



COMPARITIVE EFFICACY AND SAFETY OF TOPICAL IVERMECTIN 1% CREAM VERSUS TOPICAL METRONIDAZOLE 1.5% GEL IN STEROID-INDUCED ROSACEA: A PROSPECTIVE RANDOMIZED COMPARITIVE STUDY

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ABSTRACT

Introduction

Steroid-induced rosacea is an increasingly recognized inflammatory dermatosis resulting from prolonged or inappropriate use of topical corticosteroids on the face. It presents with persistent erythema, papules, pustules, telangiectasia, and burning sensation, often causing significant cosmetic and psychological distress. In India, misuse of topical steroid-containing creams for cosmetic purposes has led to a rising incidence of steroid-induced rosacea. Although topical metronidazole has long been used as a first-line therapy, ivermectin has recently gained attention due to its dual anti-inflammatory and acaricidal effects against *Demodex* mites. However, comparative data specifically evaluating these two agents in steroid-induced rosacea remain limited.

Methods: A prospective randomized comparative study was conducted in the Dermatology outpatient department of Rajshree Medical Research Institute, Bareilly, from March 2024 to April 2025. A total of 160 patients aged above 18 years clinically diagnosed with steroid-induced rosacea were enrolled and randomly divided into two groups of 80 each. Group 1 received topical ivermectin 1% cream once daily, while Group 2 received topical metronidazole 1.5% gel twice daily. Patients were evaluated at baseline and at 4, 8, and 12 weeks. Treatment efficacy was assessed using inflammatory lesion count, Investigator Global Assessment (IGA), Rosacea Area and Severity Index (RASI), and Visual Analogue Scale (VAS). Adverse effects such as burning, stinging, dryness, and irritation were recorded during follow-up visits.

Results: Both groups were comparable in baseline demographic and clinical characteristics. Progressive improvement was observed in both treatment groups during the study period. However, patients treated with topical ivermectin demonstrated significantly greater reduction in inflammatory lesion count compared to the metronidazole group at 4, 8, and 12 weeks ($p < 0.001$). Mean IGA scores also decreased significantly in the ivermectin group (0.95 ± 0.50) compared to the metronidazole group (1.45 ± 0.58) at 12 weeks. IGA treatment success (score 0 or 1) was achieved in 72.5% of patients

receiving ivermectin compared to 50.0% in the metronidazole group ($p=0.004$). Similarly, RASI and VAS scores showed greater improvement in the ivermectin group. Local adverse effects such as burning, stinging, dryness, and irritation were more frequently observed in patients treated with metronidazole, while ivermectin demonstrated better tolerability.

Keywords: Steroid-induced rosacea; topical corticosteroid misuse; ivermectin 1% cream; metronidazole 1.5% gel; inflammatory lesion count; Investigator Global Assessment; Rosacea Area and Severity Index; randomized comparative study.

Introduction

Rosacea is a chronic inflammatory dermatosis predominantly affecting the centropacial region and characterized by persistent erythema, telangiectasia, papules, pustules, and episodes of flushing. The condition significantly impacts patients' quality of life because of cosmetic disfigurement and associated symptoms such as burning and skin sensitivity. Although the exact pathogenesis of rosacea remains unclear, multiple mechanisms including dysregulation of innate immunity, neurovascular instability, and microbial factors such as *Demodex folliculorum* have been implicated.^{1,7}

Steroid-induced rosacea is a distinct iatrogenic variant that develops following prolonged or inappropriate use of topical corticosteroids on facial skin. Long-term corticosteroid exposure can disrupt the skin barrier and suppress local immune responses, leading to rebound inflammation after withdrawal. Clinically, patients present with diffuse facial erythema, papules, pustules, telangiectasia, and burning sensations. The prevalence of steroid-modified facial dermatoses has increased considerably in developing countries such as India due to the easy availability and misuse of topical steroid-containing cosmetic preparations.^{2,5}

Topical therapy remains the cornerstone of treatment for inflammatory rosacea. Metronidazole has been widely used because of its anti-inflammatory and antioxidant properties. Recently, ivermectin 1% cream has emerged as a promising therapeutic option due to its dual anti-inflammatory and acaricidal activity against *Demodex* mites.³ Comparative studies have suggested superior efficacy of ivermectin in papulopustular rosacea.^{4,9} However, limited data exist regarding its effectiveness specifically in steroid-induced rosacea.

Therefore, the present study was conducted to compare the efficacy and safety of topical ivermectin 1% cream with topical metronidazole 1.5% gel in patients with steroid-induced rosacea.

Materials and Methods

Study Design and Subjects

This prospective randomized comparative study was conducted in the Dermatology outpatient department of Rajshree Medical Research Institute, Bareilly, Uttar Pradesh, India, from March 2024 to April 2025. A total of 160 patients aged ≥ 18 years with clinically diagnosed steroid-induced rosacea were enrolled after obtaining written informed consent. Patients were included if they had a history of topical corticosteroid use on the face for at least one month and presented with clinical features such as persistent facial erythema, papules, pustules, telangiectasia, or burning sensation.

Patients who had received topical or systemic treatment for rosacea within the previous three months, those with classical rosacea without a history of steroid use, pregnant or lactating women, patients with hypersensitivity to ivermectin or metronidazole, and those with active cutaneous infections were excluded from the study. Eligible participants were randomly allocated into two equal groups ($n=80$ each).

Table 1: Investigator's Global Assessment (IGA) scale

Grade	Score	Clinical Description
Clear	0	No inflammatory lesions present, no erythema
Almost clear	1	Very few small papules/pustules, very mild erythema present
Mild	2	Few small papules/pustules, mild erythema
Moderate	3	Severe small or large papules/pustules, moderate erythema
Severe	4	Numerous small and/or large papules/pustules, severe erythema

Treatment

Participants in Group 1 were treated with topical ivermectin 1% cream applied once daily at night, while Group 2 received topical metronidazole 1.5% gel applied twice daily. Patients were instructed regarding proper application techniques and advised to discontinue the use of topical corticosteroids. All patients were followed up at 4, 8, and 12 weeks.

Clinical efficacy was assessed using inflammatory lesion count, Investigator Global Assessment (IGA) score, Rosacea Area and Severity Index (RASI), and Visual Analogue Scale (VAS) for burning and itching at each visit. Treatment success was defined as an IGA score of 0 (clear) or 1 (almost clear) at week 12. Adverse effects such as burning, stinging, dryness, irritation, and contact dermatitis were documented at each follow-up visit.

Statistical Methods

Data were entered into Microsoft Excel and analyzed using appropriate statistical software. Continuous variables were expressed as mean $\pm$ standard deviation, while categorical variables were presented as frequency and percentage. Comparisons between the two groups were performed using the independent t-test for continuous variables and the Chi-square test for categorical variables. A p-value <0.05 was considered statistically significant.

Compliance with Ethics Guidelines

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of Rajshree Medical Research Institute, Bareilly, prior to the commencement of the study. Written informed consent was obtained from all participants before enrollment.

Results: A total of 160 patients with steroid-induced rosacea were enrolled and randomized into two equal groups: Group 1 (topical ivermectin 1% cream, $n = 80$) and Group 2 (topical metronidazole 1.5% gel, $n = 80$). Baseline demographic characteristics and disease severity parameters were comparable between the two groups.

Baseline Characteristics

The majority of patients belonged to the 18–30 year age group (37.5% in the ivermectin group and 36.3% in the metronidazole group). Female patients constituted the majority of the study population (95% in Group 1 and 93.8% in Group 2). Most participants belonged to lower-middle socioeconomic status, and a higher proportion were from urban localities.

Regarding prior corticosteroid exposure, the most common duration of steroid use was less than 6 months, followed by 6–12 months. High-potency corticosteroids such as betamethasone and mometasone were most frequently used. The most common indications for steroid use were melasma/pigmentary disorders and cosmetic purposes, followed by acne-related conditions. There were no statistically significant differences in baseline characteristics between the two groups ($p > 0.05$).

Clinical Features

Erythema was present in 100% of patients, followed by papules and pustules (90% in Group 1 and 92.5% in Group 2) and telangiectasia (57.5% and 55%, respectively). The cheeks were the most commonly involved facial area in both groups. No cases of rhinophyma were observed. Baseline clinical features were comparable between the treatment groups.

Efficacy Outcomes

Inflammatory Lesion Count

Both treatment groups showed progressive reduction in inflammatory lesion counts during the study period. The mean lesion count at baseline was 18.6 ± 4.2 in the ivermectin group and 18.3 ± 4.5 in the metronidazole group ($p = 0.72$).

At 4 weeks, the mean lesion count decreased to 11.2 ± 3.6 in Group 1 and 13.9 ± 3.8 in Group 2 ($p = 0.01$). At 8 weeks, the values were 5.8 ± 2.9 and 8.4 ± 3.2 , respectively ($p = 0.001$). By 12 weeks, lesion counts further reduced to 2.4 ± 1.6 in the ivermectin group and 4.9 ± 2.3 in the metronidazole group ($p < 0.001$).

Investigator Global Assessment (IGA)

Baseline IGA scores were similar between the two groups (3.00 ± 0.65 vs 3.02 ± 0.67 ; $p = 0.88$). A progressive reduction in IGA scores was observed in both groups during follow-up.

At 4 weeks, mean IGA scores were 2.10 ± 0.60 in the ivermectin group and 2.45 ± 0.62 in the metronidazole group ($p = 0.01$). At 8 weeks, the scores decreased to 1.45 ± 0.55 and 1.95 ± 0.60 , respectively ($p = 0.001$). At 12 weeks, the mean IGA score further declined to 0.95 ± 0.50 in the ivermectin group compared with 1.45 ± 0.58 in the metronidazole group ($p < 0.001$).

Treatment success (IGA score 0 or 1) at week 12 was achieved in 72.5% of patients in the ivermectin group compared with 50.0% in the metronidazole group ($p = 0.004$).

Table 2 : Mean IGA score comparison at follow up visits (mean $\pm$ SD)

Visit	Group 1	Group 2	p value
Baseline	3.00 ± 0.65	3.02 ± 0.67	0.88
4 weeks	2.10 ± 0.60	2.45 ± 0.62	0.01
8 weeks	1.45 ± 0.55	1.95 ± 0.60	0.001
12 weeks	0.95 ± 0.50	1.45 ± 0.58	<0.001

RASI Score

The baseline mean Rosacea Area and Severity Index (RASI) score was 12.8 ± 3.1 in the ivermectin group and 12.6 ± 3.3 in the metronidazole group ($p = 0.79$). A progressive reduction in RASI scores was observed during follow-up in both groups, with greater reduction in patients treated with ivermectin.

Table 3 : Comparison of mean RASI scores at follow up visits

Visit	Group 1	Group 2	p value
Baseline	12.8 ± 3.1	12.6 ± 3.3	0.79
4 weeks	8.2 ± 2.7	9.9 ± 2.9	0.01
8 weeks	4.6 ± 2.2	6.8 ± 2.4	0.001
12 weeks	2.1 ± 1.4	4.3 ± 1.9	<0.001

VAS Score

Baseline Visual Analogue Scale (VAS) scores for burning and itching were comparable between the groups. Both treatments resulted in gradual reduction in VAS scores during follow-up visits at weeks 4, 8, and 12, with greater improvement observed in the ivermectin group by the end of the study period. |

Table 4: Comparison of mean VAS scores at follow up visits

Visit	Group 1	Group 2	p value
Baseline	6.9 ± 1.3	7.1 ± 1.4	0.56
4 weeks	4.1 ± 1.2	5.2 ± 1.3	0.002
8 weeks	2.3 ± 1.0	3.6 ± 1.1	<0.001
12 weeks	1.2 ± 0.8	2.4 ± 1.0	<0.001

Safety Outcomes

Local adverse effects were more frequently reported in the metronidazole group, particularly during early follow-up visits.

At week 4, burning sensation was reported in 7.5% of patients in the ivermectin group compared to 17.5% in the metronidazole group ($p = 0.04$). Similarly, stinging (6.2% vs 15.0%), dryness (10.0% vs 22.5%), and irritation (8.8% vs 18.8%) were more frequent in the metronidazole group.

The frequency of adverse effects decreased progressively over time in both groups. By week 12, only a small proportion of patients reported mild burning, stinging, dryness, or irritation, and no serious adverse events were observed during the study period.



Figure 1: Photographs of a severe subject with A an IGA of 4 before treatment and B an IGA of 1 after 12 weeks treatment with ivermectin 1% cream once daily. IGA investigator's global assessment. Informed consent was received from the patient for publication of these photographs



Figure 2: Photographs of a severe subject with A an IGA of 4 before treatment and B an IGA of 2 after 12 weeks treatment with metronidazole 1.5 % gel twice daily. IGA investigator's global assessment. Informed consent was received from the patient for publication of these photographs

Discussion

Steroid-induced rosacea represents an increasingly encountered clinical entity, particularly in developing countries where unsupervised use of topical corticosteroids is common. The present prospective randomized comparative study evaluated the efficacy and safety of topical ivermectin 1% cream versus topical metronidazole 1.5% gel in patients with steroid-induced rosacea. The findings demonstrated significant clinical improvement in both treatment groups; however, patients treated with ivermectin showed greater reduction in inflammatory lesion count, Investigator Global Assessment (IGA) scores, Rosacea Area and Severity Index (RASI) scores, and symptom severity assessed by Visual Analogue Scale (VAS), along with better tolerability. The results of the present study are consistent with previous randomized controlled trials evaluating ivermectin in papulopustular rosacea. Taïeb et al.⁴ (2015) reported significantly greater reduction in inflammatory lesion counts with ivermectin 1% cream compared to metronidazole 0.75% cream at 16 weeks, with earlier onset of improvement and higher treatment success rates. Similarly, the current study demonstrated statistically significant reduction in lesion counts as early as week 4, with highly significant differences by week 12. This suggests that ivermectin may provide faster and more sustained control of inflammatory lesions in rosacea, including steroid-induced variants. Schaller et al.⁵ (2016) further reported higher rates of “clear” or “almost clear” status based on IGA scores and improved quality-of-life outcomes in patients treated with ivermectin compared to metronidazole during long-term follow-up. In the present study, treatment success (IGA score 0 or 1) was achieved in 72.5% of patients receiving ivermectin compared to 50.0% in those receiving metronidazole, supporting the superior clinical response observed with ivermectin therapy. These findings also suggest that the benefits of ivermectin extend beyond lesion reduction to overall disease severity and patient-perceived improvement.

Similarly, Stein et al.⁸ (2014) demonstrated that ivermectin significantly improved inflammatory lesion counts and global severity scores compared with vehicle treatment, with favorable tolerability. The lower incidence of local adverse effects observed in the ivermectin group in the present study is

consistent with these findings and highlights its suitability for prolonged use in sensitive facial dermatoses.

The greater efficacy of ivermectin in steroid-induced rosacea can be explained by its dual mechanism of action. Unlike metronidazole, which primarily exerts anti-inflammatory and antioxidant effects, ivermectin possesses both anti-inflammatory and acaricidal activity against *Demodex folliculorum*.⁹ Chronic corticosteroid use leads to cutaneous immune suppression and disruption of the epidermal barrier, facilitating increased *Demodex* proliferation and microbial colonization. These mites can activate Toll-like receptor-mediated inflammatory pathways, contributing to persistent erythema and papulopustular eruptions. By reducing mite density and modulating inflammatory cytokine release, ivermectin targets two important pathogenic components of steroid-induced rosacea, thereby resulting in greater clinical improvement.

Another notable finding of the present study was the higher frequency of local adverse effects such as burning, stinging, dryness, and irritation in patients treated with metronidazole, particularly during early follow-up visits. Although these reactions were generally mild and transient, better tolerability observed with ivermectin may enhance treatment adherence and long-term disease control.

The present study has particular relevance in the Indian context. The majority of patients reported using topical corticosteroids for cosmetic indications such as melasma and fairness enhancement, reflecting widespread misuse of steroid-containing preparations. This highlights the growing burden of steroid-modified facial dermatoses in the Indian population. While previous clinical trials have evaluated ivermectin primarily in classical papulopustular rosacea, there is limited evidence focusing specifically on steroid-induced rosacea. Therefore, the current study provides important region-specific data regarding therapeutic outcomes in this distinct subgroup of patients.

Furthermore, the study's prospective randomized design, adequate sample size, and use of validated clinical severity scores such as IGA, RASI, and VAS strengthen the reliability of the findings. By directly comparing two commonly used topical therapies in steroid-induced rosacea, the study contributes valuable evidence that may help guide treatment decisions in routine dermatological practice.

The present study has certain limitations that should be acknowledged. The duration of follow-up was limited to 12 weeks, and therefore long-term remission rates and recurrence patterns could not be evaluated. Objective quantification of *Demodex* mite density using standardized skin surface biopsy or dermoscopy-based scoring was not performed, which could have provided additional insight into the mechanism of therapeutic response. Furthermore, the study was conducted at a single tertiary care center, which may limit generalizability of the findings to other populations. Patient-reported quality-of-life measures such as DLQI were also not assessed. Future multicentric studies with longer follow-up duration and microbiological correlation are warranted to better define optimal treatment strategies for steroid-induced rosacea.

Conclusion

In conclusion, both topical ivermectin 1% cream and topical metronidazole 1.5% gel were effective in reducing clinical severity of steroid-induced rosacea. However, ivermectin demonstrated greater efficacy in reducing inflammatory lesion counts, IGA scores, RASI scores, and symptom severity, along with a lower incidence of local adverse effects. These findings suggest that topical ivermectin may provide superior therapeutic outcomes and better tolerability in the management of steroid-induced rosacea. Further long-term and multicentric studies are required to evaluate relapse rates and establish standardized treatment protocols for this increasingly prevalent condition.

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