SHORT COMMUNICATION

Topical Metronidazole Versus Ivermectin for Low-density *Demodex* Rosacea: A Rater-blinded, Randomized, Split-face Trial

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Topical metronidazole and ivermectin are the standard treatments of choice for papulopustular rosacea (PPR). In addition to PPR, recent studies have also shown the efficacy of these treatments against erythematotelangiectatic rosacea (ETR) (1). Their therapeutic effects arise from eradication of overpopulated *Demodex* mites on the human face. However, few trials have measured the density of *Demodex* for each patient prior to treatment. Even though clinical improvement was sometimes observed in ETR, the rationale for using anti-parasitic agents on patients with low-or-zero density *Demodex* was not straightforward. The efficacies of topical metronidazole and ivermectin in patients with rosacea and low-density *Demodex*, especially those who present predominantly with the ETR subtype, remains unclear. Hence, the aim of this study was to evaluate the efficacy of topical metronidazole and ivermectin on ETR patients with low *Demodex* counts.

MATERIALS AND METHODS

This study screened 33 patients who presented with ETR and had not received topical ivermectin and metronidazole in the last 3 months. The study was conducted between January 2021 and December 2021. To confirm each patient's *Demodex* density 4 locations were sampled randomly (forehead, left and right cheek, chin) using 2 different techniques (squeeze method (2) and standardized skin surface biopsy (SSSB) (3)). Patients with *Demodex* counts higher than the proposed threshold (thumbnail: 11/cm^2, SSSB: 5/cm2) were excluded. An inclusion/exclusion diagram is shown in Table SI. Topical ivermectin and metronidazole were randomly assigned for split-face treatment using computer-generated permuted blocks of 4 in random order (random allocation was performed by YCH, and patient enrollment HHW by patient assignment by MCHY). The frequency of the treatment was based on the drug label: metronidazole twice daily and ivermectin before bedtime. Efficacy and tolerance were assessed at baseline and after 1, 2 and 3 months of treatment. Evaluation included clinical erythema assessment (CEA, 5-grade scale on persistent erythema) performed by a dermatologist blinded to treatment conditions and Flushing ASsessment Tool (FAST (4), 10-point scale on redness, warmth, itchiness, tingling, and skin roughness) by the patient. Finally, at the end of the 3-month study, patients also graded their overall improvement using patient self-assessment survey (PSA).

Statistical analysis

Wilcoxon signed-rank test and χ^2 test were used to evaluate statistical significance, defined as $p<0.05$. Study sample size was determined by assuming 20% difference and standard deviation (SD) of 50% between the 2 treatments, using a 2-sided test with α=0.05, 27 patients was required to reach 80% power.

RESULTS

Twenty-seven out of 33 patients screened completed the trial (4 were excluded due to high *Demodex* counts, 2 dropped out because of a surge of COVID-19 infections) The baseline demographics are shown in **Table I**. Mean *Demodex* counts were 0.6 vs 0.7 mites/cm^2 for SSSB and squeeze methods, respectively ($p=0.68$, Table SII). Both ivermectin and metronidazole significantly improved patient erythema after 1 month of treatment, but no difference was found between metronidazole and ivermectin over the 3-month course (change in CEA of metronidazole vs ivermectin: –1.07 vs –1.04, $p=0.782$ (**Table II**); the negative sign denotes improvement compared with baseline). On subjective FAST scores, patients reported better improvement with ivermectin on erythema and warmth after 2-months treatment (–1.37 vs –1.96, $p=0.048$, and –1.37 vs –1.85, $p=0.041$, respectively), and itchiness and roughness after 3-months treatment (–2.03 vs –2.70, $p<0.05$ and –1.33 vs –2.14, $p<0.05$). However, after 3-months treatment, patients reported no difference between metronidazole and ivermectin on overall improvement ($p=0.17$) (Table I and Figs S1–S7). No major adverse effects were reported.

Table I. Baseline demographics

Sex	F:M = 26: 3
Age, mean (SD)	33.9 (11.5)
20-30 years, *n* (%)	14 (48.2)
30-40 years	7 (24.1)
40-50 years	5 (17.2)
50-60 years	2 (6.9)
>60 years	1 (34.4)
Baseline ROSA-QoL score, mean (SD)	47.4 (12.2)
Duration, years, mean	8.49
Location, *n* (%)	
Cheeks	29 (100)
Forehead	16 (55.2)
Nose	14 (48.3)
Chin	14 (48.3)
Aggravating factors, *n* (%)	
Diet	18 (62.1)
Temperature	17 (58.6)
Sun expose	15 (51.7)
Stress	13 (44.8)
Cosmetics	6 (20.7)

SD: standard deviation.

Table II. Treatment efficacy evaluated by blinded dermatologist (clinical erythema assessment) and by patient (erythema, warmth tingling, itchiness, skin texture, overall self-assessment)

	Metronidazole side	Ivermectin side	*p*-value
Δ Clinical erythema assessment (grade: 0–4)			
1st month	−0.52	−0.56	0.854
2nd month	−0.74	−0.78	0.827
3rd month	−1.07	−1.04	0.782
Δ Erythema score from baseline (scores: 0–10)			
1st month	−0.96	−1.30	0.103
2nd month	−1.37	−1.85	**0.048**
3rd month	−2.04	−2.44	**0.031**
Δ Warmth score from baseline (scores: 0–10)			
1st month	−0.96	−1.22	0.388
2nd month	−1.37	−1.96	**0.041**
3rd month	−2.00	−2.37	**0.023**
Δ Tingling score from baseline (scores: 0–10)			
1st month	−1.00	−1.81	0.072
2nd month	−1.22	−1.85	0.137
3rd month	−1.67	−2.15	0.205
Δ Itchiness score from baseline (scores: 0–10)			
1st month	−1.37	−1.89	**0.020**
2nd month	−1.33	−2.33	0.065
3rd month	−2.04	−2.70	**0.027**
Δ Skin texture score (scores: 0–10)			
1st month	−0.67	−1.26	0.128
2nd month	−0.81	−1.59	0.055
3rd month	−1.33	−2.15	**0.010**
Patient self-assessment (3 months), number of patients			
Worse	0	2	
No change	10	8	
Mild improvement	7	5	
Moderate improvement	10	9	
Significant improvement	0	3	0.17 (χ^2 test)

Although no statistical difference was observed in clinical erythema score between metronidazole and ivermectin side, participants reported significant improvement on subjective erythema (2nd and 3rd month), warmth (2nd and 3rd month) itchiness (1st and 3rd month), and skin texture (3rd month) on the ivermectin side.

DISCUSSION

This study is limited by its single-blinded design. Due to the difference in texture and frequency of the medication, blinding of the participants was not possible. Although bias in clinical assessments was reduced by blinding the rater from treatment conditions, it is unclear how patients' knowledge of medications used on each side of the face may have affected self-assessed improvement. Further double-blinded study is required to investigate the efficacy of metronidazole and ivermectin.

This single-blinded, randomized, split-face study showed that both topical metronidazole and ivermectin were effective treatment against persistent erythema, even for patients with low or zero *Demodex*. Ivermectin may be more effective in improving patients' subjective symptoms, such as warmth, itchiness, and skin roughness. Considering the low *Demodex* count in the current cohort, possible mechanisms of treatment, including the anti-inflammatory effect (including the effect caused) of the anti-parasitic agents (5). The low *Demodex* patient cohort may be why no statistical difference was found between metronidazole and ivermectin, as the difference in their anti-parasitic effect was not shown. More studies are necessary to elucidate the anti-inflammatory effect of these anti-parasitic agents in patients with rosacea, especially those with low or zero *Demodex* counts.

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The authors have no conflicts of interest to declare.

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