

# Continuing Professional Development



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## Verrucae: An update and contemporary approaches to management

Ivan Bristow PhD and Alan Borthwick PhD

### BACKGROUND

Plantar warts or verrucae (Figure 1) continue to be a common reason for a visit to the podiatrist. Previous CPD articles published on this topic have focused on chemical management<sup>1</sup> and cryosurgery.<sup>2</sup>

In the last decade we have seen new research publications and the introduction of novel techniques into mainstream podiatry such as needling and microwave treatment. This article serves to provide a clinical update on the subject whilst focusing on these newer modalities, which are increasingly being used in podiatry.

It is also worth recalling that the profession was asked by the *Commission on Human Medicines* to periodically review its use of medicines, and the *Medicines and Healthcare Products Regulatory Agency* (MHRA) has made it clear that ongoing use of chemical agents such as pyrogallol and monochloroacetic acid, declassified as unlicensed medicinal products in 2009, should only be continued until suitable licensed alternatives are identified. Some of the new technologies described in this paper may soon provide the profession with the licensed alternatives needed.

### INTRODUCTION

The human papilloma virus (HPV) is a double-stranded DNA virus with over 200 strains or genotypes<sup>3</sup> that have been recognised by DNA sequencing. The HPV is associated with the development of cutaneous tumours (warts and verrucae). Studies undertaken have identified HPV types 1, 2, 7, 27 and 57 as the most common



Figure 1. Plantar warts affect around 6% of UK adults

subtypes causing cutaneous (non-genital) warts.<sup>4-7</sup> One study particularly focused on HPV types in plantar warts, reporting HPV subtypes 1, 2, 27 and 57 as the most prevalent.<sup>8</sup> Even on subjects without cutaneous warts, the carriage of the HPV virus on the hands and feet has been demonstrated.<sup>9</sup>

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**Key Point:** HPV subtypes 1, 2, 27 and 57 are the most common warts found on the plantar surface.

The prevalence of cutaneous warts in school children is around 22-33%,<sup>10, 11</sup> reducing to around 6% in the general population.<sup>12</sup> Anecdotally, it has always been reported that warts are more common in children who attend swimming pools. A study undertaken in 2013 found that the risk factors for wart development in children were being Caucasian and having siblings or classmates with warts, but the regular use of swimming facilities did not significantly increase the risk.<sup>13</sup>

**Key Point:** HPV carriage has been identified on healthy hands and feet that show no visible signs of a wart.

**Key Point:** Warts affect 22-33% of schoolchildren and around 6% of UK adults.

Studies following the natural resolution of warts are however lacking; one study demonstrated that, in primary school children, spontaneous wart resolution rate was 50% in just one year. The younger the child the higher the resolution rate.<sup>14</sup> Another older study has suggested that warts will naturally resolve in approximately 67% of children within two years.<sup>15</sup> Data from a randomised controlled trial looking at plantar wart treatment correlated HPV type to clinical responses to treatment. It found that HPV-1 genotype was more responsive to spontaneous resolution than other types such as HPV 2, 7, 27 and 57. Although preliminary research at this stage, it may suggest future treatments are informed by HPV type.<sup>16</sup>

## VIRAL ENTRY AND EVASION OF THE IMMUNE SYSTEM BY HPV INFECTION

Infection begins when the virus enters the skin, most probably through minor abrasions within the epidermis. On reaching the extracellular environment, conformational changes within the outer capsid allow entry into the cell through reverse pinocytosis. The virus then establishes a route to the nucleus and gains entry through the nuclear membrane during the natural metaphase of the basal cell layer.<sup>17</sup> During this passage, much of the HPV is degraded by internal cell mechanisms and it may be subjected to challenges from immune mechanisms such as alpha defensins, which could prevent cell surface entry.<sup>18</sup> Establishment of HPV infection in the epidermis may lead to the development of a wart. Despite spontaneous wart regression being a regular feature in children, persistence of infection of plantar warts in adults is common.

It is well established that successful eradication of warts can only come about if the adaptive and innate immune systems are appropriately primed, although HPV induces many changes to derail this process at a cellular level. Production of a range of viral proteins helps to hijack the normal cellular activities to its advantage to permit persistence and viral replication in the upper epidermal layers.<sup>19</sup> The mechanisms of HPV persistence have been reviewed by Westrich *et al.*<sup>20</sup> It has a broad range of effects that allow the infection to persist. These include:

1. **Location.** The infection produces virions, which are restricted to the remote upper layers of the epidermis, where there is little exposure to the systemic immune system.
2. **Alteration of cell gene expression during infection.**

3. **Dysregulation of natural protein function by the infection.**

4. **Alteration of cell function.** The main dendritic cell of the epidermis is suppressed in its antigen-presenting capacity whilst normal cell surface markers indicating infection are absent. Therefore, any successful treatment should lead to an alteration or disruption of these mechanisms.

**Key Point:** Active HPV infection in the skin can suppress local Langerhans cell function.

## RECENT REVIEWS OF WART TREATMENTS

Since the last wart update was published, there has been a systematic review<sup>21</sup> and updated guidelines on management from the British Association of Dermatologists (BAD).<sup>22</sup> Kwok *et al.*<sup>21</sup> undertook a review of randomised controlled trials and concluded that salicylic acid had a cure rate superior to placebo whilst evidence for cryosurgery was less convincing. Combination of the two therapies was better than either alone. It concluded, however, that there was little evidence to suggest other treatments.

Current guidelines from the BAD continue to support the idea that not all warts require treatment, only those that interfere with daily activities or cause distress. In evaluating the evidence, the guidelines point out that current evidence is based on treatment of non-genital warts at all locations on the skin. Although salicylic acid and cryosurgery show superiority over no treatment in these studies, when the figures are examined further, plantar warts generally respond poorly to either regime with responses of around 33% or less. The work of Cockayne *et al.*<sup>23</sup> where 240 patients' plantar warts were treated with either 50% salicylic acid (up to 12 weeks) or cryosurgery (up to four treatments) demonstrated only a 14% cure rate. Similarly, a study by Bruggink *et al.*<sup>24</sup> evaluated cryosurgery only, salicylic acid only or no treatment in a cohort of 240 patients. The results for plantar warts within the study analysis showed no difference in cure rates between either group. Moreover, evaluating the outcome on various factors revealed that adolescents and adults or those with plantar warts of over six months' duration could expect a treatment success of just 5%.

In conclusion, the recommendations suggest that lower cure rates for plantar warts are to be expected due to the thickness of the plantar epidermis acting as a barrier to penetration of chemical agents and so careful reduction prior to treatment is always advisable.

**Key Point:** Cure rates for plantar warts are considerably lower than for warts elsewhere on the skin.

## VERRUCA TREATMENT AND CONSENT

With current evidence suggesting response rates of plantar warts to be disappointing, podiatrists will always look to seek new modalities for the management of stubborn plantar warts. In addition, it is well recognised that the use of cryosurgery and caustics (particularly when applied in combination with other chemicals such as monochloroacetic acid) with repeat applications can potentially lead to extensive tissue damage, prolonged pain or adverse reactions.<sup>1, 25</sup>

This also raises the spectre of litigation, when patients suffer as a direct result of a chemical treatment, whether the verruca vanishes or not. Advising patients of the risks associated with

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use of chemicals such as pyrogallol, monochloroacetic acid or trichloroacetic acid is vital, particularly since the recent Supreme Court judgement in the Montgomery case (2015) now places an ever greater burden on the professional to provide fully informed consent.<sup>26</sup> This requires health professionals to ask three questions:

- Does the patient know about the material risks of the treatment?
- Does the patient know about reasonable alternatives?
- Have I taken reasonable care to ensure the patient knows this?

When advising patients about the choice of appropriate treatments and treatment plans it is recommended that informed consent, ideally written informed consent, should be obtained. Patients should also be provided with relevant information leaflets, including post-operative advice and emergency contacts and procedures.

**Key Point:** Providing patients with information leaflets on warts including post-operative advice and contact procedures is good practice.

**Key Point:** Consent should be sought from all patients before undertaking any wart treatment.

## NEW DIRECTIONS IN THE PODIATRIC MANAGEMENT OF PLANTAR WARTS

Recently, two new techniques have been introduced into podiatric practice within the UK and will be discussed further.

### Needling Technique

The needling of verrucae was first reported in the USA in 1969 by the American podiatrist, Gordon Falknor<sup>27</sup> as a technique for treating plantar warts. Reporting in the *Journal of the American Podiatric Medical Association*, he described anaesthetising the area and then undertaking multiple punctures to the verruca to penetrate the full depth of the lesion, through the lesion capsule into the underlying hypodermis. The technique of puncturing was carried out from the periphery to the centre of the lesion. For a wart measuring half an inch in diameter (1.27cm) he suggested around 60 punctures to be sufficient. The treated area was then dressed and reviewed in a week. In the paper, he suggested he had successfully treated 126 lesions with just two failures in eight months.

### Research

The concept behind needling is akin to auto-implantation where wart particles are introduced from the peripheral epidermis, deeper in the body either locally or remotely. Two studies from India have reported successful treatment of cutaneous warts by implanting wart tissue subcutaneously into the upper thigh or forearm.<sup>28,29</sup> The two studies reported resolution rates of around 73% at three months follow up.

Subsequently, the needling technique remained relatively unreported until 2011 when a paper was published in *Podiatry Now*.<sup>30</sup> Skilton & Mehar reported a case series of 14 adult patients who had undergone the procedure and were subsequently reviewed at eight weeks. A cure rate of 50% was observed overall, with 70% success in patients with solitary lesions. This work was followed by a second UK paper in 2013,<sup>31</sup> which presented a retrospective review of 46 adults at one practice in Hampshire

where patients had undergone the procedure in a manner similar to that described by Falknor. Of the 45 patients available for review, 69% demonstrated complete resolution of their lesions (seven requiring a second attempt of the procedure to attain resolution).

A subsequent Australian study<sup>32</sup> was published comparing the technique to cryosurgery. In a cohort of 37 adults, patients were randomly ascribed needling of their largest plantar wart using up to three treatments delivered at least three weeks apart or two applications of liquid nitrogen (five seconds) applied by cotton wool. At the end of the study, just over 64% of needled lesions had fully resolved compared to 6.2% of the lesions treated with cryosurgery.

Hashmi *et al*<sup>33</sup> in the UK published the largest randomised controlled trial of the technique to date, randomising 60 adults to either a single needling or simple debridement, and reviewing patients at 24 weeks. The study showed there was little difference between the two techniques, with only 14.3% of needled warts resolving versus 16% of debrided lesions.

The stark contrast in results from the Australian and Hashmi studies is not fully explained although the Australian study permitted multiple needling to warts whereas the Hashmi study only allowed one. Moreover, the average age of patients in the Hashmi study was higher and the warts had a longer reported duration than the Australian study.

For podiatrists, the technique has gained popularity, as it requires little equipment and can be conducted in a clinic, under local anaesthesia utilising the skills already held by the practitioner. Moreover, with a good technique the risk of complications is low. The full technique as outlined by Longhurst & Bristow is given in Box 1.

### BOX 1: NEEDLING TECHNIQUE

A local anaesthetic is administered by tibial nerve block, digital block or local infiltration according to the location of the lesion. Once the area of skin is anaesthetised, any overlying callus is debrided. In cases where a patient presents with mosaic or multiple plantar warts, the largest and thickest lesion is selected for treatment. The area surrounding the lesion is first cleansed with povidone-iodine before an empty 27-gauge needle is used to puncture through the lesion to the subcutaneous tissue. Each puncture produces pinpoint bleeding and this is continued until there is no more resistance, or reactive pressure, from the epidermis and the entire lesion is perforated enough to produce a 'beefy' red wound (Figure 2). The total number of punctures varies according to the size of the lesion (see above).

After treatment (Figure 3), pressure is applied to the wound with sterile gauze and dressed with a non-adherent sterile dressing and fixing tape. A semi-compressed felt aperture pad can be applied on weight bearing sites to deflect pressure and reduce post-operative bruising. Patients should be issued with post-operative written guidelines and advised to lightly shower and wash the area after keeping the dressing dry for 24 hours. Patients should be advised to avoid taking anti-inflammatory medication for 48 hours to increase the likelihood of a successful controlled inflammatory response. Wound inspection and debridement of any uncomfortable eschar is normally performed one week later. The final inspection for verrucae resolution is typically carried out about eight weeks later.

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**Figure 2.** A plantar wart immediately after needling procedure (Longhurst & Bristow)<sup>31</sup>



**Figures 3a & 3b.** A plantar wart before and after needling. Resolution has occurred (Longhurst & Bristow)<sup>31</sup>

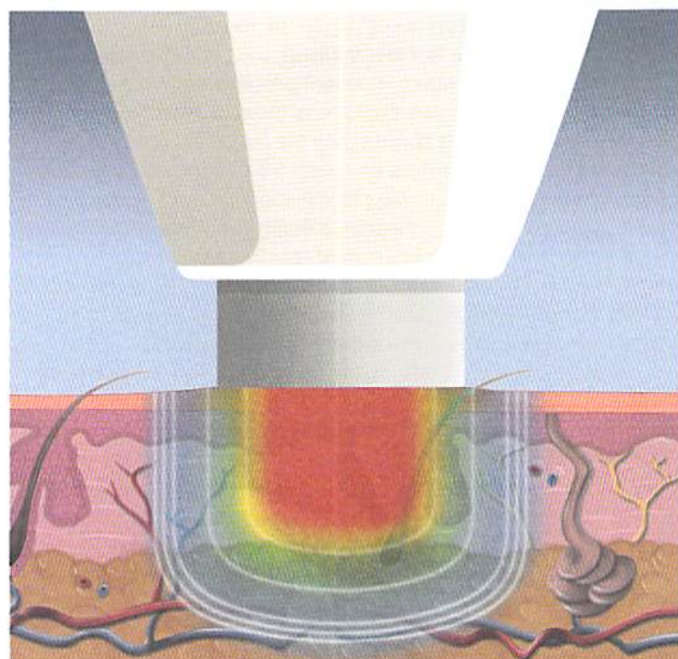
## Microwave Treatment

Microwave treatment is a new modality for the treatment of plantar warts, and was licensed and introduced in the UK in 2016. The use of microwave energy confers some useful advantages over traditional wart techniques. Firstly, microwaves travel in straight lines and to a fixed depth of a few millimetres and so there is little or no collateral spread of heating during treatment and a low risk of damage to underlying structures (Figure 4). In addition, unlike high-powered lasers, there is no smoke or plume. The device at the normal therapeutic dosages does not break the skin so no ulceration is produced. Treatment applications also are fast

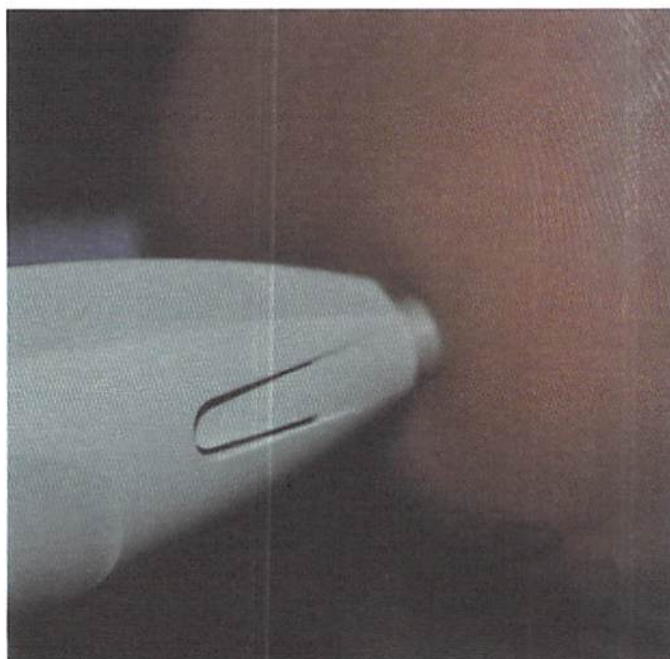
at around 2–5 seconds per application. The typical application technique is outlined in Box 2.

## Research

Using a microwave generator, microwave energy is delivered into the plantar wart via a 6mm probe which is in contact with the skin (Figure 5). Microwaves heat the skin dielectrically by exciting water molecules to around 41–44°C (termed the hyperthermic range), which is not hot enough to cause ablation but sufficient to cause 'heat shock' in exposed tissues.<sup>34</sup> Hence, no smoke or steam is observed during its use.



**Figure 4.** Microwave energy is delivered to a fixed depth with little collateral damage to surrounding tissue



**Figure 5.** Microwave applicator applied to the skin

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The effects of hyperthermia on the skin have been well studied,<sup>35</sup> particularly in HPV infection where heating to the hyperthermic range has been shown to increase plantar wart clearance.<sup>36</sup> A number of mechanisms are likely to be at play. In order for wart clearance to occur, HPV particles need to be recognised and collected by the Langerhans cell in the skin. The Langerhans cell subsequently presents the virus to T-cells within the lymph, which then elicits an appropriate immune response.

However, during active infection, Langerhans cell suppression by the HPV is known to occur, preventing antigen presentation to T-cells in the lymph and subsequently suppressing the immune response. When cells are exposed to hyperthermic conditions, such as under microwave treatment, the suppression pathway is lifted – restoring Langerhans cell function and increasing anti-HPV and clearance.<sup>37</sup> In addition, creating heat shock in skin cells has been shown to lead to the release of heat shock proteins (HSP). HSP release has been shown to enhance Langerhans cell maturation and migration to the lymph.<sup>38</sup> Most recently, heating HPV-infected tissue has been shown to increase destruction within the viral DNA genome, leading to increased immunity and clearance in warts.<sup>39</sup>

**Key Point:** Heating the skin to just above body temperature has been shown to enhance Langerhans cell function.

The effects of microwave heating of the skin have been studied with demonstration of HSP release and subsequent Langerhans cell activity.<sup>40</sup> In the first clinical evaluation of the device, a clearance rate of nearly 76% was observed in a cohort of 32 adults with treatment-resistance warts.<sup>41</sup> See Figure 6a, b and c. The device is now marketed in the UK to podiatrists.



Figures 6a, 6b & 6c. A wart before, during and 12 months after microwave treatment demonstrating resolution

## BOX 2: MICROWAVE TECHNIQUE

Prior to microwave treatment, lesions are debrided. The microwave tip is then applied to the lesion and a timed limited dosage is applied. Typically, a two-second application at 10 watts will deliver 20 joules of energy into the lesion. Normally, no anaesthesia is required at this energy level. Treatment can be re-applied to the same area at a similar dosage (typically up to three or four times depending on the area treated). For larger lesions, re-application is required until the majority of the treated lesion has been treated. Unless bleeding has occurred upon debridement, no dressing is required and the patient is typically reviewed on a fortnightly to monthly basis for around three or four treatment sessions. At the conclusion of the course of treatment resolution may have occurred, but it should be noted that, if resolution has not occurred, or is not apparent, it can take up to 10 weeks following the final treatment.

\*Regimens based on the author's clinical experience and research.

## CONCLUSION

Newer techniques for the treatment of plantar warts are emerging and are being adopted into everyday podiatry practice. Currently, research for these is at an early stage although promising results suggest they may offer a higher cure rate than older techniques such as caustics. In addition, these newer techniques offer the prospect of safer treatments for patients with fewer complications.

## Footnote

The use of microwave therapy is covered by the Society but all users must have completed the accredited course of training and notified the College that they have been trained to use the equipment.

## Declaration

Ivan Bristow is a consultant for Emblation Medical Limited.

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## AUTHOR CONTACT DETAILS

Address: University of Southampton Faculty of Health Sciences, Building 45, Highfield, Southampton SO17 1BJ  
Email: A.Borthwick@soton.ac.uk, I.Bristow@soton.ac.uk

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