

Potential Uses of Nonthermal Atmospheric Pressure Technology for Dermatologic Conditions in Children

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PRACTICE POINTS

- Nonthermal atmospheric plasma (NTAP)(also known as cold atmospheric plasma) has been shown to cause minimal damage to skin when application time is minimized.
- Beyond its diverse applications, treatment with NTAP yields a unique advantage to pharmacologic therapies in that there is no risk for medication interactions or pharmacologic adverse effects.
- Although the use of NTAP in pediatric dermatology is scarcely described in the literature, the technology will certainly have applications in the future treatment of a wide variety of pediatric disorders.

Nonthermal atmospheric plasma (NTAP)(also known as cold atmospheric plasma [CAP]) is a rapidly emerging technology showing promising treatment results for a wide variety of dermatologic conditions. Research on NTAP for the treatment of pediatric dermatologic conditions is limited. We conducted a systematic review to elucidate reported applications of NTAP for skin conditions in children. Overall, NTAP offers a promising safety profile and painless treatment option that has the potential to deliver similar efficacy to many standard therapies in pediatric dermatology.

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Nonthermal atmospheric plasma (NTAP)(or cold atmospheric plasma [CAP]) is a rapidly developing treatment modality for a wide range of dermatologic conditions. Plasma (or ionized gas) refers to a state of matter composed of electrons, protons, and neutral

atoms that generate reactive oxygen and nitrogen species.¹ Plasma previously was created using thermal energy, but recent advances have allowed the creation of plasma using atmospheric pressure and room temperature; thus, NTAP can be used without causing damage to living tissue through heat.¹ Plasma technology varies greatly, but it generally can be classified as either direct or indirect therapy; direct therapy uses the human body as an electrode, whereas indirect therapy creates plasma through the interaction between 2 electrode devices.^{1,2} When used on the skin, important dose-dependent relationships have been observed, with CAP application longer than 2 minutes being associated with increased keratinocyte and fibroblast apoptosis.² Thus, CAP can cause diverse changes to the skin depending on application time and methodology. At adequate yet low concentrations, plasma can promote fibroblast proliferation and upregulate genes involved in collagen and transforming growth factor synthesis.¹ Additionally, the reactive oxygen and nitrogen species created by NTAP have been shown to inactivate microorganisms through the destruction of biofilms, lead to diminished immune cell infiltration and cytokine release in autoimmune dermatologic conditions, and exert antitumor properties through cellular DNA damage.¹⁻³ In dermatology, these properties can be harvested to promote wound healing at low doses and the treatment of proliferative skin conditions at high doses.¹

Because of its novelty, the safety profile of NTAP is still under investigation, but preliminary studies are promising and show no damage to the skin barrier when excessive plasma exposure is avoided.⁴ However, dose- and time-dependent damage to cells has been shown. As a result, the exact dose of plasma considered safe is highly variable

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depending on the vessel, technique, and user, and future clinical research is needed to guide this methodology.⁴ Additionally, CAP has been shown to cause little pain at the skin surface and may lead to decreased levels of pain in healing wound sites.⁵ Given this promising safety profile and minimal discomfort to patients, NTAP technology remains promising for use in pediatric dermatology, but there are limited data to characterize its potential use in this population. In this systematic review, we aimed to elucidate reported applications of NTAP for skin conditions in children and discuss the trajectory of this technology in the future of pediatric dermatology.

Methodology

A comprehensive literature review was conducted to identify studies evaluating NTAP technology in pediatric populations using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines. A search of PubMed, Embase, and Web of Science articles was conducted in April 2023 using the terms *nonthermal atmospheric plasma* or *cold atmospheric plasma*. All English-language articles that described the use of NTAP as a treatment in pediatric populations or articles that described NTAP use in the treatment of common conditions in this patient group were included based on a review of the article titles and abstracts by 2 independent reviewers, followed by full-text review of relevant articles (M.G., C.L.). Any discrepancies in eligible articles were settled by a third independent researcher (M.V.). One

hundred twenty studies were identified, and 95 were screened for inclusion; 9 studies met inclusion criteria and were summarized in this review.

Results

A total of 9 studies were included in this review: 3 describing the success of NTAP in pediatric populations⁶⁻⁸ and 6 describing the potential success of NTAP for dermatologic conditions commonly seen in children (Table).⁹⁻¹⁴

Studies Describing Success of NTAP—Three clinical reports described the efficacy of NTAP in pediatric dermatology. A case series from 2020 showed full clearance of warts in 100% of patients (n=5) with a 0% recurrence rate when NTAP treatment was applied for 2 minutes to each lesion during each treatment session with the electrode held 1 mm from the lesional surface.⁶ Each patient was followed up at 3 to 4 weeks, and treatment was repeated if lesions persisted. Patients reported no pain during the procedure, and no adverse effects were noted over the course of treatment.⁶ Second, a case report described full clearance of diaper dermatitis with no recurrence after 6 months following 6 treatments with NTAP in a 14-month-old girl.⁷ After treatment with econazole nitrate cream, oral antibiotics, and prednisone failed, CAP treatment was initiated. Each treatment lasted 15 minutes with 3-day time intervals between each of the 6 treatments. There were no adverse events or recurrence of rash at 6-month follow-up.⁷ A final case report described full clearance of molluscum contagiosum (MC), with no recurrence after 2 months

Potential Success of NTAP Technology in Treating Common Dermatologic Conditions in Children

Reference (year)	Condition	Sample size	Result
Suwanchinda and Nararatwanchai ⁹ (2022)	Striae distensae	N=23	After 1 session, significant improvement in patient and observer scar assessment scale compared with control sites ($P<.05$)
Suwanchinda and Nararatwanchai ¹⁰ (2022)	Keloid scars	N=18	After 2 treatments, significant improvement in color, melanin, texture, and hemoglobin in half of treated keloids vs untreated controls ($P<.05$)
Kim et al ¹¹ (2021)	Mild to moderate atopic dermatitis	N=22	After 3 treatments, significant reduction in the ADAS score at wk 4 ($P\leq.0001$)
Gareri et al ¹² (2020)	Psoriasis	N=1	After 2 treatments, complete resolution of single psoriasis plaque at 14 d
Zheng et al ¹³ (2020)	Inverse psoriasis	N=2	After 5 and 8 treatments, improvement in lesions and pruritus without recurrence at 6 and 4 wk, respectively
Arisi et al ¹⁴ (2020)	Acne vulgaris	N=2	After 5 and 8 treatments, there was a reduction in the number of inflamed lesions with no clinical relapse in either patient at 3 mo follow-up

Abbreviations: ADAS, Atopic Dermatitis Antecubital Severity; NTAP, nonthermal atmospheric plasma.

following 4 treatments with NTAP in a 12-year-old boy.⁸ The patient had untreated MC on the face, neck, shoulder, and thighs. Lesions of the face were treated with CAP, while the other sites were treated with cantharidin using a 0.7% collodion-based solution. Four CAP treatments were performed at 1-month intervals, with CAP applied 1 mm from the lesional surfaces in a circular pattern for 2 minutes. At follow-up 2 months after the final treatment, the patient had no adverse effects and showed no pigmentary changes or scarring.⁸

*Studies Describing the Potential Success of NTAP—*Beyond these studies, limited research has been done on NTAP in pediatric populations. The Table summarizes 6 additional studies completed with promising treatment results for dermatologic conditions commonly seen in children: striae distensae, keloids, atopic dermatitis, psoriasis, inverse psoriasis, and acne vulgaris. Across all reports and studies, patients showed significant improvement in their dermatologic conditions following the use of NTAP technology with limited adverse effects reported ($P < .05$). Suwanchinda and Nararatwanchai⁹ studied the use of CAP for the treatment of striae distensae. They recruited 23 patients and treated half the body with CAP biweekly for 5 sessions; the other half was left untreated. At follow-up 30 days after the final treatment, striae distensae had improved for both patient and observer assessment scores.⁹ Another study performed by Suwanchinda and Nararatwanchai¹⁰ looked at the efficacy of CAP in treating keloids. They recruited 18 patients, and keloid scars were treated in halves—one half treated with CAP biweekly for 5 sessions and the other left untreated. At follow-up 30 days after the final treatment, keloids significantly improved in color, melanin, texture, and hemoglobin based on assessment by the Antera 3D imaging system (Miravex Limited) ($P < .05$).¹⁰

Kim et al¹¹ studied the efficacy of CAP for the treatment of atopic dermatitis in 22 patients. Each patient had mild to moderate atopic dermatitis that had not been treated with topical agents or antibiotics for at least 2 weeks prior to beginning the study. Additionally, only patients with symmetric lesions—meaning only patients with lesions on both sides of the anatomical extremities—were included. Each patient then received CAP on 1 symmetric lesion and placebo on the other. Cold atmospheric plasma treatment was done 5 mm away from the lesion, and each treatment lasted for 5 minutes. Treatments were done at weeks 0, 1, and 2, with follow-up 4 weeks after the final treatment. The clinical severity of disease was assessed at weeks 0, 1, 2, and 4. Results showed that at week 4, the mean (SD) modified Atopic Dermatitis Antecubital Severity score decreased from 33.73 (21.21) at week 0 to 13.12 (15.92). Additionally, the pruritic visual analog scale showed significant improvement with treatment vs baseline ($P \leq .0001$).¹¹

Two studies examined how NTAP can be used in the treatment of psoriasis. First, Gareri et al¹² used CAP to treat a psoriatic plaque in a 20-year-old woman. These plaques

on the left hand previously had been unresponsive to topical psoriasis treatments. The patient received 2 treatments with CAP on days 0 and 3; at 14 days, the plaque completely resolved with an itch score of 0.¹² Next, Zheng et al¹³ treated 2 patients with NTAP for inverse psoriasis. The first patient was a 26-year-old woman with plaques in the axilla and buttocks as well as inframammary lesions that failed to respond to treatment with topicals and vitamin D analogues. She received CAP treatments 2 to 3 times weekly for 5 total treatments with application to each region occurring 1 mm from the skin surface. The lesions completely resolved with no recurrence at 6 weeks. The second patient was a 38-year-old woman with inverse psoriasis in the axilla and groin; she received treatment every 3 days for 8 total treatments, which led to complete remission, with no recurrence noted at 1 month.¹³

Arisi et al¹⁴ used NTAP to treat acne vulgaris in 2 patients. The first patient was a 24-year-old man with moderate acne on the face that did not improve with topicals or oral antibiotics. The patient received 5 CAP treatments with no adverse events noted. The patient discontinued treatment on his own, but the number of lesions decreased after the fifth treatment. The second patient was a 21-year-old woman with moderate facial acne that failed to respond to treatment with topicals and oral tetracycline. The patient received 8 CAP treatments and experienced a reduction in the number of lesions during treatment. There were no adverse events, and improvement was maintained at 3-month follow-up.¹⁴

Comment

Although the use of NTAP in pediatric dermatology is scarcely described in the literature, the technology will certainly have applications in the future treatment of a wide variety of pediatric disorders. In addition to the clinical success shown in several studies,⁶⁻¹⁴ this technology has been shown to cause minimal damage to skin when application time is minimized. One study conducted on ex vivo skin showed that NTAP technology can safely be used for up to 2 minutes without major DNA damage.¹⁵ Through its diverse mechanisms of action, NTAP can induce modification of proteins and cell membranes in a noninvasive manner.² In conditions with impaired barrier function, such as atopic and diaper dermatitis, studies in mouse models have shown improvement in lesions via upregulation of mesencephalic astrocyte-derived neurotrophic factor that contributes to decreased inflammation and cell apoptosis.¹⁶ Additionally, the generation of reactive oxygen and nitrogen species has been shown to decrease *Staphylococcus aureus* colonization to improve atopic dermatitis lesions in patients.¹¹

Many other proposed benefits of NTAP in dermatologic disease also have been proposed. Nonthermal atmospheric plasma has been shown to increase messenger RNA expression of proinflammatory cytokines (IL-1, IL-6) and upregulate type III collagen production in early stages of wound healing.¹⁷ Furthermore, NTAP has been

shown to stimulate nuclear factor erythroid 2–related pathways involved in antioxidant production in keratinocytes, further promoting wound healing.¹⁸ Additionally, CAP has been shown to increase expression of caspases and induce mitochondrial dysfunction that promotes cell death in different cancer cell lines.¹⁹ It is clear that the exact breadth of NTAP's biochemical effects are unknown, but the current literature shows promise for its use in cutaneous healing and cancer treatment.

Beyond its diverse applications, treatment with NTAP yields a unique advantage to pharmacologic therapies in that there is no risk for medication interactions or risk for pharmacologic adverse effects. Cantharidin is not approved by the US Food and Drug Administration but commonly is used to treat MC. It is a blister beetle extract that causes a blister to form when applied to the skin. When orally ingested, the drug is toxic to the gastrointestinal tract and kidneys because of its phosphodiesterase inhibition, a feared complication in pediatric patients who may inadvertently ingest it during treatment.²⁰ This utility extends beyond MC, such as the beneficial outcomes described by Suwanchinda and Nararatwanchai¹⁰ in using NTAP for keloid scars. Treatment with NTAP may replace triamcinolone injections, which are commonly associated with skin atrophy and ulceration. In addition, NTAP application to the skin has been reported to be relatively painless.⁵ Thus, NTAP maintains a distinct advantage over other commonly used nonpharmacologic treatment options, including curettage and cryosurgery. Curettage has widely been noted to be traumatic for the patient, may be more likely to leave a mark, and is prone to user error.²⁰ Cryosurgery is a common form of treatment for MC because it is cost-effective and has good cosmetic results; however, it is more painful than cantharidin or anesthetized curettage.²¹ Treatment with NTAP is an emerging therapeutic tool with an expanding role in the treatment of dermatologic patients because it provides advantages over many standard therapies due to its minimal side-effect profile involving pain and nonpharmacologic nature.

Limitations of this report include exclusion of non-English-language articles and lack of control or comparison groups to standard therapies across studies. Additionally, reports of NTAP success occurred in many conditions that are self-limited and may have resolved on their own. Regardless, we aimed to summarize how NTAP currently is being used in pediatric populations and highlight its potential uses moving forward. Given its promising safety profile and painless nature, future clinical trials should prioritize the investigation of NTAP use in common pediatric dermatologic conditions to determine if they are equal or superior to current standards of care.

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