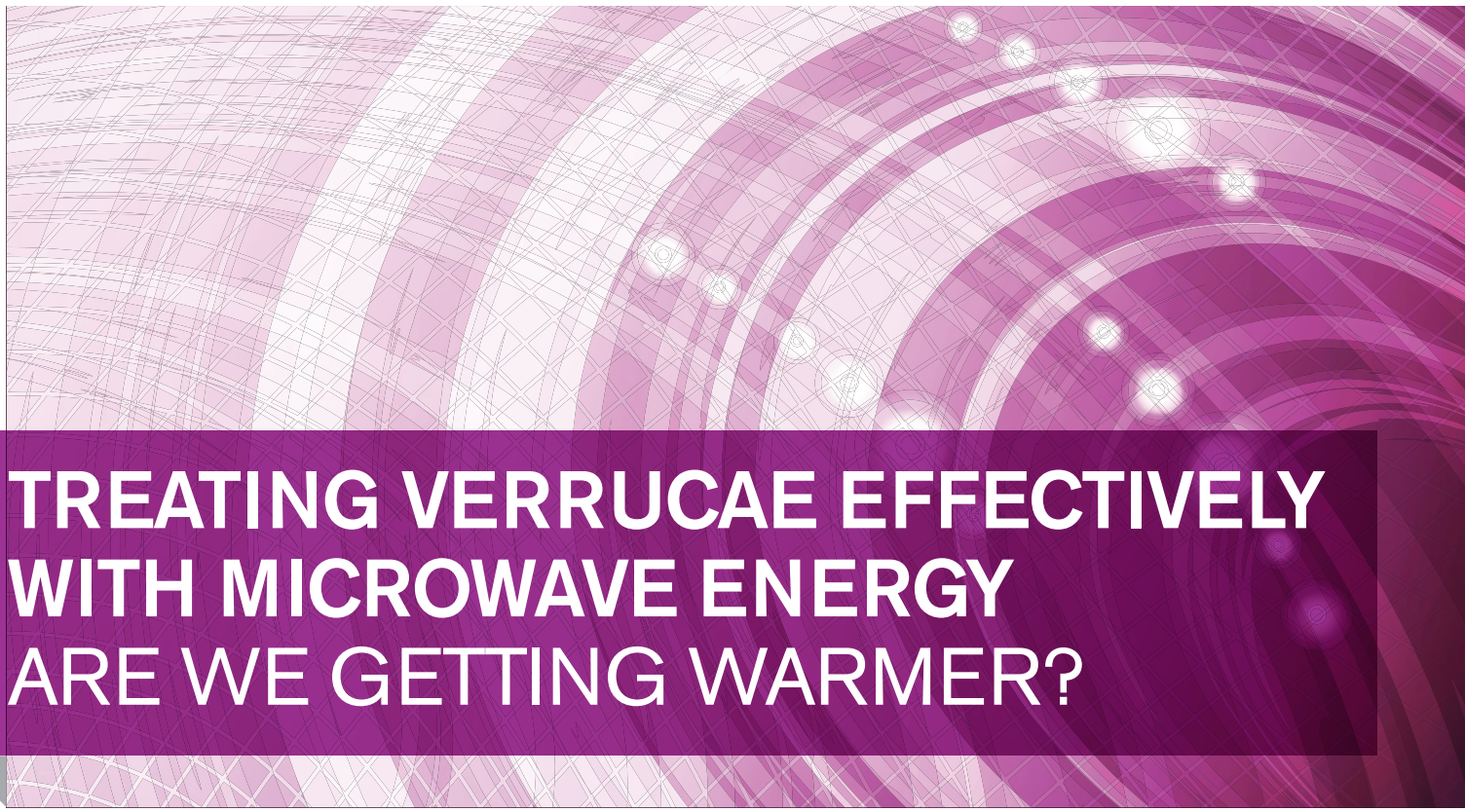

TREATING VERRUCAE EFFECTIVELY WITH MICROWAVE ENERGY ARE WE GETTING WARMER?

‘Those who cannot be cured by medicine can be cured by surgery. Those who cannot be cured by surgery can be cured by heat. Those who cannot be cured by heat are to be considered incurable’

Hippocrates

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The treatment of cutaneous warts has not significantly changed in decades. In 2000, Dyall-Smith [1] remarked how little verruca treatments had changed since the fifties and this still holds true today, perhaps with the additions of some newer topical antiviral drugs [2] and photodynamic therapies [3]. Over the years, podiatric training for the treatment of warts is still largely based on chemical means including salicylic acid, monochloracetic acid, trichloracetic acid and liquid nitrogen as cryotherapy.

Looking at the evidence for these modalities, years on, it does not make for particularly good reading. The latest guidelines published by the British Association of Dermatologists [4] in 2014 continue to review the common remedies such as salicylic acid and liquid nitrogen closely. Although success is reported as being ‘modest’, in most cases it offers a disappointing outlook for sufferers. Particularly notable is the lower response rates from plantar warts. Salicylic acid treatment has better outcomes than placebo, and response rates for both cryotherapy and salicylic acid are just over 30%. Moreover, the science explaining how they may work is lacking.

Cryotherapy, like chemical therapies, is something that has been taught for many years in podiatry as an established treatment for plantar warts. The latest review by Sterling [4] suggests how its effects are, at best, limited. Moreover, the likelihood of prolonged pain and blistering is always a possibility particularly when longer freeze times have been applied. It is this unpredictability that perhaps has resulted in its decline in podiatric practice. Cryotherapy, like the rest, is a reasonable treatment for warts but unfortunately not on the sole of the foot. Keratin is an excellent insulator, reducing the penetration of the cold temperatures and thereby protecting the underlying skin and virus from frost damage.

In 2015, the authors undertook a study using microwave as a treatment for plantar warts. This was an emerging technology that had been developed over several years. The use of this device switched from the cold treatment of liquid nitrogen to that of localised tissue heating utilising dielectric energy. Microwaves when applied to human tissue have the ability to agitate water molecules. As a polar molecule, water attempts to align with the electrical field, but because the oscillating frequency is in constant movement the water molecule is unable to rest. This effect causes the molecule to rotate rapidly and generate heat at a molecular level within the tissues.

The work from this clinical study of the device, conducted through the University of Southampton, demonstrated that this technique is capable of eradicating stubborn warts and it has now been adopted more widely into clinical practice. Logically, the next question to explore is how microwaves work against this viral infection of the epidermis.

Microwaves travel easily through tissues, unlike heat energy from an infra-red source, such as a cautery device, where heat is transmitted by conductance. In contrast to a carbon dioxide laser, for example, energy levels delivered by the Swift microwave device (Emblation Medical Limited, Alloa) are low and not designed to be ablative in nature so there is no tissue vaporisation, hence no smoke, steam or burn.

The temperature is raised to a level that is termed 'heat shock', within the range 41-44˚C, compared with the normal body temperature of 37˚C. At this hyperthermia level the increase in temperature has several effects - hyperthermia is widely acknowledged to provide an anti-tumour response through [5]:

1. Heat dissipation – tumours are more compact and disorganised and so cannot dissipate heat as readily as normal tissue and are therefore more sensitive to heating.
2. Tissue damage or death (apoptosis) to cell membranes and intra-cellular structures.
3. Modulation of a number of immune processes.

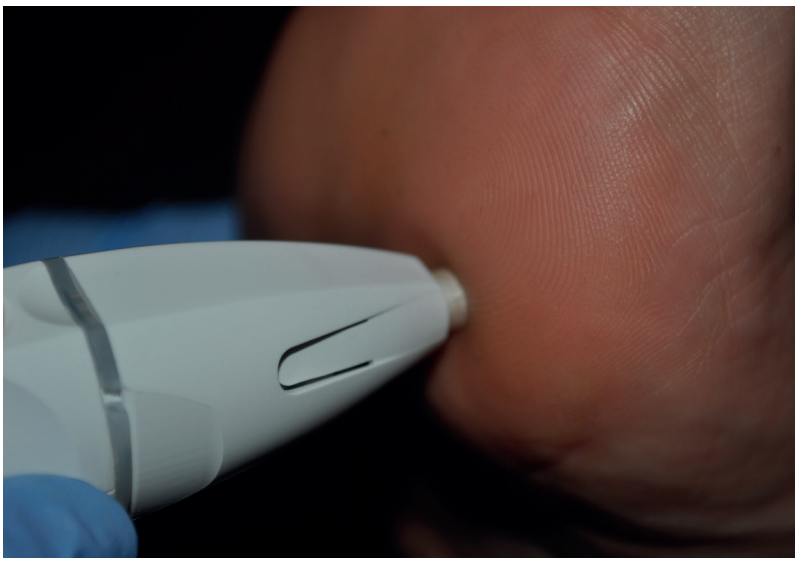
It is this latter point that potentially holds the key to new developments in treatment. Studies have highlighted successful eradication of tumours treated with temperatures in the heat shock temperature range [6]. More specifically, heating has been used to successfully eradicate warts. Huo & colleagues [7]undertook a randomised controlled trial of 54 patients to assess how repeated heating of warts to 44˚C affected resolution. At the end of the study, 54% of the treated group had resolved versus just 12% in the placebo arm. This work also reported that treatment of a single 'target' lesion could promote an immune response that cleared all lesions, resulting in a more tolerable treatment. A downside to this proposed heating treatment regimen that employed infrared energy was the use of 30-minute treatment cycles, which clinically may not be practical.

For normal adaptive immunity to occur in the skin, virally infected tissue must to be taken up by skin dendritic cells and carried to the lymph nodes for priming of CD8+ T cells. Primed T cells migrate from the lymph node and recirculate to the skin where they can then recognise and kill HPV infected skin cells. Warts on the skin are well known for their persistence, suggesting that host immunity is imperfect in dealing with this infection.

A variety of well-established mechanisms for host immune evasion exist, including down-regulation of antigen-processing machinery, and impaired dendritic cell function [8]. For example, previous work has demonstrated that, during HPV skin infection, up-regulation of the PI3-K pathway suppresses anti-HPV responses in Langerhans cells. Inhibition of this pathway increased anti-HPV activity, leading to rapid clearance of HPV [8]. Heating skin has been shown to enhance Langerhans cell migration from the epidermis [9] and, additionally, it has been shown that, by heating tissue, increased temperatures may exert an effect by preventing PI3-K activation, thereby potentiating the immune recognition of HPV infection [10] .

If tissue is exposed to temperatures above 41˚C, cell damage and death is likely. However, cells under stress (such as heating) produce chemicals known as Heat Shock Proteins (HSP). These have evolved to protect cells in extreme stress conditions from cell death. HSPs have a number of functions: as protein chaperones that are involved with the folding, shape regulation and degradation of intracellular proteins [1]. However, their effects on the immune system are of more interest. HSP-70 has been shown to induce the maturation of Langerhans cells and enhance their migration to the lymph nodes. When comparing normal skin to HPV infected skin, it was discovered that the migratory response was more marked in the HPV-infected skin[12]. HSP release also has been shown to stimulate cytokine release from antigen-presenting cells, as well as nitric oxide, chemotactic factors from macrophages and stimulate anti-tumour responses [5].

Other work has discovered that when HPV-infected cells are heated there is a greater release of the natural anti-viral group of cytokines known as interferons. These are important



cell signals that promote immune function. A study by Zhu et al [13] compared the release of interferons by heating virally infected human cells versus uninfected cells, and demonstrated that HPV-infected skin when exposed to 42-45˚C produced larger quantities of interferon than uninfected tissue. It has also been demonstrated that, during hyperthermically induced wart regression, a high level of CD4+ and CD8+ T-lymphocyte infiltration was identified in the treated areas, suggesting that cellular recruitment is enhanced by heat-induced epithelial damage, which is likely to be central to anti-viral immune responses [14].

The above work has demonstrated how research into hyperthermia has shown some positive insights into how raising skin temperature into the 41–45˚C range can bring about cellular changes conducive to resolution, but is there any evidence that such effects are induced by microwave heating? We have previously reported a study of human skin explant sections that were subjected to treatment using the Swift Microwave device and liquid nitrogen to observe for anti-HPV immune activity. Skin keratinocytes normally reside in a non-activated state. However, those from microwave-treated human skin were found to show increased expression of HSP-70 and were able to signal to dendritic cells. Even at a low energy, keratinocyte induced dendritic cell activation induced enhanced cross-presentation of HPV antigens to CD8+ T cells, with consequent interferon-γ production [5.] Interestingly, in liquid nitrogen treated control experiments, similar keratinocyte driven dendritic cell activation was not found.

Most recently the authors demonstrated that microwave treatment of cutaneous warts can be effective. In the first study of its kind, a cohort of 32 adults with refractory warts were treated with a course of microwave therapy using the Swift® device. At the conclusion, the resolution rate was 75.9%, with 41 of the 54 warts reported as resolved [16.]

Taken together, the basic science of microwave effects on skin and clinical responses noted suggest a mechanism for the observed action of microwaves in cutaneous warts, although more research is required to further this knowledge. Our understanding of the molecular mechanisms of hyperthermia provides a strong case for this new technology to be explored further as a local immune response activator therapy. Additionally, it seems likely that there may be many other potential dermatology applications for this exciting technology. ■

Declaration of interests:
Ivan Bristow is a consultant for Emblation Medical Limited.

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