



## Curettage + microneedling + topical ALA-PDT for the treatment of acral resistant warts: Our experience

S. Caccavale<sup>a,\*</sup>, A. Iocco<sup>a</sup>, G. Pieretti<sup>b</sup>, R. Alfano<sup>c</sup>, G. Argenziano<sup>a</sup>

<sup>a</sup> Dermatology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania Luigi Vanvitelli, Naples, Italy

<sup>b</sup> Department of Plastic Surgery, University of Campania Luigi Vanvitelli, Naples, Italy

<sup>c</sup> Department of Anesthesiology, Surgery and Emergency, University of Campania Luigi Vanvitelli, Naples, Italy

### ARTICLE INFO

#### Keywords:

Curettage  
Microneedling  
Photodynamic therapy  
Warts  
5-aminolevulinic acid

### ABSTRACT

**Background:** Cutaneous warts are an extremely common problem, whose eradication can be challenging. Topical PDT involves applying a porphyrin precursor, 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) to the affected area. ALA-PDT has been well documented to be successful in the treatment of recalcitrant warts. PDT has a limited role in the treatment of thicker lesions because the photosensitizer does not penetrate keratotic lesions well, though this is vehicle dependent.

**Objective:** The aim of this study was to evaluate the efficacy and safety of curettage + microneedling + ALA-PDT for the treatment of resistant acral warts. We hypothesized that microneedling may increase the efficacy of PDT, providing a channel to deliver the ALA to deeper areas of warts.

**Methods:** Our study was carried out between November 2017 and July 2018. Eligible participants had one or more resistant plantar or palmar warts. Thirteen patients were recruited. They underwent a thorough curettage, followed by the application of 5-ALA 10% cream on the wart, and by microneedling. Later, the pricked skin was covered for three hours by an occlusive polyurethane dressing, and finally irradiated with a red-light source. Patients performed one session every three weeks for a total of three cycles.

**Results:** After 3 treatments of curettage + microneedling + ALA-PDT, 11 patients (84.6%) showed complete remission (defined as complete disappearance of their warts). One patient (7.7%) showed partial remission (defined as greater than 50% decrease in the wart area) after 3 sessions; this patient needed other 2 sessions to achieve complete remission. The mean follow-up period after healing was 4.3 months. Adverse effects were recorded.

**Conclusion:** We have demonstrated, for the first time to our knowledge, that the combination of curettage + microneedling + topical ALA-PDT may offer an effective and safe alternative for the treatment of acral resistant warts, even when PDT alone has already been insufficient.

### 1. Introduction

Cutaneous warts, caused by the human papilloma virus (HPV), are an extremely common problem that most people experience at least once in their lives. The eradication of warts can be challenging despite the presence of a large variety of treatments available [1,2].

ALA-PDT has been well documented by Stender et al. [3] and Wang et al. [1] to be successful in the treatment of recalcitrant warts. PDT has a limited role in the treatment of thicker lesions because the photosensitizer does not penetrate keratotic lesions well, though this is vehicle dependent. To overcome this limitation, various pretreatments and strategies with de-bulking methods or the use of penetration

enhancers have been attempted [4]. To increase the penetration of the photosensitizer, we decided to combine PDT with curettage and microneedling.

Microneedling is a minimally invasive technique used to treat many dermatologic diseases (acne, scars, alopecia, facial rejuvenation, and melasma). The devices have multiple fine needles, 0.5–2.5 mm in length, disposed on a barrel, and are rolled on the skin to prick it into stratum corneum and papillary dermis. This microtrauma creates micro channels in the skin, thus inducing the release of many growth factors, promoting the growth of new collagen and elastin in the dermis [5]. Actually, modern devices can penetrate vertically into the skin without rolling on it. The small pinpoint bleeding injuries heal in a few days,

\* Corresponding author at: Dermatology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania Luigi Vanvitelli, Via Sergio Pansini, 5, 80131, Naples, Italy.

E-mail address: [stefano85med@libero.it](mailto:stefano85med@libero.it) (S. Caccavale).

<https://doi.org/10.1016/j.pdpdt.2019.04.008>

Received 3 March 2019; Received in revised form 19 March 2019; Accepted 5 April 2019

Available online 06 April 2019

1572-1000/ © 2019 Elsevier B.V. All rights reserved.

without any significant skin changes. Microneedling can also increase the penetration and bioavailability of topically applied drugs (transdermal drug delivery) in different ways:

- pore creation followed by topical drug application;
- drug-coated microneedle arrays;
- direct injection of the drug through hollow microneedles [6].

Recent studies have shown that microneedling can be synergistically combined with other procedures [7].

We hypothesized that microneedling-assisted drug delivery may also increase the efficacy of PDT, providing a channel to deliver the ALA to deeper areas of acral warts, inducing local inflammation and stimulating a cell-mediated immune response against human papilloma virus (HPV) [8].

## 2. Materials and methods

Our study was carried out over a 9-month period between November 2017 and July 2018. Eligible participants had one or more plantar or palmar warts, all were older than 18 years and had undergone many sessions of liquid nitrogen cryotherapy or other topical treatments, without results. All patients were seen at the Dermatology Unit of the University of Campania Luigi Vanvitelli. The exclusion criteria were: pregnancy, breast-feeding, age less than 18 years, immunosuppression, and a history of photosensitivity or collagen vascular disease.

Thirteen (7 males, 6 females) patients affected by very resistant acral warts were recruited. 12 patients completed the study. Only 1 patient interrupted the treatment protocol. Mean age of the patients was 28.8 years (range 18–52 years). Eight patients had plantar warts and 5 patients had hand warts. The mean duration of the viral warts was 11.5 months. Some patients had multiple lesions and a total of 137 acral warts underwent treatment. In 3 patients, 5-ALA 10% PDT had already failed (3 sessions with 75 J/cm<sup>2</sup>, every 3 weeks).

After written consent was obtained, the patients entered in the following protocol. First, patients applied at home a topical anesthetic cream (prilocaine and tetracaine) on the area to be treated. Then, the patients moved to the hospital where they underwent a thorough curettage with a circular blade used to pare down the lesions (until the visualization of blood vessels), primarily followed by the application of 5-ALA 10% cream on the viral wart and a 0.5-cm rim around it, and secondly by microneedling, performed with a modern device with 12 needles penetrating vertically into the skin, to enhance the penetration of the photosensitizer. Later, the pricked skin was covered for three hours by an occlusive polyurethane dressing (Tegaderm), and finally irradiated with a red-light source (630 nm) for 17 min (75 J/cm<sup>2</sup>). Patients performed one session every three weeks for a total of three cycles. Digital photographs were taken at the baseline visit and at the end of the protocol. Pain was assessed on a five-point scale (Table 1) [1] during treatment, immediately after treatment, and at 24 and 48 h after treatment.

**Table 1**  
Pain scale [1].

Scale	Level of pain	Description
0	Pain free	No pain
1	Mild	Only aware of pain when it is focused on
2	Tolerable	Can be ignored
3	Moderate	Able to continue some physical activity
4	Severe	Cannot concentrate and cannot do all but simple activities
5	Disabling	Unable to continue with even simple activities



**Fig. 1.** Plantar warts before (left) and after (right) the treatments.

## 3. Results

After 3 treatments of curettage + microneedling + ALA-PDT, 11 patients (84.6%) showed complete remission (defined as complete disappearance of their warts) (Figs. 1 and 2). One patient (7.7%) showed partial remission (defined as greater than 50% decrease in the wart area) after 3 sessions; this patient needed other 2 sessions to achieve complete remission. Of the 12 patients who showed complete remission, 8 had plantar warts and 4 had hand warts. Among them, 1 patient required only one treatment, another one required two sessions, 9 patients required three treatments, and the remaining patient required five sessions for complete clearance. The mean follow-up period after healing was 4.3 months (range, 3–7 months). Adverse effects, including pain, erythema, crusting, ulceration, and pigmentary changes, were recorded. Ten of the 13 patients had immediate erythema after treatment, and this resolved within 24–72 h. One patient had hyperpigmentation after five combined treatments, but this resolved after 1 month without any treatment. Four patients developed crusting and one patient ulceration. All patients had pain over the wart immediately after PDT and for the ensuing 24–48 h, with 11 patients (84.6%) reporting that the pain peaked at 24 h. The pain caused by PDT was considered to be mild and most patients rated it to be 1/5–3/5 (Table 1). Four patients had severe pain (rated 4/5), and this was experienced mostly at 24 h post-treatment (three of the four patients). Three patients required oral paracetamol for analgesia. Only one patient asked to discontinue treatment because of pain.

Microneedling before PDT was tolerated by all patients, even though 30.8% of patients had moderate pain and 69.2% had no or mild pain (probably because patients applied at home a topical anesthetic cream on the area to be treated that reduced the pain and discomfort during microneedling). The cosmetic result was considered excellent without scar or permanent pigmentary abnormalities.

## 4. Discussion

The potential efficacy of PDT has been investigated in a wide range of infectious skin diseases as well as in off-label skin tumors [9]. Off-label indications for PDT are still at an exploratory stage since clinical evidence for their use is generally poor, based on case reports, small case series, or few randomized clinical trials (RCTs) with few patients and short follow-up [9].

The response of HPVs to PDT has been demonstrated in several animal models. Systemic PDT with porphyrin derivatives and 5-ALA resulted in the marked regression of infected papillomas in rabbits. Abramson et al. studied the efficacy of porfimer sodium-based PDT in the treatment of laryngeal HPV lesions, and reported high response rates [10]. Consequently, several studies have demonstrated high efficacy of PDT for warts. Frank et al. observed a 75–100% decrease in genital warts in five of seven patients after ALA-PDT [11]. ALA-PDT showed to achieve superior clearance to cryotherapy in 30 patients with recalcitrant warts [12]. Stender et al. compared six repetitive 5-ALA-PDT treatments and placebo for recalcitrant acral warts in 45 patients and found statistically significant favorable results for 5-ALA-PDT (complete clearance rate was 56%) and a median reduction in wart area



Fig. 2. Other patients before and after the treatments.

of 98% with PDT and 52% by placebo [3]. In 2001, Fabbrocini et al. reported a high complete response rate of 75% with concomitant treatment of the warts with 20% 5-ALA-PDT (tungsten lamp 400–700 nm; total dose, 50 J/cm<sup>2</sup>; incubation period, 5 h) and keratolytics and gentle curettage [13]. Schroeter *et al.* obtained a complete response rate of 88% after application of ALA-PDT on plantar warts [14].

A comparison of three ALA concentrations (5%, 10%, 20%) in one study suggested 10% ALA to be the optimal concentration for both efficacy and side-effect profile [15]. The authors found that the clearance was lowest in the 5% ALA group, while the 20% group showed elevated incidences of temporary hyperpigmentation [15,16]. MAL-PDT dramatically cleared a recalcitrant hand wart in a case report, but literature remains limited on its use in warts [17]. More studies with higher power should be done to compare MAL to ALA [16].

While the efficacy of PDT on warts is well-known in literature and clinical practice, the efficacy of microneedling for the treatment of acral warts is less clear in the literature. Falknor was the first author to describe the treatment of warts with needling in 1969 and obtained only 2 recurrences in 126 warts treated over 8 months with a 25-gauge needle [18]. Longhurst found that 69% of patients had complete response and wart resolution using Falknor's needle method [19]. Parton and Sommerville hypothesized a cell-mediated immune response against the HPV and obtained a good effectiveness (94%) of an abrasive treatment on plantar warts compared with a standard treatment (salicylic acid) [20]. The aim of the abrasive treatment was to lead to a process of immune response activation and stimulation that the authors defined "autoimmunization", breaking down the basement membrane and allowing T lymphocytes to access the site and locate the virus antigens [20]. Chapman and Visaya explored the hypothesis of Parton and Sommerville of a triggered cell-mediated immune response against the virus by demonstrating that abrasion of one pedal wart resulted in the regression of other pedal warts in 55% of patients [21]. Cunningham hypothesized that cell-mediated immune response could be due to: 1) the migration of immune cells in the area treated with needling induced by the needle injury; 2) the infected epidermis cells lysis with release and exposure of HPV; 3) induction of translocation of HPV in area of the skin where there is a higher concentration of T lymphocytes (papillary skin layer); 4) sensitization of immune system to the HPV antigens [8,20]. The same author proposed that cell-mediated immune response may be systemic, justifying the observation of Chapman and Visaya of untreated satellite pedal wart disappearance described above [8,21].

Microneedling is associated with a low rate of adverse effects, with transient erythema being most common. Systemic hypersensitivity reactions [22], foreign body-type facial granulomas [23], tram-track markings [24] have been rarely reported.

## 5. Conclusions

Recalcitrant warts can be challenging to treat and often frustrating

to both dermatologists and patient alike. Topical PDT should be considered as a mode of treatment in recalcitrant warts. More studies with larger patient numbers are needed to evaluate the optimal light source and dosing of ALA-PDT or MAL-PDT in the treatment of warts, as well as to compare its efficacy with other conventional treatments [1]. PDT alone is often effective on acral recalcitrant warts, but sometimes it may be insufficient. We have demonstrated, for the first time to our knowledge, that the combination of curettage + microneedling + topical ALA-PDT may offer an alternative for the treatment of acral resistant warts.

## Funding sources

None.

## Conflict of interest

None.

## References

- [1] Y.S. Wang, Y.K. Tay, C. Kwok, E. Tan, Photodynamic therapy with 20% aminolevulinic acid for the treatment of recalcitrant viral warts in an Asian population, *Int. J. Dermatol.* 46 (2007) 1180–1184.
- [2] W.S. Chong, G.Y. Kang, Dramatic clearance of a recalcitrant acral viral wart using methyl aminolevulinic acid-red light photodynamic therapy, *Photodermatol. Photoimmunol. Photomed.* 25 (2009) 225–226.
- [3] I.M. Stender, R. Na, H. Fogh, C. Gluud, H.C. Wulf, Photodynamic therapy with 5-aminolevulinic acid or placebo for recalcitrant hand and foot warts: randomized double-blind trial, *Lancet* 355 (2000) 963–966.
- [4] J.E. Kim, S.J. Kim, J.I. Hwang, K.J. Lee, H.J. Park, B.K. Cho, New proposal for the treatment of viral warts with intralesional injection of 5-aminolevulinic acid photodynamic therapy, *J. Dermatolog. Treat.* 23 (2012) 192–195.
- [5] A. Hou, B. Cohen, A. Haimovic, N. Elbuluk, Microneedling: A comprehensive review, *Dermatol. Surg.* 43 (2017) 321–339.
- [6] J. Vandervoort, A. Ludwig, Microneedles for transdermal drug delivery: a minireview, *Front Biosci* 13 (2008) 1711–1715.
- [7] S.A. Braun, P.A. Gerber, P.A. Hevezi, Needling-assisted drug delivery: Enhanced response to ingenol mebutate after microneedling, *Dermatol. Surg.* 43 (2017) 978–979.
- [8] D.J. Cunningham, J.T. Brimage, R.N. Naraghi, V.M. Bower, Needling versus liquid nitrogen cryotherapy for the treatment of pedal warts: a randomized controlled pilot study, *J. Am. Podiatr. Med. Assoc.* 104 (2014) 394–401.
- [9] P.G. Calzavara-Pinton, M.T. Rossi, R. Sala, Italian Group For Photodynamic Therapy. A retrospective analysis of real-life practice of off-label photodynamic therapy using methyl aminolevulinic acid (MAL-PDT) in 20 Italian dermatology departments. Part 2: oncologic and infectious indications, *Photochem. Photobiol. Sci.* 12 (2013) 158–165.
- [10] A.L. Abramson, M.J. Shikowitz, V.M. Mullooly, B.M. Steinberg, C.A. Amella, H.R. Rothstein, Clinical effects of photodynamic therapy on recurrent laryngeal papillomas, *Arch. Otolaryngol. Head Neck Surg.* 118 (1992) 25–29.
- [11] R.G. Frank, J.D. Bos, Photodynamic therapy for condylomata acuminata with local application of 5-aminolevulinic acid, *Genitourin. Med.* 72 (1996) 70–71.
- [12] I.M. Stender, J. Lock-Andersen, H.C. Wulf, Recalcitrant hand and foot warts successfully treated with photodynamic therapy with topical 5-aminolevulinic acid: a pilot study, *Clin. Exp. Dermatol.* 24 (1999) 154–159.
- [13] G. Fabbrocini, M.P. Di Costanzo, A.M. Riccardo, M. Quarto, A. Colasanti, G. Roberti, G. Monfrecola, Photodynamic therapy with topical delta-aminolevulinic acid for the treatment of plantar warts, *J. Photochem. Photobiol. B* 61 (2001) 30–34.

- [14] C.A. Schroeter, J. Pleunis, C. van Nispen tot Pannerden, T. Reineke, H.A. Neumann, Photodynamic therapy: new treatment for therapy-resistant plantar warts, *Dermatol. Surg.* 31 (2005) 71–75.
- [15] Q. Li, B. Jiao, F. Zhou, Q. Tan, Y. Ma, L. Luo, J. Zhai, Q. Luan, C. Li, G. Wang, T. Gao, Comparative study of photodynamic therapy with 5%, 10% and 20% aminolevulinic acid in the treatment of generalized recalcitrant facial verruca plana: a randomized clinical trial, *J. Eur. Acad. Dermatol. Venereol.* 28 (2014) 1821–1826.
- [16] E.L. Maranda, V.M. Lim, A.H. Nguyen, K. Nouri, Laser and light therapy for facial warts: a systematic review, *J. Eur. Acad. Dermatol. Venereol.* 30 (2016) 1700–1707.
- [17] W.S. Chiong, G.Y. Kang, Dramatic clearance of a recalcitrant acral viral wart using methyl aminolevulinate-red light photodynamic therapy, *Photodermatol. Photoimmunol. Photomed.* 25 (2009) 225–226.
- [18] G.W. Falknor, Needling: a new technique in verruca therapy, *J. Am. Podiatry Assoc.* 59 (1969) 51–52.
- [19] B. Longhurst, I. Bristow, The treatment of verrucae pedis using Falknor's needling method: A review of 46 cases, *J. Clin. Med.* 2 (2013) 13–21.
- [20] A.M. Parton, Sommerville RG: The treatment of plantar verrucae by triggering cell-mediated immunity, *J. Br. Podiatr. Med.* 49 (1994) 205.
- [21] C. Chapman, Visaya GA: Treatment of multiple verrucae by triggering cell-mediated immunity: a clinical trial, *Br J Podiatr* 1 (1998) 89–90.
- [22] P. Pratsou, J. Gach, Severe systemic reaction associated with skin microneedling therapy in 2 sisters: a previously unrecognized potential for complications? *J. Am. Acad. Dermatol.* 68 (2013) AB219.
- [23] R. Soltani-Arabshahi, J.W. Wong, K.L. Duffy, D.L. Powell, Facial allergic granulomatous reaction and systemic hypersensitivity associated with microneedle therapy for skin rejuvenation, *JAMA Dermatol.* 150 (2014) 68–72.
- [24] N.C. Harris Adam, D. Murrell, Skin needling as a treatment for acne scarring: an up-to-date review of the literature, *Int. J. Women Dermatol.* 1 (2015) 77–81.