-severe acne because it targets the major pathogenic mechanisms of the disease. However, its use is limited by dose-dependent adverse effects, including mucocutaneous dryness, cheilitis, dyslipidemia,

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hepatotoxicity, and teratogenicity.[6-10] Low-dose regimens have therefore been investigated as an approach to improve tolerability while maintaining clinical efficacy.[10,11]

Fractional RF microneedling is an established device-based treatment capable of reducing sebum production and improving acne and acne scarring.[12-14] Unlike systemic therapy, RF delivers localized thermal energy and may produce direct sebaceous gland injury and dermal remodelling. Previous concerns regarding the performance of procedures during isotretinoin therapy have increasingly been challenged, with available evidence suggesting that selected fractional and non-ablative procedures can be performed safely.[15,16]

Metabolic factors may also influence acne severity and treatment response. Obesity and Insulin resistance have been associated with increased sebaceous activity and inflammation through Insulin-like growth factor-1 (IGF-1) and related metabolic pathways.[17,18] Thus, combining localized RF treatment with low-dose isotretinoin may provide complementary effects while reducing systemic isotretinoin exposure.

Methods

The research was conducted as a pilot investigation through a randomised controlled trial at Ibn Sina Teaching Hospital from April 2025 to April 2026. The study was approved by the Ethical Committee of the College of Medicine, University of Mosul (UOM/COM/MREC/25-26/MAY8 dated 20.05.2026). Written informed consent was obtained from all participants before enrolment in the study, including separate consent for the publication of clinical photographs.

Patients aged 18-33 years with moderate to severe facial acne, defined by an Investigator Global Assessment (IGA) score of 3 or 4,[19] were eligible. Patients were excluded if they had used Isotretinoin within the previous 12 months, had retinoid hypersensitivity, active hepatic, renal, or metabolic disease, pregnancy or inability/unwillingness to follow contraception requirements, active infection at RF treatment sites, or RF microneedling within the preceding 6 months.

Forty patients were randomly assigned in a 1:1 ratio using sequentially prepared sealed envelopes. Group A received fixed-dose Isotretinoin 20 mg/day together with three fractional RF microneedling sessions at 4-week intervals. Group B received Isotretinoin 0.5 mg/kg/day without procedural treatment. In Group A, the weight-adjusted Isotretinoin exposure ranged from 0.18 to 0.36 mg/kg/day, approximately 46% lower than the standard dose.

RF treatment was performed using the Virtue RF device (ShenB Co., Ltd, Seoul, South Korea). The sterile tip contained a 7 × 7 matrix of non-insulated, gold-plated microneedle electrodes. Needle depth was adjustable to a maximum of 3.5 mm, with physician-controlled power and pulse duration. **Figure 1** shows the flow of the study.

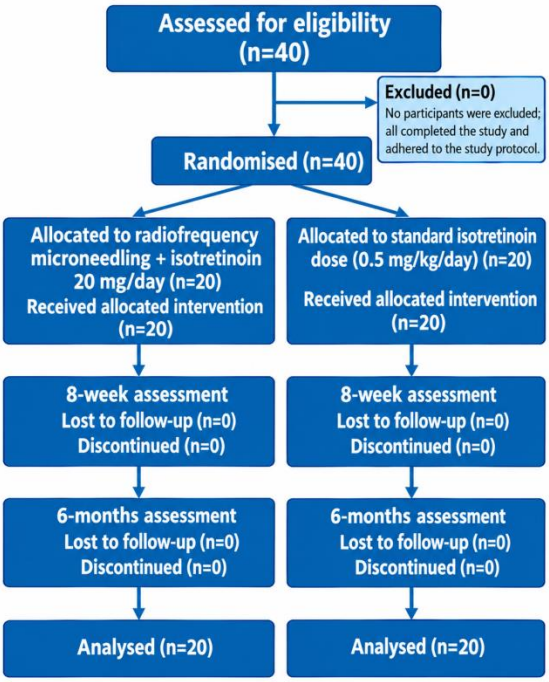


Figure 1 CONSORT flow diagram of patient enrolment, allocation, follow-up and analysis.

The primary outcomes of this study were evaluated through comparison of IGA scores at Week 8 between the two treatment groups. Responders to treatment are defined as a reduction of ≥ 2 grades in IGA score and/ or >50-70% reduction in inflammatory lesions.

The study measured secondary outcomes, which included inflammatory lesion count at Week 8, treatment failure at 6 months, and safety and tolerability. Treatment failure was defined as an IGA score ≥3 at the 6-month assessment. Standardized photographs were obtained at baseline and follow-up visits and independently assessed by two blinded evaluators.

Statistical analysis was performed using SPSS version 26.0 and GraphPad Prism 9. The Shapiro–Wilk test assessed normality. Independent-samples t-tests were used for normally distributed continuous variables and Mann–Whitney U tests for non-normal or ordinal data. Categorical variables were analyzed using Chi-square or Fisher's exact tests. Point-biserial correlation assessed the association between BMI and treatment failure. Statistical significance was defined as $P<.05$. BMI was categorized as normal (<25 kg/m²), overweight (25-29.9 kg/m²), or obese (≥30 kg/m²).[18]

Table 1 Baseline Patient Demographics and Clinical Characteristics

Parameter	*Group A Combination (n=20)*	*Group B ISO Only (n=20)*	*P-value*
Age mean±SD (years)	25.6 ± 5.6	24.4±3.5	.515
Age range (years)	18-33	18-33	
Sex Female n (%)	13 (65%)	11 (55%)	.747
Sex Male n (%)	7 (35%)	9 (45%)	
Weight mean±SD (kg)	78.4±13.5	85.0±21.2	.490
Weight range (kg)	55-110	60-130	
ISO dosing strategy	Fixed 20 mg/day	0.5 mg/kg/day	
Actual ISO dose (mg/kg/day)	0.18-0.36 (mean ~0.27)	0.50 (fixed)	
BMI mean±SD (kg/m²)	28.5±4.1	28.9±6.9	.579
Baseline IGA mean±SD	3.2±0.4	3.5±0.5	.196
Baseline lesion count mean ± SD	30.6±7.3	31.8±7.7	.715
No. RF microneedling sessions	3	0	

Result

All 40 patients completed the study and were included in the intent-to-treat (ITT) analysis. No patients were lost to follow-up. Both groups were well-matched at baseline with no statistically significant differences in any variable (all $P>.05$). Complete baseline data are presented in **Table 1**.

At Week 8, mean IGA decreased to 1.55±0.83 in Group A compared with 2.90±0.72 in Group B ($P<.0001$). The corresponding mean reductions from baseline were 1.70 and 0.55 points, respectively. IGA ≤2 was achieved by 18/20 patients (90%) in Group A compared with 6/20 (30%) in Group B ($P<.001$) **(Figures 2, 3)**.

Inflammatory lesion counts were also significantly lower with combination therapy at Week 8 (9.2±9.3 vs. 20.6±10.2; $P<.0001$). At end of treatment (EOT), lesion counts were 5.4±9.2 versus 12.8±12.1 ($P=.0003$), while at EOT IGA was 0.7±1.1 versus 2.0±1.0 ($P<.0001$) in Groups A and B, respectively **(Table 2)**.

In the ITT analysis, 16 patients (80%) in Group A achieved treatment success compared to 15 (75%) in Group B. Treatment failure at 6 months occurred in 2 (10%) in Group A and 5 (25%) in Group B. Two Group A patients (10%) were classified as slow responders.

In the per-protocol analysis (excluding the two lifestyle-confounded slow responders), Group A achieved a success rate of 18/18 (100%) versus 15/20 (75%) in Group B ($P=.048$). As shown in **Table 3**.

All seven treatment failures occurred among obese patients (BMI ≥30 kg/m²). No treatment failures were observed among patients with BMI <30 kg/m². BMI was significantly associated with treatment



Figure 2 A 23-year-old female with moderate acne severity A) Baseline B) After 8 weeks of treatment using Virtue RF. Sessions and a low dose of isotretinoin



Figure 3 An 18-year-old male with severe acne. A) Baseline B) after 8 weeks of treatment using Virtue RF. Sessions and a low dose of isotretinoin

failure (r=.82, *P*<.0001). The distribution of treatment outcomes according to BMI category is presented in **Table 4**.

Both treatments were generally well tolerated. Adverse events included mild to moderate mucocutaneous dryness, cheilitis, and occasional epistaxis, with symptoms appearing milder in the low-dose group. Transient post-procedural erythema after RF treatment resolved within 24-48 hours. No serious adverse events, clinically significant laboratory abnormalities, or wound-healing complications were recorded.

Discussion

This randomized pilot study found that fractional RF microneedling combined with low-dose isotretinoin produced substantially greater early improvement than standard-dose isotretinoin monotherapy. At week 8, the majority of the patients receiving combination therapy achieved IGA ≤2 compared with 30% receiving isotretinoin alone, despite approximately 46% lower weight-adjusted Isotretinoin exposure. Lesion counts and EOT IGA were also significantly improved with combination therapy.

The rapid response may reflect complementary mechanisms. Isotretinoin acts systemically on the major pathogenic pathways of acne, including sebaceous gland activity, follicular keratinization, and inflammation.[20,21] RF microneedling provides localized thermal injury that can directly affect sebaceous structures while promoting dermal remodelling.[12-14] Combining these approaches may therefore provide more rapid local control while reducing systemic isotretinoin exposure.

The findings are clinically relevant because adverse effects remain an important limitation of Isotretinoin therapy, particularly when higher doses are required. Low-dose Isotretinoin has demonstrated efficacy with improved tolerability in selected patients.[10,11]

Table 2 Primary and Secondary Efficacy Outcomes.

Outcome Measure	*Group A (n=20)*	*Group B (n=20)*	*P-value*
Week 8 IGA: mean±SD	1.55 ± 0.83	2.90 ± 0.72	< 0.0001*
IGA ≤2 responders: ITT n (%)	18/20 (90%)	6/20 (30%)	< 0.001*
IGA ≤2 responders: per-protocol n (%)	16/18 (89%)	6/20 (30%)	< 0.001*
Week 8 lesion count: mean±SD	9.2 ± 9.3	20.6 ± 10.2	< 0.0001*
Week 8 lesion reduction: mean	21.3 lesions	11.2 lesions	< 0.0001*
Treatment failure at 6 months: ITT n (%)	2/20 (10%)	5/20 (25%)	0.494
Per-protocol success rate n (%)	18/18 (100%)	15/20 (75%)	0.048*

**P*-value <.05 is statistically significant. IGA- Investigator Global Assessment. EOT- end of trial. ITT- intention-to-treat.

Table 3 Treatment Outcomes at 6 Months.

Outcome	*Group A Combination (n=20)*	*Group B ISO Only (n=20)*	*P-value*	*Analysis*
Treatment success n (%)	16 (80%)	15 (75%)	0.494	ITT
Success: per-protocol n (%)	18/18 (100%)	15/20 (75%)	0.048 *	Per-protocol
Slow responder n (%): Group A only	2 (10%)	0 (0%)	-	ITT
Treatment failure n (%)	2 (10%)	5 (25%)	0.494	ITT
All failures were obese (BMI ≥30)	Yes (2/2 failures obese)	Yes (5/5 failures obese)	-	Confirmed
Failures in non-obese patients (BMI < 30)	0/13 (0%)	0/14 (0%)	-	Subgroup

**P*-value <.05 is statistically significant. ITT= intention-to-treat. ISO =isotretinoin.

Table 4 Treatment Outcomes Stratified by BMI Category

BMI Category	*BMI (kg/m²)*	*Group A*	*Group B*	*Group A Outcome*	*Group B Outcome*
Normal	< 25	4	6	0 failures (0%)	0 failures (0%)
Overweight	25 – 29.9	9	8	0 failures (0%)	0 failures (0%)
Obese	≥ 30	7	6	2/7 fail (29%) | 4/7 success (57%) | 1/7 slow responder	5/6 fail (83%) | 1/6 success (17%)

In the present study, adverse effects appeared milder in the combination group, although the pilot sample was too small to establish differences in adverse-event rates.

The combination therapy has faced a major historical obstacle because medical guidelines prohibit cutaneous procedures during Isotretinoin treatment and the following 6 to 12 months.[15,16,22] Spring *et al*. (2017) analyzed 32 studies which documented 1,485 procedures, but they determined that evidence did not support postponing most dermatological treatments for Isotretinoin users except for fractional RF microneedling, which they deemed safe.[22] The researchers developed official care standards according to multicentric research, which showed that fractional RF microneedling can be used safely during Isotretinoin treatment.[23]

The study found that 60 Virtue RF treatments, which were conducted on 20 combination patients who received low-dose isotretinoin treatment, resulted in no wound healing problems or hypertrophic scar formation or post-inflammatory hyperpigmentation that had clinical importance. The insulated microneedling design, which delivers thermal energy to deep dermal tissue while minimizing thermal spread to epidermal tissue, can decrease the potential risks associated with this procedure.[15] Controlled studies which provide prospective evidence now confirm that fractional RF microneedling can be safely used during isotretinoin treatment according to existing medical consensus on this practice.[22,23]

An additional finding was the strong association between BMI and treatment failure. All seven treatment failures occurred among obese patients, whereas no patient with BMI <30 kg/m² failed treatment. Obesity has been associated with acne severity and metabolic pathways involving insulin and IGF-1 signalling, which may influence sebaceous activity and inflammation.[17,24] In this study, obese patients receiving standard-dose isotretinoin had a higher observed failure proportion than obese patients receiving combination therapy. The localized action of RF may provide an effect that is less dependent on systemic metabolic pathways. However, these BMI findings should be interpreted cautiously. The study included only 13 obese patients overall, and the subgroup comparisons were therefore underpowered. The observed association should be regarded as hypothesis generating rather than evidence that obesity causes Isotretinoin resistance or that RF specifically overcomes metabolic resistance.

The study found that both treatment groups were generally well tolerated with fewer side effects. The absence of serious wound-healing complications during all 60 Virtue RF sessions provide additional proof that fractional RF microneedling can be safely performed with patients who are undergoing Isotretinoin treatment.

Conclusion

Fractional RF microneedling with low-dose Isotretinoin produced faster clinical improvement than standard-dose isotretinoin, with lower drug exposure and no serious procedural complications. Higher BMI was associated with treatment failure. Larger studies with longer follow-ups are needed to confirm these findings

Limitations This study had several limitations. First, the pilot sample included only 20 patients per group and was not powered to detect differences in secondary outcomes or long-term treatment success. Second, the two groups received different isotretinoin dosing strategies, limiting direct pharmacological comparison. Third, the 6-month follow-up was insufficient to establish long-term remission or relapse. Finally, the BMI subgroup analysis involved small numbers and should be considered exploratory.

Declaration of patient consent Authors certify that they have obtained all appropriate patient consent.

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Conflict of interest No conflict of interest.

Author's contribution

AMA: Substantial contributions to study design, acquisition, analysis and interpretation of date, manuscript writing.

QSA: Substantial contributions to analysis and interpretation of data, manuscript writing.

Every author has given final approval of the manuscript version to be published and agreed to be accountable for all aspects of the work.

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