

Safety and Efficacy of Nanosecond Pulsed Electric Field Treatment of Sebaceous Gland Hyperplasia

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BACKGROUND Nanosecond pulsed electric field (nsPEF) technology involves delivery of ultrashort pulses of electrical energy and is a nonthermal, drug-free technology that has demonstrated favorable effects on cellular structures of the dermis and epidermis.

OBJECTIVE Determine the tolerability and effectiveness of nsPEF treatment of sebaceous gland hyperplasia (SGH).

METHODS This study was a prospective, randomized, open-label, multisite, nonsignificant risk trial in which each subject served as their own control. After injection of local anesthetic, high-intensity, ultrashort pulses of electrical energy were used to treat 72 subjects resulting in a total of 222 treated lesions. Subjects returned for 3 to 4 follow-up evaluations with photographs.

RESULTS At the final study visit, 99.6% of treated SGH lesions were rated clear or mostly clear and 79.3% of the subjects were satisfied or mostly satisfied with the outcome. At 60 days after nsPEF treatment, 55% of the lesions were judged to have no hyperpigmentation and 31% exhibited mild post-treatment hyperpigmentation. At the last observation for all lesions, 32% of the 222 lesions were noted as having slight volume loss.

CONCLUSION Nanosecond pulsed electric field procedure is well tolerated and is very effective in the removal of SGHs.

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Sebaceous gland hyperplasia (SGH) is a common condition that appears as white or lightly pigmented, indented papules or bulges on the skin that occur when hyperactive sebaceous glands produce excess oil (sebum) that pushes up on the skin surface. There are sebaceous glands all over the body; so, the

SGH papules can form almost anywhere, although they are more frequently observed and treated when they appear on facial skin. These benign lesions are more likely to occur in middle-aged and older people and are reported to occur in approximately 1% of the healthy US population. However, the prevalence of

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sebaceous hyperplasia has been reported to be as high as 10% to 16% in patients receiving long-term immunosuppression.¹

Traditional methods of treatment include cryosurgery, electrodesiccation, curettage, shave excision, and topical trichloroacetic/bichloroacetic acid, but these treatments can lead to skin discoloration and/or scarring.² Photodynamic therapy (PDT) has also been used with aminolevulinic acid or methyl aminolevulinate as a photosensitizer usually requiring 2 to 6 treatment sessions.³ Laser therapy has also been attempted (typically infrared in nature) with varying success.³

This study evaluated the application of a novel, non-thermal energy device that applies nanosecond pulsed electric fields (nsPEFs) as ultrashort pulses of electrical energy in the nanosecond range called Nano-Pulse Stimulation (NPS) therapy to SGH lesions. Nanosecond pulsed electric field treatment has been found to target cellular components of the dermis and epidermis to stimulate a delayed form of regulated cell death (RCD) while leaving surrounding fibrous, acellular components unaffected.^{4,5} A primary goal of this study was to evaluate the tolerability and efficacy of an nsPEF device (PulseTx) in clearing SGH lesions after 1 or 2 nsPEF treatments.

The hypothesized primary mechanism of action caused by nsPEF technology is RCD,^{6,7} which is not immediately evident in contrast to other available treatments such as radiofrequency ablation, whose primary mechanism of action is thermal necrosis⁸ with skin effects visible almost immediately. Previous studies have demonstrated that this form of RCD can be immunogenic and has stimulated a secondary and lasting immune response in preclinical murine models of malignant lesions, such as murine human papilloma virus tumors and hepatocellular carcinoma.^{7,9,10} This ability to cause direct tumor cell death and a subsequent vaccine-like immunity with a drug-free modality has implications for the treatment of both benign and malignant lesions.

Methods

This was a prospective, randomized, open-label, multicenter, nonsignificant risk study where subjects

with multiple SGH lesions served as their own control. The study protocol was reviewed and approved by an institutional review board (Biomedical Research Institute of America, protocol NP-SH-006) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Subjects

Up to 19 subjects were recruited in each of the 5 centers with 2 to 5 SGHs on their faces for a total of 72 subjects.

Treatment Procedures

Principal investigators (PIs) were identified at the 5 participating study centers. Baseline photographs of each of the 2 to 5 selected SGHs were taken before anesthesia or treatment. Local anesthetic lidocaine was injected at the sites of the selected SGHs. One to 4 lesions underwent a single treatment with the NPS system, whereas one lesion was treated as a sham. The sham treatment involved injection of lidocaine at the site like the nsPEF-treated lesions. The treatment tip was then placed on the sham control lesion and a mock delivery of energy for 45 seconds was performed. Timing of the mock treatment was monitored using a stopwatch. The sham control served as a clinical assessment comparative group and the pretreated state of each treated lesion also served as a control. The nsPEF system consists of an electrical console that produces predetermined pulse sequences (a “cycle”) of high-intensity, ultrashort electrical energy pulses through a handpiece applicator connected to a sterile, single-patient use treatment tip, which is applied to the skin on and around the SGH lesion. Treatment tips consist of a polymer shell encasing an array of electrically conducting microneedles that penetrate the reticular dermis (Figure 1).

The nsPEF treatment of a single SGH lesion entailed selecting the treatment energy level (0.5–6.3 J), applying sterile contact gel, pressing the treatment tip into the skin, and actuating the footswitch to initiate the nsPEF treatment cycle that lasts less than one minute. The 2 treatment tips used treated an area of 1.5 × 1.5 mm or 2.5 × 2.5 mm, respectively. The

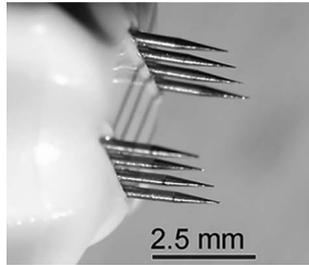


Figure 1. Typical configuration of microneedles on the treatment tips used.

subjects rated their degree of pain using a standardized pain scale of 0 to 10. The sham lesion underwent an identical process with the exception that no energy was delivered to the lesion.

After the initial treatment visit, subjects returned at intervals of 5, 30, 60, and, if applicable, 90 days for photographs of the lesions and investigator evaluation of the treated areas. Photographs were taken of all 5 lesion areas at each study visit using both a Sony Cybershot DSC-RX100 and a Handyscope (FotoFinder Systems GmbH, Columbia, MD). Before SGH lesion treatment, a clear acetate “Lesion Map” was created for each lesion location to correctly reidentify the location of the original lesion area throughout the 60- to 90-day evaluation window. This was needed because complete lesion clearance occurred in most instances, and the original lesion area was not visually apparent. A ruler was placed in each photograph to enable precise scaling of the images in comparison with baseline photograph of the lesion.

Subjects were asked to rate their level of satisfaction with the outcome for each of their treated lesions, taking into consideration both lesion clearance and the

residual skin appearance. The 5-point rating scale included satisfied, mostly satisfied, partially satisfied, dissatisfied, and highly dissatisfied.

Results

Establishing Safety by Treating Facial Skin Before Resection

A range of nsPEF treatment energies was first applied to 7 subjects on a facial region that was scheduled for resection in a facelift procedure. This made possible histological analysis of the treated skin at several time points after treatment so that the appropriate nsPEF energy to target cellular structures in the skin while sparing the acellular components could be determined. This histology indicated that sebaceous glands could be slowly eliminated after nsPEF treatment (Figure 2).

Subjects

A total of 72 study subjects had 2 to 5 SGH lesions treated. Seventy-eight percent ($n = 56$) of the subjects were female and 22% ($n = 16$) were male. Subject age ranged from 31 to 71 years with an average age of 55 years and median age of 56 years. Most subjects reported being Caucasian ($n = 68, 94\%$), 1 reported being (1%) Hispanic/Latino, and 3 reported being (4%) Asian.

Most subjects ($n = 36; 50\%$) were classified as a Class III-medium skin type on the Fitzpatrick Skin Sun Classification scale, 46% ($n = 33$) were Class II-fair, 1% ($n = 1$) was Class I-very fair, and 3% ($n = 2$) were Class IV-moderate brown.

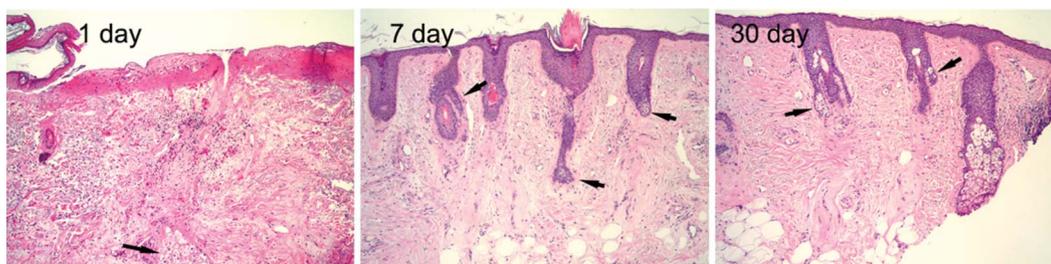


Figure 2. Three H&E-stained sections from facial skin that had been treated with nanosecond pulsed electric field therapy and resected and fixed 1, 7, and 30 days later, respectively. Arrows indicate sebaceous glands undergoing regulated cell death. On the 30-day image, a sebaceous gland can be seen on the right that was outside of the treatment zone and remained intact.

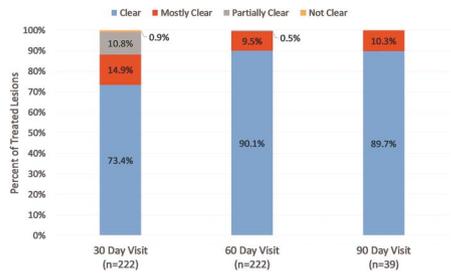


Figure 3. Principal investigator-assessed lesion clearance at the 30-, 60-, and 90-day visits.

Clinical Outcome

Lesion Clearance

Lesion clearance was assessed by the PIs at the 30-day and 60-day visits for subjects who received a single treatment (Figure 3). If at the 30-day visit, a subject had one or more lesions that were not rated *Clear* or *Mostly Clear*, the investigator could, with subject consent, provide a second nsPEF treatment to those lesions. A total of 18 out of the 222 study lesions on 13 of the 72 subjects in the study were treated with a second nsPEF treatment 30 days after the initial nsPEF treatment. Fourteen of those lesions were rated *Partially Clear* at the 30-day follow-up visit, 2 were rated *Not Clear*, and 2 were rated *Mostly Clear*. For the subjects who had one or more lesions that underwent a second nsPEF treatment, all lesions were assessed 60 and 90 days after the initial nsPEF treatment (first visit).

Seventy-one subjects returned for the subsequent 5-day, 30-day, 60-day, and 90-day (as applicable) follow-up visits, and 222 treated lesions were assessed by the investigator at these time points. Of the treated lesions, 163 lesions (73%) were rated *Clear*, 33 lesions (15%) were rated *Mostly Clear*, 24 lesions (11%) were rated *Partially Clear*, and 2 lesions (1%) were rated *Not Clear* at the 30-day visit. At the 60-day visit, the percentage of lesions rated *Clear* increased to 90% (200) with smaller percentages of lesions rated *Mostly* or *Partially Clear*.

Twenty-one lesions (9%) were rated *Mostly Clear*, 1 was rated *Partially Clear*, and none were rated *Not Clear*.

These ratings were based on the clinical evaluation of the lesions (Figure 4). All 13 subjects who had 1 or more lesions that received a second nsPEF treatment (Figure 5) attended the 90-day visit and all lesions on these 13 subjects were evaluated, 18 lesions with 2 treatments and 21 lesions that had only 1 treatment. Ninety percent (35) were rated *Clear* and 10% were rated *Mostly Clear*; no lesions were rated *Partially Clear* or *Not Clear* at the

90-day visit. By day 60, most lesion areas required the original lesion map to identify and photograph the treated area because neither the lesion nor signs of skin damage were evident to the investigator. None of the 72 sham SGHs exhibited clearance.

Clinical Experience

All SGH study lesions were located on the face, with 53% of them on the forehead and 46% on the cheeks or chin. Subjects received small-volume intradermal lidocaine injections before lesion treatment. Subjects were asked to rate their level of discomfort using a 10-point pain scale after the treatment of each lesion (i.e., after each delivery of energy). Most subjects reported *No Pain* (29%) or *Mild Pain* (54%). Fifteen percent of subjects reported *Moderate-Severe*, 1% reported *Very Severe*, and no subjects reported *Worst Possible Pain*. There were no reported adverse events, and only one subject had a localized skin infection to one of the treated lesions that cleared without sequelae using a topical antibiotic ointment. Differences in pain scores were likely attributed to differences in lidocaine injection volumes and the depth of injection.

Investigator Skin Assessment

Hyperpigmentation

Principal investigators were asked to assess the degree of postinflammatory hyperpigmentation on the 5-day, 30-day, 60-day, and, if applicable, 90-day visits.

When considering lesions that received both 1 and 2 nsPEF treatments, hyperpigmentation peaked at the 30-day visit, and decreased with time. By the 60-day visit, 45% of lesions exhibited some degree of hyperpigmentation. A total of 39 lesions were assessed at the 90-day visit, of which 44% and 54% were rated *None* and *Mild*, respectively; 1 lesion (3%) was rated *Moderate* and no lesions were rated *Moderately Severe* or *Severe* (Figure 6). In summary, 101 of 222 treated lesions (45%) showed some degree of hyperpigmentation at the last observation available.

Erythema and Swelling

Mild erythema was observed in 3% of lesions before treatment. Immediately after the initial nsPEF treatment, erythema was observed in 91% of lesions, of

which 82% was *Mild* and 9% was *Moderate* (Figure 7A). Erythema (Figure 7B) was usually present 5 days later, decreased substantially by 30 days, and was only observed in 7% of the treated lesions at 60 days. The typical early response to nsPEF treatment is shown in Figure 9. *Moderate-Severe* or *Severe* erythema was not noted at any of the time points.

Swelling was also quite common immediately after nsPEF treatment (Figures 7B and 8A). However, by 5 days, only 37% of lesions showed swelling and this fell to 1% at 30 days. No swelling was observed at 90 days.

Volume Loss at the Lesion Site

Starting as early as the 30-day visit, investigators reported depressions at the treated lesion sites (Figures 4B and 5C). Some described these as “divots” or “a slight volume loss.” At the last observation for all lesions, 32% of the 222 lesions were noted as having a slight volume loss (Figure 9). When examining volume loss with time, 44% of lesions that had 2 nsPEF treatments noted volume loss, whereas 19% of single treatment lesions that were examined at 90 days noted volume loss.

Subject Satisfaction

Subjects were asked to rate their level of satisfaction with the treatments (Figure 10). Seventy-seven percent of the subjects were satisfied or mostly satisfied at 60 days with the appearance of the 222 treated lesions. The 13 subjects who had 18 lesions treated with a second nsPEF treatment also provided satisfaction ratings

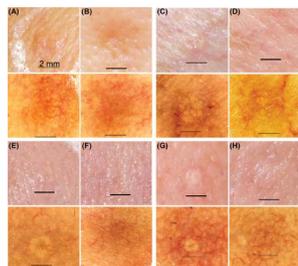


Figure 4. Pairs of images from 4 sebaceous gland hyperplasias taken before (A, C, E, G) and 60 days after nanosecond pulsed electric field treatment (B, D, F, H) from four different subjects. Upper photograph in each pair is the reflected light image showing skin surface and lower photograph is the Handyscope image of the same region showing sebaceous glands. Scale bar in each image is 2-mm long.

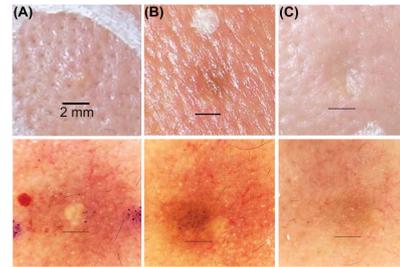


Figure 5. Pairs of images taken before and after 2 nsPEF treatments. Upper photograph is the reflected light image of skin surface. Lower photograph of each pair is a Handyscope image of sebaceous gland. (A) Before treatment; (B) 30 days after the first nsPEF treatment and before second treatment; (C) 90 days after the first nsPEF treatment. nsPEF, nanosecond pulsed electric field.

at the 90-day visit for all their lesions (39 lesions). The distribution of subject satisfaction scores was similar between all lesions and lesions that received a single nsPEF treatment. Lesions that received 2 nsPEF treatments had a similar percentage of *Satisfied* ratings.

Discussion

This multicenter study represents the first controlled clinical trial to evaluate the efficacy of nsPEF technology in the treatment of SGH, a common benign epidermal lesion. Based on previous studies in normal skin,^{4,5} the nsPEF mechanism has been demonstrated to have specificity for cellular structures in the epidermis and dermis, and minimal effect on the adjacent acellular dermis. Based on the clinical results from this study showing very nearly all lesions cleared or mostly clear, the presumed nsPEF mechanism of nonthermal destruction of sebaceous glands resulted in reliable SGH lesion clearance with a single nsPEF treatment, with minimal apparent damage to the acellular dermis.

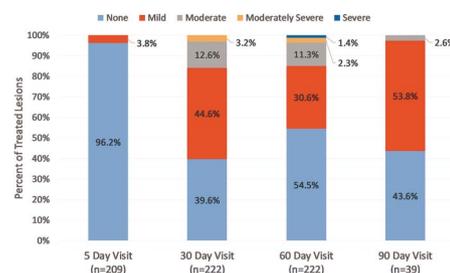


Figure 6. Hyperpigmentation score for all lesions on the 5-, 30-, 60-, and 90-day visits.

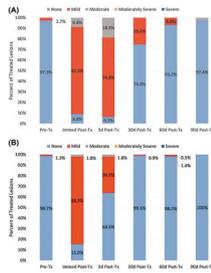


Figure 7. Percentage of treated sebaceous gland hyperplasia lesions with erythema (A) and swelling (B) at the indicated times with respect to nanosecond pulsed electric field treatment (Tx).

Pain

Although most subjects reported that the nsPEF treatment caused only mild or no pain, 16% reported moderate to severe pain. Based on the authors’ experience with similar treatments in other clinical trials,^{4,5} this was probably caused by inadequate lidocaine injection.

Hyperpigmentation and Skin Depressions

The lesions scored as moderately to severely hyperpigmented grew slightly from 0% at 5 days to 16% at 30 and 60 days. However, by 90 days, only 3% of the lesions were in that category, indicating that the hyperpigmentation fades over time. Further studies are planned to optimize this therapy for SGH, which might result in a reduction in the applied energy, which could reduce the hyperpigmentation. Another approach would be the use of hydroquinone in darker pigmented subjects after procedure as is commonly used to reduce postinflammatory hyperpigmentation caused by other therapies.



Figure 8. Time course of the response to nanosecond pulsed electric field treatment of 3 separate sebaceous gland hyperplasia lesions on different subjects. (A–C): each row has photographs of the same lesion taken at the times indicated at the top of row (A). Each scale bar represents 2 mm.

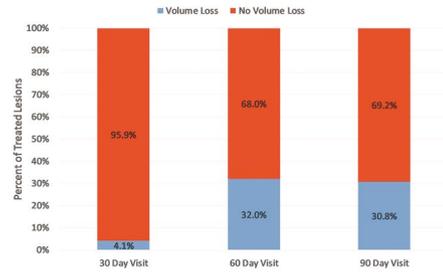


Figure 9. Percent of lesions exhibiting volume loss at 3 visits.

Small skin volume losses due to the elimination of the sebaceous glands were evident in some of the treatment sites, and 19% of single treatment lesions that were examined at 90 days noted volume loss. These volume losses improve over time, and ongoing studies indicate that their frequency is reduced with a reduction in treatment energy.

Nanosecond pulsed electric field technology has been applied to cells and tissues for over a decade; so, much is known about the mechanism of action. The 2 critical properties of this technology are: (1) high-amplitude electric field and (2) fast rise time (time between 10% and 90% maximum field amplitude). The electric field applied is large enough to drive water molecules into lipid bilayers to form nanopores in both the plasma membrane of cells and the membranes surrounding their much smaller intracellular organelles. This has been documented using patch clamp techniques and fluorescence imaging.^{11,12} In addition, the pulses applied have very fast rise times that enable them to penetrate cells before ion rearrangements can occur to block imposed fields. This allows them to generate nanopores in the mitochondria and endoplasmic reticulum to trigger RCD. The pulses are so short that they do not deliver enough energy to significantly heat the cellular targets; so, the nsPEF mechanism is

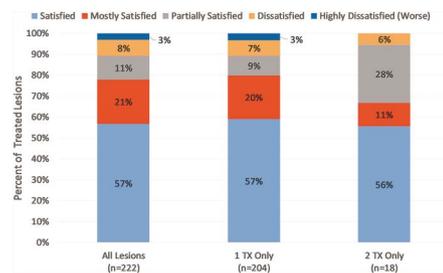


Figure 10. Sixty-day subject satisfaction ratings for all lesions.

nonthermal.^{13,14} This nonthermal energy does not affect proteins and fibrous structures, but can permeabilize membranes to target cellular structures specifically, leading to the successful SGH lesion elimination.⁴

Competing Technologies

Sebaceous gland hyperplasia treatment is challenging due to the need to destroy or excise the entire sebaceous gland. The common destructive modalities including cryosurgery, electrodesiccation, curettage, shave excision, and topical trichloroacetic acid have a propensity to cause skin discoloration and scarring.² Another approach used is short-burst oral isotretinoin but it was associated with adverse effects and rapid recurrence on discontinuation of the medication.¹⁵ In addition, patient hesitance to use oral isotretinoin (due to side effects) for other medical skin conditions, such as acne vulgaris, is widely documented.¹⁶ Seven studies using PDT and laser therapy have shown some success with small subject numbers.³ One of these used a 1720-nm laser and reported nearly complete clearance of SGH lesions with 2 treatments on 4 subjects.¹⁷ Another study used a 1,450-nm diode laser to obtain 50% to 75% shrinkage of SGH lesions on 10 subjects.¹⁸ Thus, none of the previous studies have reported the success rates and the large numbers of treated subjects forming the basis of this work.

Conclusion

These results demonstrate that the nsPEF procedure provides a safe and effective treatment for SGHs with a low risk of scarring and long-term hyperpigmentation. Furthermore, the treatment time is very short and the SGH clearance is highly localized with no systemic side effects. The mechanism of this localized nsPEF therapy targets cellular structures within the epidermis and dermis, making it ideal to eliminate sebaceous glands with minimum treatment sessions, a very high clearance rate, and high degree of subject satisfaction.

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