

## The Effect of Different Therapeutic Modalities on Demodex Densities and Clinical Symptoms of Patients with Demodicosis

Başak Yalıcı Armağan<sup>1</sup>

ORCID: 0000-0001-9745-1331

Nilgün Atakan<sup>2</sup>

ORCID: 0000-0002-8790-1607

<sup>1</sup>Hacettepe University Faculty of Medicine, Instructor, Department of Dermatology and Venereology, Ankara, Turkey.

<sup>2</sup>Dermatology and Venereology, Private Clinic, Turkey.

Corresponding Author: Başak Yalıcı Armağan  
Hacettepe University Faculty of Medicine, Instructor,  
Department of Dermatology and Venereology, Ankara,  
Turkey.

E-mail: basakarmagan@gmail.com

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### ABSTRACT

**Background:** Demodicosis represents cutaneous diseases caused by cutaneous overpopulation of Demodex mites. The aim of this study was to evaluate the effect of different treatment options on Demodex densities (Dds) and clinical symptoms of patients with demodicosis.

**Methods:** Patients with high Dds in two consecutive standardized skin surface biopsies (SSSB1>5 D/cm<sup>2</sup> or SSSB2>10 D/cm<sup>2</sup>) and concomitant clinical symptoms were evaluated retrospectively. Measurements of treatment effectiveness included clinical improvement and normalization or reducing of Dds.

**Results:** A total of 21 patients included in the study. Five patients received topical permethrin and crotamiton whereas 16 patients received systemic metronidazole in combination with topical permethrin and/or crotamiton. The treatment was continued with topical ivermectin in 2 patients who had failure with other treatments. The median treatment duration was 3 months (IQR 1-4). Pre- and post-treatment median Dds decreased 30 to 14 D/cm<sup>2</sup> on SSSB1 whereas 81 to 80 D/cm<sup>2</sup> on SSSB2, respectively. There was no statistically significant decrease in Dds on SSSB1 and SSSB2 after the treatment (p=0.173 and p=0.134, respectively). Clinical improvement was recorded in a total of 14 patients (66.6%) of whom only 2 patients (9.5%) had normalization on Dds. Additionally, topical ivermectin provided a rapid clinical improvement and normalization on Dds in both 2 patients.

**Conclusion:** Irrespective of the treatment, more than two-thirds of the patients improved clinically without a significant change in Dds. This finding may suggest that the treatment response has been mostly associated with the anti-inflammatory properties of the agents. Topical ivermectin seems to be a more suitable treatment option for demodicosis with positive effects on both clinical findings and Dds.

**Keywords:** Demodicosis, demodex mites, treatment outcome

## INTRODUCTION

*Demodex folliculorum* is a microscopic mite which asymptotically parasitizes the human pilosebaceous unit. The prevalence of mite increases with age up to 100% in late adulthood [1-3]. Although the role of *Demodex* mites as causative agents of human disease has been unclear, they are considered to play a pathogenic role when they multiply or penetrate to the dermis. The presence of more than 5 mites/cm<sup>2</sup> measured by the first standardized skin surface biopsy (SSSB1) or >10 mites/cm<sup>2</sup> on the second, deeper biopsy (SSSB2) defined as increased *Demodex* density (Dd) [1,4]. Increased numbers of mites have been identified mainly in demodicosis and papulopustular (PPR) or erythematotelangiectatic rosacea (ETR) [5-7].

Demodicosis is the term used to describe the cutaneous disease caused by increased *Demodex* mites and concomitant complaints including erythema, telangiectases, burning or stinging sensation, itching, scaling, dryness, irregular or rough skin [5,8,9]. "Pityriasis folliculorum" (PF), "rosacea-like demodicosis", and "granulomatous rosacea-like demodicosis" are the classical clinical forms of *D. folliculorum* infestation. Recently, rosacea-like demodicosis and PPR are considered to be the two phenotypes of the same disease [10]. It has been suggested to describe *Demodex* infestation in human beings in two clinical forms as noninflammatory demodicosis (NID) including PF and inflammatory demodicosis (ID) including rosacea-like demodicosis or PPR, demodex folliculitis, demodex pigmentation, follicular eczematids, isolated inflammatory papule [11]. NID manifests as a nutmeg grater appearance with discrete, fine, whitish, spiky follicular scales with or without faint erythema which can be completely asymptomatic or accompanied by dryness, itching, burning or stinging sensation [5,8,12,13]. ID usually shares the same features with NID and concomitant rosacea-like lesions consisting of papules and pustules [5,10,11,13]. The inflammatory stages can show predilection for perioral, periorbital and periauricular regions [12]. Less frequently, ID can manifest as folliculitis or abscesses, hyperpigmentation, follicular eczematids, isolated inflammatory papules, and ocular demodicosis.

Various treatments have been used for *Demodex*-associated skin eruptions, including topical sulfur products, permethrin, topical metronidazole, crotamiton, benzyl benzoate, ivermectin, tea tree oil (TTO), and systemic metronidazole or ivermectin [14-17]. However, there is no consensus on standard of care for the treatment of demodicosis yet. The aim of this study was to evaluate the effects of different treatment modalities on Dds and its impact on clinical outcomes in patients with demodicosis.

## MATERIALS AND METHODS

We retrospectively analysed the data of patients who were diagnosed with facial inflammatory or non-inflammatory demodicosis in dermatology unit of a tertiary hospital in Turkey between January 2019 and December 2019. After obtaining ethical approval, data were collected from the electronic medical records of the patients. Demographic characteristics of the patients, clinical features with the type of demodicosis, type of treatment modality, clinical response to therapy, pre and post-treatment Dds, Dd normalization status were recorded. Patients with a history of immunosuppression, pregnancy or lactation were excluded from the study. Informed consent was obtained for the diagnostic procedures from all patients.

The term "demodicosis" used for describing the patients who had increased Dd with any complaints of the followings: erythema, papules or pustules, burning or stinging sensation, itching, scaling, dryness, irregular or rough skin. Patients who had increased Dds with discrete, fine, whitish, spiky follicular scales with or without erythema but no papules or pustules accepted as NID. Patients who had increased Dds with central or periorificial papulopustules without comedones accepted as ID.

The patients were evaluated in two treatment groups, whether they received systemic treatment or not. Topical treatment group included topical permethrin once nightly in combination with crotamiton once daily whereas combined treatment

group included metronidazole tablet 500 mg two times a day in combination with topical permethrin and/or crotamiton. Dds (mite/cm<sup>2</sup>) were measured by 2 consecutive SSSBs (superficial [SSSB1] and deep [SSSB2]) [4]. A density of more than 5 mite/cm<sup>2</sup> in SSSB1 or more than 10 mite/cm<sup>2</sup> in SSSB2 defined as positive result. Normalization defined as existing  $\leq 5$  mites/cm<sup>2</sup> in SSSB1 and  $\leq 10$  mite/cm<sup>2</sup> in SSSB2. The site used for SSSBs was the clinically affected zone, mainly the cheek of the patients if it was affected.

Measurements of treatment effectiveness included a decrease in Dd to normal levels (SSSB1 $\leq 5$  D/cm<sup>2</sup> and SSSB2 $\leq 10$  D/cm<sup>2</sup>) and general reduction of Dds for each treatment. Secondary outcome measure was defined as clinical improvements in itching, burning or stinging sensation, erythema, xerosis, roughness, and papules or pustules of the skin. Clinical improvements were recorded as improvement, no improvement or worsening of the symptoms.

### Statistical analysis

Statistical analyses were performed by SPSS software version 21.0 statistical package. Categorical variables summarized as frequencies and percentages. Descriptive analyses were presented using mean and standard deviation (SD) for the normally distributed variables or medians and interquartile range (IQR) for the non-normally distributed variables. Since the SSSB1 and SSSB2 measurements were not normally distributed; nonparametric tests were conducted to compare these parameters. Wilcoxon sign-rank test was used to compare the change in pre- and post-treatment Dds on SSSB1 and SSSB2. A p-value of less than 0.05 was considered to show a statistically significant result.

## RESULTS

A total of 21 patients with demodicosis, 15 female and 6 male, were recruited in the study. The mean age was 43 $\pm$ 13.02 years (range 21 to 66 years) and the median follow-up period was 4 months (IQR 1-4 months). The type of demodicosis were recorded as follows: 11 patients (52.3%) had NID and 10 patients (47.6%) had ID. Before the treatment Dds were positive on both SSSB1 and SSSB2 in all patients except 4 patients who had not been performed SSSB2.

Papulopustular lesions recorded in 10 patients with ID (47.6%). Erythema was seen in 18 patients (85.7%) of whom 8 had PF and 10 had ID. Xerosis was noted in 11 patients (52.4%) of whom 7 had PF and 4 had ID. Fifteen patients (71.4%) had itching of whom 8 had PF and 7 had ID. Fourteen patients (66.7%) had roughness of whom 6 had PF and 8 had ID. Twelve patients (57.1%) had burning or stinging sensation of whom 6 had PF and 6 had ID. Three patients (14.3%) had hyperpigmentation.

There were 5 patients in topical treatment group and 16 patients in combined treatment group. The treatment was continued with topical ivermectin in 2 patients who had failure with topical or combined treatments. All 21 patients recommended to wash their face 2 times a day with soap or gel.

Pre and post-treatment Dds were summarized in Table 1 for each treatment groups. In topical treatment group, there was no statistically significant difference between pre and post-treatment Dds on both SSSB1 and SSSB2 (p=0.465 and p=0.686, respectively). SSSB1 and SSSB2 were positive in 4 patients (80%) whereas they were normalized in 1 patient (20%) after a median 4 months (IQR 2-4.5 months) treatment duration.

**Table 1.** Pre- and post-treatment Demodex densities of the treatment groups.

Treatment group	Pre-treatment Dds (D/cm <sup>2</sup> ) Median (IQR)		Post-treatment Dds (D/cm <sup>2</sup> ) Median (IQR)		P value	
	SSSB1	SSSB2	SSSB1	SSSB2	SSSB1	SSSB2
Topical	42 (13-60.5)	122 (44.5-199.5)	78 (6-105.5)	158 (9.5-190)	0.465	0.686
Combined	27.5 (17-53)	79.5 (39.8-151.3)	13 (4.8-41)	77 (17.8-94.5)	0.06	0.09
Overall	30 (17-50.5)	81 (41.5-150)	14 (5.5-43)	80 (17-106)	0.173	0.134

Dds: Demodex densities, SSSB: standardized skin surface biopsy

Clinical improvement was recorded in 4 patients (80%) of whom 1 patient (20%) had normalization on Dds.

In combined treatment group, there was no statistically significant difference between pre and post-treatment Dds on both SSSB1 and SSSB2 ( $p=0.06$  and  $p=0.09$ , respectively). SSSB1 and SSSB2 were positive in 12 patients (75%), SSSB1 was negative and SSSB2 was positive in 3 patients (18.75%) whereas they were normalized in 1 patient (6.25%) after a median of 2 months (IQR 1-4 months) treatment duration. Metronidazole tablet was used with a median duration of 30 days, ranging from 5 to 90 days. Topical therapy was continued after the systemic metronidazole stopped. None of the patients with a systemic treatment reported any adverse effect or terminated the treatment early. Clinical improvement was noted in 10 patients (62.5%) of whom 1 patient (6.25%) had normalization of Dds.

The treatment was continued with topical ivermectin in 2 patients who did not respond to the therapy. Of whom the first patient was recommended topical ivermectin after failure with 2 months usage of systemic metronidazole in combination with topical permethrin and crotamiton. The second patient was recommended topical ivermectin after failure with 4 months usage of topical permethrin and crotamiton. Before topical ivermectin therapy, Dds were 38 and 106 D/cm<sup>2</sup> for the first patient and 112 and 215 D/cm<sup>2</sup> for the second patient on SSSB1 and SSSB2, respectively. One month after treatment, Dds had normalized on SSSB1 and SSSB2 for both two patients. Clinical improvement was also noted on both of them.

Overall, there was no statistically significant difference between pre and post-treatment Dds on SSSB1 and SSSB2 in the whole group ( $p=0.173$  and  $p=0.134$ , respectively). There were a 53.3% decrease on SSSB1 and 1.3% decrease on SSSB2 after the treatment. SSSB1 and SSSB2 were positive in 16 patients (76.2%), SSSB1 was negative and SSSB2 was positive in 3 patients (14.2%) whereas SSSB1 and SSSB2 were normalized in 2 patients (9.5%) after the treatment. With regard to clinical improvement in the whole group, 7 patients (33.3%) had no change whereas any clinical improvement was noted in 14 patients (66.6%) of whom 4 patients were in topical treatment group and 10 patients were in combined treatment group.

No patients had worsening of the symptoms. When the improvement in each symptom after the treatment was evaluated separately; 60%, 33.3%, 36.3%, 53.3%, 50%, 66.6% and 66.6% improvement was recorded in papulopustular lesions, erythema, xerosis, itching, roughness, burning or stinging sensation and hyperpigmentation, respectively.

## DISCUSSION

*Demodex*-associated skin diseases remain a diagnostic and therapeutic challenge in human beings. There are no standardized therapeutic recommendations for the treatment of human *Demodex*-associated skin diseases yet which may be mainly due to the lack of knowledge about the pathogenicity of the mite which also exists in healthy skin. Our study showed that irrespectively of the clinical features, demographics and treatment, our patients were clinically improved without a significant change in Dds. Additionally, both of 2 patients, whose treatment continued with topical ivermectin, had clinical improvement and normalization in Dds within 1 month.

In a recent systematic review about the treatment of *Demodex*-associated inflammatory skin conditions, topical permethrin is recommended as a first-line treatment option and oral metronidazole therapy as a second-line treatment option, with unknown long-term efficacy and safety [18]. In a recent larger study with 394 patients by Forton et. al. topical therapy with benzyl benzoate and crotamiton showed that Dds had normalized in 35% patients and symptoms had cleared in 31% of patient whereas both Dds normalized and symptoms had cleared in 20% of patients [16]. In current study, symptoms had improved in 80% of patients whereas Dds had normalized in only 20% of them after topical permethrin and crotamiton treatment. There was no significant decrease in Dds, conversely the median Dds increased on both SSSB1 and SSSB2 after the treatment. High clinical improvement rate with lack of significant decreasing in Dds may be related to the low acaricidal effect of these agents which cannot be demonstrated in a small sample in the current study.

SSSB is an easily accessible and practical tool in the determination of *Demodex* infestation. A second deep biopsy (SSSB2) performed at the same area



increases the sensitivity of the procedure by providing the sampling of deeper located mites [4]. Thus, if the post-treatment Dds were measured by only SSSB1 in our study, the normalization rate would have increased from 9.5% to 23.8%. We think that sampling with two consecutive SSSBs is important to provide more accurate and comparable results for future research.

There have been a few reports, mainly case reports, on systemic metronidazole therapy for *Demodex* mites with variable results [19-23]. In 2003 Schaller et al. reported a case of demodicosis treated with oral administration of 250 mg metronidazole three times a day for 2 weeks resulted in a rapid and long-lasting recovery including negative scrapings and symptoms following 9 months [21]. Hoekzema et al. reported complete clearing of symptoms and disappearance of facial mites in one patient, with oral metronidazole tablet (500 mg twice daily for 15 days) in combination with 1% metronidazole cream twice daily [23]. On the other hand, it was also reported that a patient who had only slight improvement with 750 mg of metronidazole for 8 months, cleared after 6 weeks of treatment with topical crotamiton [22]. A single-blind, randomized controlled trial by Salem et al. demonstrated that the combined therapy with two doses of ivermectin 200 mcg/kg orally given 1 week apart and metronidazole 250 mg orally three times daily for 2 weeks was superior in reducing the mite count to the normal level in rosacea and in blepharitis lesions from ivermectin alone [24]. They attributed the difference to the anti-inflammatory effect of metronidazole against the mite induced immune response. Supporting that idea, the clinical improvement rate of the symptoms (66.6%) were not associated with the normalization rate of Dds (9.5%) in our study. Although we cannot explain exactly whether the clinical improvement was caused by reducing Dds under a threshold level, even if not yet normalized, with a direct acaricidal effect or by anti-inflammatory properties of agents or both; the relatively high clinical improvement rate against the low normalization rate on Dds may suggest the anti-inflammatory effects of the agents are at the forefront. Since the mite has the ability for inducing inflammatory response, the effect of the agents in an anti-inflammatory way can be explained by suppression of mite-induced inflammation [19,25-27].

Topical ivermectin is a semi-synthetic, antiparasitic agent which is also approved by FDA for papulopustular rosacea in 2014 due to a dual mechanism of action, having both anti-inflammatory and acaricidal activity against *Demodex* mites [28-30]. Recently Trave et al. reported a complete remission of inflammatory lesions in 50 patients affected by PPR treated with topical ivermectin 1% once daily over 16 weeks. Thirty-two percent of their patients were positive for *Demodex* mites, and all of them reported to turn negative after 16 weeks [31]. Additionally, good responses to single dose or repeated weekly doses of oral ivermectin on ocular or cutaneous demodicosis have been reported before [15,32,33]. In accordance with the previous data, 2 patients who received topical ivermectin treatment in our study had both normalization of Dds and reducing in clinical symptoms within one month. Although the delayed benefit resulting from earlier treatments cannot be excluded, topical ivermectin can be considered as a preferential treatment option for *Demodex*-associated skin diseases due to both its acaricidal and anti-inflammatory effects.

The current terminology for describing human demodicosis is quite confusing. In general, human demodicosis has been classified into three main groups as PF, rosacea-like demodicosis and granulomatous rosacea-like demodicosis. Chen W. and Plewig G. proposed a new classification that divides human demodicosis into a primary and secondary form [12]. According to this classification the primary demodicosis includes PF, papulopustular/nodulocystic or conglobate demodicosis, ocular and auricular demodicosis whereas the secondary form describes skin lesions associated with an abnormal increase of *Demodex* mites in patients with other known skin or systemic diseases including rosacea. Traditionally, rosacea-like demodicosis thought to differ from PPR in several clinical criteria; including its rapid onset, asymmetric distribution of more superficial and smaller papules or pustules with periorificial predilection, presence of follicular scales and pruritus without flushing or persistent erythema. However, it is not always straightforward to differentiate it from PPR with these clinical signs in daily practice. Moreover, some authors consider PPR and rosacea like demodicosis are two phenotypes of the same disease and proposed to describe

demodicosis in two clinical forms as NID and ID [11]. Indeed, NID may be considered to include PF or ETR with increased Dds while ID includes PPR with increased Dds or rosacea-like demodicosis. Additionally, vascular findings cannot help to clearly distinguish these two diseases [8,9,13]. In a study by Forton et al. 83% of the patients with PF reported to have vascular symptoms including persistent erythema or flushing [13]. In another study evaluating facial signs and symptoms of *Demodex* infestation showed 65.6% of the patients presented with nonspecific erythema and itching [9]. Similarly, erythema and itching were the most common findings in our study that observed in 85.7% and 71.4% of the patients, respectively. It was followed by roughness (66.7%), burning or stinging sensation (57.1%), xerosis (52.4%) and hyperpigmentation (14.3%). In the current study we preferred to describe patients with increased Dd and concomitant symptoms as NID and ID because we think that demodicosis may be an entity associated with another dermatosis, not secondary to it.

The limitations of this study include its retrospective nature and small sample size. Secondly, the heterogeneous treatment protocol and duration of follow-up period which makes it difficult to compare treatment responses.

Topical permethrin and crotamiton alone or in combination with oral metronidazole provided a clinical improvement in two-thirds of patients with demodicosis in the current study. It is interesting that irrespective of the clinical features, demographics

and treatment, patients improved clinically without a significant change in Dds. The low normalization rate on Dds in patients with clinical improvement might suggest that the treatment response was mostly due to the anti-inflammatory properties of the agents. Although it needs to be confirmed in larger studies, topical ivermectin seems to be most effective and etiological option in demodicosis with positive effects on both clinical findings and Dds. Understanding the causative role of *Demodex* mites in the pathogenesis of human skin diseases will pave the way for more effective treatment options.

### Author contribution

Study conception and design: BYA and NA; data collection: BYA; analysis and interpretation of results: BYA and NA; draft manuscript preparation BYA. All authors reviewed the results and approved the final version of the manuscript.

### Ethical approval

The study was approved by the local ethics committee (GO20/100/27.01.2020).

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The authors declare that the study received no funding.

### Conflict of interest

The authors declare that there is no conflict of interest.

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