DOI: 10.1111/pde.14180

CASE REPORT

Pediatric Dermatology WILEY

Using cold plasma to treat warts in children: A case series

Peter C. Friedman MD, PhD[1] | Gregory Fridman PhD[2] | Alexander Fridman PhD[2]

[1]The Skin Center Dermatology Group, New City, NY, USA

[2]C&J Nyheim Plasma Institute, Drexel University, Camden, NJ, USA

Correspondence
Peter C. Friedman, MD,PhD The Skin Center Dermatology Group, 200 E Eckerson Rd New City, NY 10956, USA.
Email: pbc9@columbia.edu

Abstract

Treatment of warts is especially challenging in the pediatric patient population because of the pain associated with many of available treatments. Cold atmospheric pressure plasma is a novel treatment with expanding clinical uses for a variety of skin conditions. In this case series, we present five pediatric patients who achieved full clearance of warts with cold plasma treatment. While further studies are needed, these results are promising because of the efficacy and entirely painless nature of this treatment modality.

KEYWORDS

cold plasma, infection—viral, therapy—topical, warts

1 | INTRODUCTION

Warts are a common problem for pediatric patients. Management options include a wide range of over-the-counter, prescription, and in-office treatments, all of which have variable cure rates between 15% and 95%.[1] A 2012 Cochrane review of 85 studies[2] and a subsequent 2016 Cochrane Clinical Answer[3] concluded that the most commonly used modalities, salicylic acid and cryotherapy, showed only modest advantage when compared to placebo. There was limited evidence, due to the poor quality of available studies, to determine the efficacy of less frequently used methods, including intralesional injection of Candida antigen, mumps measles rubella vaccine, 5-fluorouracil, or bleomycin. Additionally both cryotherapy and salicylic acid require repeated application and are often too painful for use in children.



FIGURE 1 Cold atmospheric plasma device used for wart treatment. Custom made cold atmospheric pressure plasma device with hand-held electrode and pulse generator

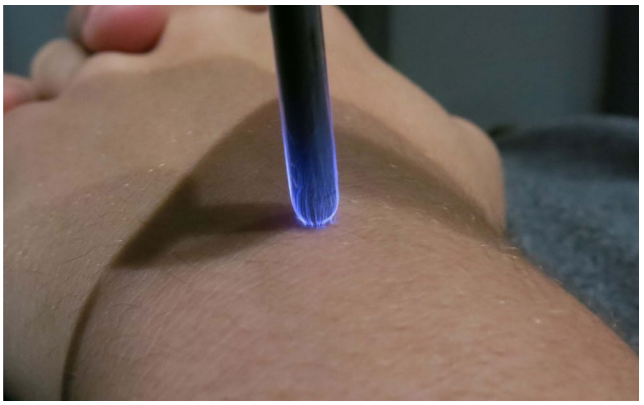


FIGURE 2 Cold atmospheric plasma treatment. Dielectric-barrier discharge plasma generated on the skin surface using the tip of the electrode

IRB approval: Western Institutional Review Board, date: 11/10/2016, protocol number: 20130084.

Trial registration: ClinicalTrials.gov, registration number: NCT02759900.

 © 2020 Wiley Periodicals LLC

TABLE 1 Results of pediatric patients with warts treated with cold atmospheric plasma

Patient	Age years/ Sex	Number/Location of Warts	Previous treatment/ Duration	Number of CAP treatments	AE	Time to clearance	Follow-up/ Outcome
1	9 F	6 Hand, subungual	None >1 y	1	None	4 wk	9 mo No recurrence
2	11 F	6 Foot	None 5 mo	1	None	4 wk	7 mo No recurrence
3	15 F	9 Hands	None 7 mo	2	None	7 wk	10 mo No recurrence
4	17 M	6 Foot	Sal. acid 7 mo	4	None	16 wk	6 mo No recurrence
5	15 F	1 Dorsal toe	Cryotherapy 4 mo	2	None	7 wk	7 mo No recurrence

Abbreviations: AE, adverse events; CAP, cold atmospheric plasma.

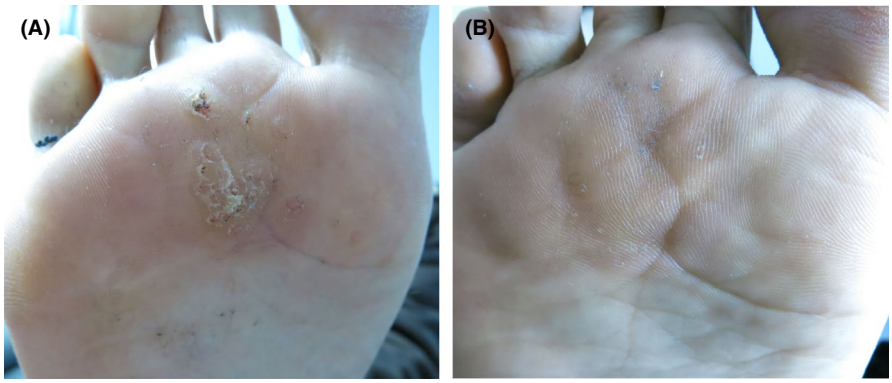


FIGURE 3 Patient 4: A, Warts on the right plantar surface before treatment. B, All warts cleared fully after four treatment sessions. Photograph taken one month after the last treatment

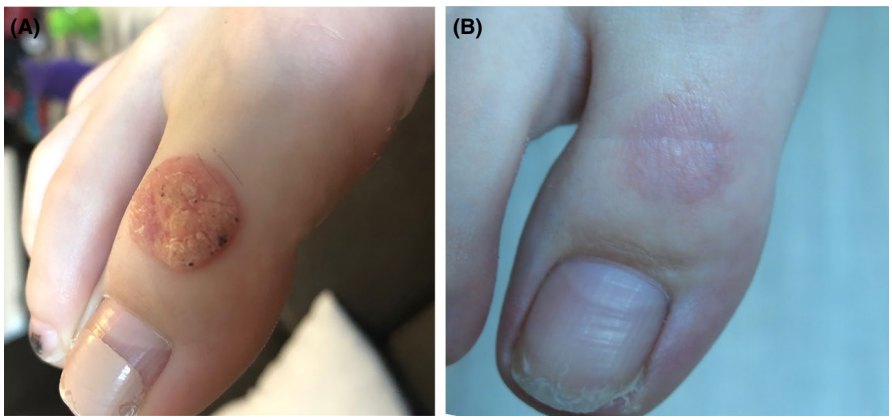


FIGURE 4 Patient 5: A, Wart on the right first toe before treatment. B, Photograph at 1-month follow-up. Wart resolved after two treatments. Residual erythema resolved with no scarring or recurrence

Recently, cold atmospheric pressure plasma (CAP) has emerged as a way of modifying various cells and tissues.[4] CAP, essentially an ionized gas, is typically generated using short pulsed high voltage. Some devices use a gas stream to carry plasma to the treated surface (plasma jet) while others create plasma directly on the treated surface by placing an electrode near the target area.[5] CAP has been extensively studied for its effects on living tissues in vitro and in animal models, leading to recent clinical trials in various skin conditions, such as chronic leg ulcer and actinic keratosis. In this case series, we report using CAP for the treatment of warts in five pediatric patients.

2 | PROCEDURE

This study was approved by Western Institutional Review Board (20130084). The CAP device used in this study is not commercially available. To create dielectric-barrier discharge (DBD) plasma, we used a pulse generator supplying 20 kV pulse of 20 ns pulse-width at 400 Hz (FPG10-01NM10; FID GmbH, Germany, www.fidtechnology.com) to a 5-mm diameter quartz-covered copper electrode of 10 cm length, 1 mm quartz thickness. These nanosecond pulse parameters were chosen to provide sufficient treatment dose at the high level of plasma uniformity required to avoid tissue damage.[6] The treatment

consisted of holding the electrode tip approximately 1 mm from the treated wart and slowly moving it around to cover the entire wart surface. (Figures 1 and 2) Treatments were applied for two minutes to each lesion separately. Depending on the number of lesions treated, the treatment sessions lasted from 2 to 20 minutes. The patients were evaluated at 3-4-week intervals and the treatment was repeated for persistent lesions. After obtaining informed consent, five patients (age 9-17 years) were enrolled. Demographic information and treatment results are detailed in Table 1. Figures 3 and 4 show the clinical improvement in patients 4 and 5. None of the patients reported pain or discomfort, during treatment. There were no adverse effects reported in the follow-up period, including blistering, scarring, significant pigmentary alteration, or persistent nail changes.

3 | DISCUSSION

We previously reported the in vivo efficacy of CAP for treatment of warts in two adults with warts on the hand and wrist. Complete clearance was noted in four out of five lesions with an average of three treatments.[7]

The mechanism of action of CAP in warts is unknown. It has been reported that CAP selectively induces apoptosis in malignant cells *in vitro*,[8,9] and the device has been successfully used in the treatment of actinic keratoses.[10,11] Induction of local immune response by CAP as a mechanism of action has been proposed for actinic keratosis treatment, but in vivo data are insufficient. The complete lack of clinical visible inflammation also militates against this hypothesis. Other possible mechanisms include induction of oxidative stress and direct virus inhibition based on previously demonstrated in vitro effect of CAP on adenoviruses,[12] which are non-enveloped DNA viruses similarly to human papillomavirus (HPV), the causative agent of warts.

One known effect of CAP is to substantially increase intracellular calcium level.[4] There are data connecting higher intracellular calcium concentration to enhanced susceptibility to cytostatic agents.[13] In vitro studies also demonstrated CAP triggering cell senescence in melanoma cells via inducing calcium influx.[14] HPV-infected keratinocytes may also be susceptible to calcium influx. Recent data show that the topical chemotherapeutic and anti-wart agent, imiquimod, induces endoplasmic reticulum stress and resulting apoptosis in a Toll-like receptor independent manner, via triggering cellular calcium influx and endoplasmic reticulum calcium depletion.[15] This calcium influx–triggered cell death is suggested to be at least partly responsible for the in vivo effect of imiquimod on warts, actinic keratosis, and malignancies. While direct evidence is lacking, it can be hypothesized that CAP induces cell death in warts by triggering cellular calcium influx. Influencing intracellular calcium levels may be the principal way how CAP exerts many of its biological effects, including its ability to induce stem cell differentiation, and possibly its yet unexplained, curious beneficial effect reported in a single case of Hailey-Hailey disease,[16] a condition resulting from mutations in the *ATP2C1* gene. It was shown that the activity of the Ca^2/Mn^2 ATPase encoded by *ATP2C1* is influenced by calcium concentrations making it possible that CAP had a calcium-mediated effect on the transport function leading to clinical improvement.[17] Further study on the mechanism of action of CAP in warts is needed.

The CAP system used in this study is not currently commercially available. Therefore, we do not have accurate cost estimates for treatment. The device has no consumable parts and because of its simplicity, it is expected to have a long life span without need for regular maintenance. Nonetheless, the initial investment may represent a barrier for clinical use. On the other hand, performing CAP treatment is simple, requires minimal training, and is very safe with no reported adverse events, which should facilitate adoption of this technology. The limitations of this study include the small number of treated patients and the lack of control group.

In conclusion, we demonstrated in this small case series that CAP is well tolerated, easy to administer, and an effective treatment for warts in pediatric patients. If larger studies confirm our initial findings, and an affordable device can be developed, CAP may become a valuable treatment modality for pediatric patients with warts.

ORCID

Peter C. Friedman https://orcid.org/0000-0002-1276-7300

REFERENCES

1. Lipke MM. An armamentarium of wart treatments. *Clin Med Res*. 2006;4(4):273-293.
2. Kwok CS, Gibbs S, Bennett C, Holland R, Abbott R. Topical treatments for cutaneous warts. *Cochrane Database Syst Rev*. 2012;(9):CD001781.
3. Kirtschig G. What are the benefits and harms of topical treatments in people with cutaneous warts? In: *Cochrane Clinical Answers*. Hoboken, NJ: John Wiley & Sons, Ltd; 2016. https://doi.org/10.1002/cca.468
4. Dobrynin D, Fridman G, Friedman G, Fridman A. Physical and biological mechanisms of direct plasma interaction with living tissue. *New J Phys*. 2009;11:115020.
5. Von Woedtke T, Schmidt A, Bekeschus S, Wende K, Weltmann KD. Plasma medicine: a field of applied redox biology. *Vivo (Brooklyn)*. 2019;33(4):1011-1026.
6. Fridman G, Friedman G, Gutsol A, Shekhter AB, Vasilets VN, Fridman A. Applied plasma medicine. *Plasma Process Polym*. 2008;5(6):503-533.
7. Friedman PC, Miller V, Fridman G, Fridman A. Use of cold atmospheric pressure plasma to treat warts: a potential therapeutic option. *Clin Exp Dermatol*. 2019;44(4):459-461.
8. Liu Y, Tan S, Zhang H, et al. Selective effects of non-thermal atmospheric plasma on triple-negative breast normal and carcinoma cells through different cell signaling pathways. *Sci Rep*. 2017;7(1):7980.
9. Zucker SN, Zirnheld J, Bagati A, et al. Preferential induction of apoptotic cell death in melanoma cells as compared with normal keratinocytes using a non-thermal plasma torch. *Cancer Biol Ther*. 2012;13(13):1299-1306.
10. Friedman PC, Miller V, Fridman G, Lin A, Fridman A. Successful treatment of actinic keratoses using nonthermal atmospheric pressure plasma: a case series. *J Am Acad Dermatol*. 2017;76(2):349-350.
11. Friedman PC, Miller V, Fridman G, Fridman A. Various cold plasma devices for the treatment of actinic keratosis. *J Eur Acad Dermatology Venereol*. 2018;32(12):e445-e446.
12. Zimmermann JL, Dumler K, Shimizu T, et al. Effects of cold atmospheric plasmas on adenoviruses in solution. *J Phys D Appl Phys*. 2011;44(50):505201.

13. Doignon I, Fayol O, Dellis O. Improvement of the rituximab-induced cell death by potentiation of the store-operated calcium entry in mantle cell lymphoma cell lines. *Oncotarget*. 2019;10(43):4466-4478.
14. Schneider C, Gebhardt L, Arndt S, et al. Cold atmospheric plasma causes a calcium influx in melanoma cells triggering CAP-induced senescence. *Sci Rep*. 2018;8(1):10048.
15. Nyberg WA, Espinosa A. Imiquimod induces ER stress and Ca2+ influx independently of TLR7 and TLR8. *Biochem Biophys Res Commun*. 2016;473(4):789-794.
16. Isbary G, Morfill G, Zimmermann J, Shimizu T, Stolz W. Cold atmospheric plasma: a successful treatment of lesions in hailey-hailey disease. *Arch Dermatol*. 2011;147(4):388-390.
17. Chen J, Smaardijk S, Mattelaer CA, et al. An N-terminal Ca2+-binding motif regulates the secretory pathway Ca2+/Mn2+-transport ATPase SPCA1. *J Biol Chem*. 2019;294(19):7878-7891.

How to cite this article: Friedman PC, Fridman G, Fridman A. Using cold plasma to treat warts in children: A case series. *Pediatr Dermatol*. 2020;00:1–4. https://doi.org/10.1111/pde.14180