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RESEARCH LETTER

Cold atmospheric plasma reduces demodex count on the face comparably to topical ivermectin, as measured by reflectance confocal microscopy

Demodex mites have been implicated in the pathogenesis of skin disorders, including rosacea, for which a topical formulation of the anti-parasitic drug ivermectin is used as an effective treatment.[1] Reflectance confocal microscopy (RCM) is a non-invasive tool that can be used to assess demodex infestation.[2] It has a proven utility to monitor the presence and number of demodex mites during topical ivermectin treatment.[3,4] Cold (physical) atmospheric plasma (CAP), an ionized gas generated by electric devices, is an emerging technology in dermatology with multiple current and proposed applications.[5] The physics and generation of CAP, its biological effects on the skin, and potential medical uses have been comprehensively reviewed and discussed by Busco et al.[6] While CAP is very well tolerated on the skin, it has deleterious effect on human lice, including egg forms.[7] Based on its effect on lice, we hypothesized that CAP may be effective against demodex mites as well.

To assess the ability of CAP to kill demodex in vivo, we obtained informed consent from and enrolled three patients in a split face study (Western Institutional Review Board: 20130084) comparing twice a week cold plasma application to daily topical ivermectin. All three patients had a prior diagnosis of rosacea, and they were not using any other treatments during the study.

The patients were instructed to apply topical ivermectin 1% cream (Soolantra, Galderma Laboratories, L.P.) on the right cheek once daily. The instructions were repeated, and compliance confirmation was received at every treatment session. For the CAP treatment, we used a pulse generator supplying 20 kV pulse at

TABLE 1 Demodex counts before and after topical ivermectin and cold atmospheric plasma (CAP) treatment of patients with rosacea

		Patient 1			Patient 2			Patient 3		
Ivermectin treatment duration		**6 weeks**			**2 weeks**			**6 weeks**		
CAP treatment count		**12 sessions**			**4 sessions**			**10 sessions**		
	Treatment type	**Before**	**After**	**Change**	**Before**	**After**	**Change**	**Before**	**After**	**Change**
Total follicle count	Ivermectin	565	566	n/a	160	149	n/a	688	650	n/a
	CAP	403	384	n/a	181	170	n/a	435	476	n/a
Follicles with mites	Ivermectin	71	31	−56.4%	10	6	−35.6%	80	16	−78.8%
	CAP	75	38	−46.8%	9	5	−40.8%	110	33	−72.6%
Total mite count	Ivermectin	215	30	−86.0%	19	8	−57.9%	362	28	−92.3%
	CAP	197	31	−84.3%	9	6	−33.3%	388	91	−76.5%
Mites per infested follicle	Ivermectin	3.0	1.0	−66.7%	1.9	1.3	−31.6%	4.5	1.8	−60.0%
	CAP	2.6	0.8	−69.2%	1.0	1.2	+20.0%	3.5	2.8	−20.0%
Infested follicle ratio	Ivermectin	12.6%	5.5%	−56.4%	6.3%	4.0%	−36.5%	11.6%	2.5%	−78.4%
	CAP	18.6%	9.9%	−46.8%	5.0%	2.9%	−42.0%	25.3%	6.9%	−72.7%
Mite count/total follicle count	Ivermectin	0.380	0.053	−86.1%	0.11	0.05	−54.8%	0.526	0.043	−91.8%
	CAP	0.488	0.080	−83.5%	0.049	0.035	−29.0%	0.891	0.191	−78.6%

Note: Demodex mite counts obtained from reflectance confocal microscopy images are organized by patient and treatment type. The length of topical ivermectin treatment and the number of CAP treatment sessions performed are also listed. Cold atmospheric plasma and topical ivermectin treatments both resulted in the reduction of the overall number of demodex mites, and the ratio of follicles containing mites. There is a variation in the degree of reduction between patients, which may be partly related to differences between treatment duration and number of CAP treatment sessions.

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200 Hz (FPG10-01NM10, FID GmbH) to a 5 mm diameter quartz-covered copper electrode of 10 cm length, as described previously.[8] To treat the skin, the electrode was placed over the skin of the left cheek lengthwise, and slowly but continuously moved back and forth over an approximately 5 × 5 cm area for 5 min, to maintain even and continuous plasma generation. The CAP treatments were performed twice weekly. To evaluate efficacy, RCM images were obtained using Vivascope 1500 (Caliber Imaging & Diagnostics, Inc.), which enabled us to quantify the demodex infestation of the treated areas. Identical imaging locations for the pre- and post-treatment images were identified using clinical photographs of the marked sites. To ensure comparable counts, the evaluated portion of the follow-up image sets was based on the size of the at least 300 mm^2 size continuous high-quality area of the initial images. Images taken at 60 μm depth were used for counting in all sets, consistently. Follicular units and demodex mites were counted. Two patients completed 6 weeks of treatment. One patient was unable to attend the treatment sessions after 2 weeks due to unplanned travel commitments, but without any correlation to the CAP or ivermectin treatments. The patients tolerated the treatment procedure well. There was no visible change on the skin after the treatment, no signs of inflammation, no discoloration, no reported adverse aftereffects. RCM-based demodex mite counts were obtained from the treatment sides (Figure S1). Pre- and post-treatment demodex count data obtained from the RCM images are shown in Table 1. All three patients showed a comparable reduction in the ratio of mite-infested follicles, and the total number of demodex mites on both the ivermectin and CAP-treated sites.

Our proof-of-concept study—although limited by the small number of patients and lack of non-treated controls—demonstrated that CAP treatment may cause a reduction of demodex mites on the skin, which is comparable to the effect of topical ivermectin, without side effects. Our device is an experimental prototype. Certain CAP devices are licensed for clinical use in different countries but, to our knowledge, none of those have been tested for treating demodicosis. Further studies are needed to determine whether CAP treatment achieves actual clinical improvement of demodex related dermatoses and optimal treatment protocols will have to be developed for it to become a practical tool to treat skin conditions caused by demodex infestation.

AUTHOR CONTRIBUTIONS

For: EXD-22-0095 (Cold atmospheric plasma reduces demodex count on the face comparably to topical ivermectin, as measured by reflectance confocal microscopy by Malik et al.). All authors have read and approved the final version of the manuscript. All authors have substantially contributed to this work, their detailed contributions are listed below: SM: Conducting patient encounters, imaging, collecting and compiling data, writing paper. MG: Designing RCM image collection part of study, evaluating RCM images and collecting RCM data. GF: developing CAP device, designing treatment part of study, developing treatment settings. AF: developing CAP device, developing treatment settings. PCF: Designing entire study, developing treatment and imaging protocols, overseeing patient encounters, imaging, data collection, organizing and evaluating data, writing paper.

KEYWORDS

cold plasma, demodex, non-thermal atmospheric plasma, reflectance confocal microscopy, rosacea

CONFLICT OF INTEREST

The authors have no conflict of interest to declare, except Dr. Gregory Fridman is an inventor of a provisional patent concerning the device used in this study.

IRB APPROVAL

Western Institutional Review Board, date: 4/9/2019, protocol number: 20130084 ClinicalTrials.gov, registration number: NCT02759900.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Figure S1 Reflectance confocal microscopy (RCM) images of demodex mites before and after topical ivermectin and cold atmospheric plasma (CAP) treatment of patients with rosacea. Before (left panels) and after (right panels) treatment images of 8X8 mm areas of facial skin (Patient 1). Panels (a) and (b) are images of the topical ivermectin 1% cream treated side. Panels (c) and (d) are images of the CAP-treated side. Both sides show significant decrease of demodex mite count. Panels (e) and (f) are magnified images of the CAP-treated areas, corresponding to the red rectangles. Follicles with demodex mites are marked by red arrows.

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