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CLINICAL REVIEW

Management of cutaneous viral warts

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The prevalence of cutaneous viral warts in the general population is estimated to be 7-12%. Many patients present to primary care with pain and discomfort along with other concerns, such as cosmetic appearance. Although cutaneous viral warts are ubiquitous, no definitive treatment exists. Nevertheless, most warts resolve spontaneously and a large proportion of the remainder respond to simple recommended treatment. For these reasons, potential treatments must have minimal side effects and a favourable risk profile.

High quality evidence based studies are lacking in this discipline owing to confounding factors such as high rates of spontaneous resolution and a subpopulation of warts that seem recalcitrant to most treatments. Occasionally in medicine the longer the list of potential treatments the less effective they seem to be, and this situation is exemplified by viral warts.[1 2] This article focuses on the preferred treatment of viral warts in primary care and alternative management in secondary care.

What are cutaneous viral warts and how common are they?

Viral warts are benign papillomas that arise from infection of epidermal or mucosal cells with the human papillomavirus. A distinction is made between viral warts that affect mucosal surfaces—genital or oral—and those that solely affect the skin. This article focuses on viral warts that affect the skin. According to the 2010 Global Burden of Disease study,[3] cutaneous viral warts represent a major economic and public health problem. Risk factors include immunosuppression, close contact with affected people, and activities such as nail biting and walking barefoot.[4] In general, cutaneous viral warts are uncommon in infancy, common in childhood, and decreasingly less common from the second decade onwards.[1]

Subtypes

Clinically, several subtypes of warts can be distinguished. Verruca vulgaris, the most common, manifests as hyperkeratotic papules, often on the hands.[4] Plantar warts appear as thick hyperkeratotic plaques, particularly beneath pressure points on the soles of the feet, and they may be painful. When plantar warts are grouped into clusters, they are referred to as "mosaic" (fig 1⇓). Periungual warts occur around the nails and are particularly common in people who bite their nails. Planar warts can be more subtle, manifesting as single or grouped flat topped papules (fig 2⇓), most often on the face.[4]

What is the differential diagnosis?

The diagnosis of viral warts is usually clear and can be made on clinical grounds; in some situations, however, uncertainty can arise. Facial warts can be mistaken for syringoma, molluscum, or lichen nitidus. The presence of thrombosed capillaries is a characteristic feature; however, these are absent in facial and planar warts. Plantar warts may be similar to corns, although corns do not exhibit pinpoint bleeding when pared and usually show preserved markings on the skin surface. Common warts may be mistaken for hypertrophic actinic keratoses or basal cell carcinomas. Planar warts may be mistaken for flat seborrhoeic keratoses or melanocytic lesions. Large hyperkeratotic warts may mimic squamous cell carcinoma.

What is the clinical course of viral warts and when should they be treated?

Observational studies have shown that most viral warts resolve without treatment, albeit potentially after several years. A study of children in residential care found that two thirds of warts resolved without treatment over a two year period.[5] The risk of malignancy in immunocompetent patients with cutaneous viral warts is not considered to be significantly increased. Consequently it can be argued that asymptomatic warts in non-cosmetically sensitive areas do not require treatment. However, many patients request treatment because of pain or discomfort, cosmetic concerns, or the duration of lesions. A further argument in favour of treating warts is that, particularly for schoolchildren, infected individuals may represent a pool of infection[5] and consequently there is a role for preventive measures, such as verruca socks which cover the affected foot, acting as a physical barrier to prevent transmission. In many areas of the United Kingdom, health authorities advise limiting treatment to symptomatic warts.

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Summary points

- Viral warts are common in children and most resolve spontaneously without treatment
- Salicylic acid with regular paring and occlusion is the preferred treatment for cutaneous viral warts
- Cryotherapy in combination with salicylic acid is recommended as second line treatment
- Several third line treatments are available in secondary care that can be effective against warts recalcitrant to earlier treatments

Sources and selection criteria

We searched Medline, Embase, and the Cochrane databases for evidence relating to the treatment of cutaneous viral warts. Although a large number of trials have been published, the quality of evidence varied and only a few were randomised and of adequate sample size. Proof of efficacy is challenging, with relatively high rates of spontaneous resolution; furthermore, studies of second and third line treatments are limited as these treatments are typically reserved for recalcitrant warts.

What is the best topical treatment?

Topical treatments aim to physically or chemically ablate warts or to stimulate an immune response. Salicylic acid is an organic acid that ablates epidermal cells infected with human papillomavirus and softens hyperkeratotic epidermis associated with warts. Treatment is generally well tolerated and several preparations are available over the counter and by prescription only at similar strengths. Salicylic acid is suitable for any cutaneous site except the face. A recent Cochrane review[1] meta-analysed six studies of salicylic acid compared with placebo and found evidence of benefit (relative risk 1.56, 95% confidence interval 1.20 to 2.03). It is essential that patients receive clear instructions on use as compliance has a large impact on rates of response. Warts should be soaked in warm water for a few minutes each day, pared with a file, and then treated by application of salicylic acid under occlusion. Patients should be informed of the potential for an irritant reaction. No studies have assessed the optimum duration of treatment with salicylic acid; however, it is the authors' practice to continue treatment for at least 12 weeks in the first instance before considering other treatment types.

What is the role of cryotherapy?

Cryotherapy is another common treatment for cutaneous viral warts. It is directly destructive and also induces secondary inflammation. In the United Kingdom, cryotherapy with liquid nitrogen is more usually employed in secondary care or specialist community clinics owing to the logistical challenges of obtaining and storing liquid nitrogen in a primary care setting. Liquid nitrogen can be applied in several ways. The authors' preferred method for application is by spray gun for adults and by cotton buds for children. Over the counter products containing dimethyl ether and propane are advertised as suitable for "freezing" warts, but they are not as effective as liquid nitrogen as they only achieve temperatures of around −57°C compared with −196°C.[6]

A recent Cochrane review[1] incorporated 21 trials of cryotherapy. Unexpectedly, no benefit of cryotherapy compared with placebo could be found, which may reflect heterogeneity in study design and the high rates of spontaneous resolution. When compared with using salicyclic acid alone, cryotherapy showed evidence of benefit for warts on hands but not on feet.[1 7 8] This disparity may be due to the smaller number of foot warts treated, with reduced study power to show a difference.

On the basis of the Cochrane review, evidence to justify the use of cryotherapy in isolation is scarce. Although published evidence is inconclusive,[1 7 8] it is the authors' practice to combine cryotherapy with salicylic acid treatment. Evidence is not clear as to whether an interval of two, three, or four weeks between treatment is superior.[1 7 9] For cryotherapy used every three weeks, no additional benefit was found for continuing treatment beyond three months.[10] Complications include pain, hypopigmentation or hyperpigmentation, and blistering. Patients should be warned that blistering may be severe. Meta-analysis of four trials found aggressive cryotherapy—either longer duration or multiple freezes—to have a higher cure rate than less aggressive cryotherapy[1] (relative risk 1.90, 95% confidence interval 1.15 to 3.15), although such treatment increases the risk of complications.

Which other treatment options are available in primary care?

Duct tape has been used as a treatment option in primary care. A prospective randomised controlled trial of 61 children found cure rates of 85% for duct tape compared with 60% for a cryotherapy regimen.[11] However, subsequent studies failed to show a clear advantage when duct tape was compared with a corn pad[12] or moleskin[13] control. It is difficult to reconcile these results, although on the basis of current evidence duct tape would not be advised in isolation as the preferred treatment. However, it could be used as a second line treatment for children who are unable to tolerate salicylic acid or cryotherapy.

When should referral be made to secondary care or specialist community clinics?

Most cases of cutaneous viral warts can be managed in primary care. Referral to secondary care should be considered when diagnostic uncertainty exists, patients are immunocompromised, or warts are large or extensive (particularly when symptomatic or affecting cosmetically sensitive sites) or have shown recalcitrance to the preferred treatment for at least three months.

What additional treatments are available in secondary care?

In situations where the preferred treatment and second line treatments have failed, several third line options are available. Third line treatments are generally restricted to secondary care. Studies of such treatments are problematic because they are generally restricted to recalcitrant warts that have failed other treatment modalities and few head to head studies have compared the relative efficacy of the treatment types.

Imiquimod

Imiquimod is an agonist of Toll-like receptors, which are instrumental in the induction of an innate immune response.

Imiquimod is used widely to treat actinic keratoses and superficial basal cell carcinomas and is also an established treatment for genital warts.[14] The evidence for non-genital warts is less clear cut. In small non-controlled trials of 50,[15] 15,[16] and 18[17] patients, 30%,[15] 80%,[16] and 89%,[17] respectively, achieved complete clearance of cutaneous warts after a mean 9.2 weeks of treatment. A recent Cochrane review, however, reported manufacturer derived data from an unpublished trial on use of imiquimod in non-genital warts, and failed to show evidence of effectiveness compared with placebo.[1] Since these data are not publicly available, the reasons for discordance with published studies are unclear.

The authors have found imiquimod to be an effective treatment for facial warts where other treatment options are limited. Five per cent imiquimod should be applied daily to the warts for eight weeks. Imiquimod is not licensed for this indication and patients should be warned of the potential for a severe inflammatory reaction.

Bleomycin

Bleomycin is an antimitotic chemotherapy agent that can be used intralesionally to treat recalcitrant warts. Treatment leads to intense inflammation, which ablates the virus and may stimulate an immune response to human papillomavirus. Reported response rates vary from 16% to 94%,[1] possibly because of major differences in protocol and trial design. Side effects include intense inflammation, pain, and pigmentary change, in addition to the risk of tissue necrosis. Bleomycin can be administered topically or by injection into the lesion. Intralesional injection is associated with an increased risk of extensive necrosis and therefore the authors' practice is to use topical application every 4-6 weeks after scarifying the wart surface. The wart is subsequently occluded with a plaster to enhance percutaneous absorption.

Diphencyprone

Diphencyprone is a sensitising agent that induces a local type IV hypersensitivity reaction. Patients are initially sensitised with 2% diphencyprone to the inner arm. Subsequent treatment involves exposing the wart to increasing concentrations of diphencyprone until a contact reaction is elicited. This treatment is generally reserved for recalcitrant warts and requires substantial commitment from patients because of the need for regular monthly attendance for up to a year. Moreover, diphencyprone is a highly potent sensitising agent and adverse reactions include the induction of a local reaction at the contact site resulting in severe blistering or generalised eczema. Partners and healthcare workers are also at risk of becoming sensitised. Nevertheless, for patients with recalcitrant warts who complete a course of treatment, response rates of up to 88% have been reported.[18] A subsequent study in a population comprising both immunocompromised and immunocompetent participants found overall response rates of 60%, with an average time to response of six months in the immunocompetent group and nine months in the immunocompromised group.[19] Owing to the logistical difficulty of using diphencyprone and the potential for side effects, the authors do not consider this agent to be suitable for children.

Curettage and cautery

Although curettage and cautery is one of the oldest methods to treat warts, little evidence is available to assess the response rate to this treatment. Curettage and cautery is now less commonly used because of the requirement for local anaesthetic injection, the risk of scarring, and high rates of recurrence.[20] Identification of trials to assess the effectiveness of curettage and cautery was problematic, possibly reflecting the unpopularity of such treatment in the modern era. However, curettage and cautery has the advantage of providing tissue for histopathological examination, which can be useful when the diagnosis is uncertain.

Emerging treatment options

Currently, these treatments are less commonly used in clinical practice, and evidence for efficacy is limited. However, they may come to play a greater part in the future. Most of these treatments are not suitable for children.

Laser ablation

Carbon dioxide lasers and pulsed dye lasers are the two major laser modalities used to ablate cutaneous viral warts. Carbon dioxide lasers cause non-selective destruction of tissue through the vaporisation of water. Early studies found a high recurrence rate and frequent complications,[21] although more recently higher success rates have been reported.[22] Pulsed dye lasers target blood vessels that are more prevalent in rapidly growing warts. The rate of response has been variable; in one study the response rates between conventional treatment and treatment using the pulsed dye laser were similar.[23] An uncontrolled study of 134 patients found total remission rates of 63%.[24] A placebo controlled study found overall response rate of 64%.[25] A typical treatment regimen would comprise three or four sessions at monthly intervals. At present, the availability of laser treatment on the National Health Service is limited.

Photodynamic therapy

When activated by ultraviolet light, the photosensitising agent aminolevulinic acid produces a phototoxic product. Aminolevulinic acid is used widely in the treatment of basal cell carcinomas and extensive areas of precancerous change (epidermal field change). It is typically applied to the wart several hours before phototherapy. Only a small number of controlled trials are available on this agent, and results are variable.[26-28]

Immunomodulation

Failure to eliminate epidermal cells infected with the human papillomavirus represents a failure of cell mediated immunity and therefore presents the rationale for stimulating cell mediated immunity. Various strategies have been attempted. Products containing *Candida*, the mumps virus (*Rubulavirus* genus), and *Trichophyton* skin antigens are commercially available. These have been administered intralesionally with the goal of triggering an immune reaction against human papillomavirus. A single blind trial of 233 patients treated with immunotherapy, interferon, or placebo every three weeks for a maximum of five treatments reported response rates of 60% in the antigen treated group compared with 24% in the groups that did not receive antigen.[29]

Systemic treatments

Several systemic treatments have been proposed for cutaneous warts. In general, assessment of efficacy is limited by the high rate of spontaneous resolution and small, poorly designed trials. Acitretin has been reported as a treatment for extensive and recalcitrant viral warts.[30] A recent review[31] concluded that in

general the evidence for efficacy of other systemic treatments is lacking.

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Additional educational resources

Resources for healthcare

Children's Medical Center. Verrucae: a treatment approach (childrens.com/healthcare-professionals/continuing-education/online-cme/)—a comprehensive description of clinical presentation and treatment modalities

DermNet NZ. Viral warts (dermnetnz.org/viral/viral-warts.html)—a concise summary of viral wart subtypes and treatments

Primary Care Dermatology Society. Warts (www.pcds.org.uk/clinical-guidance/warts)—includes images of wart subtypes and a summary of treatment modalities

Resources for patients

British Association of Dermatologists. Plantar warts: patient information leaflet. (www.bad.org.uk/for-the-public/patient-information-leaflets/plantar-warts#.U3dJLcfPkXw)—a detailed information sheet for patients

NHS Choices. Warts and verrucas (www.nhs.uk/Conditions/Warts/Pages/Introduction.aspx)—offers concise explanation of viral warts and the treatment options available

Patient.co.uk. Warts and verrucas (www.patient.co.uk/health/warts-and-verrucas)—provides answers to questions commonly raised by patients

When to refer to a specialist community clinic or secondary care

- Diagnostic uncertainty
- Lack of success with first line treatment for symptomatic warts
- Extensive warts
- Immunocompromised patient or transplant recipient

Figures

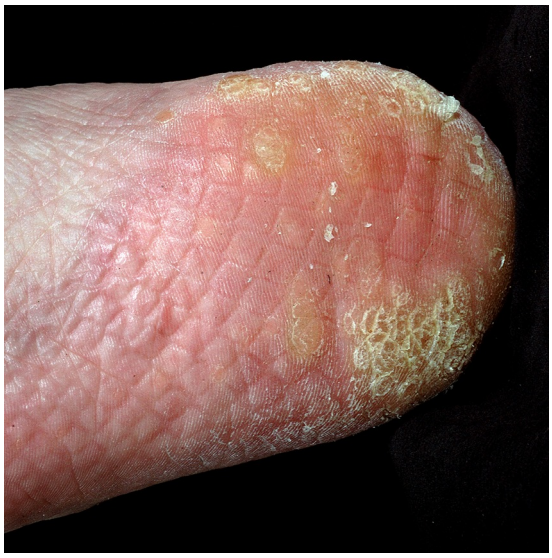

Fig 1 Hyperkeratotic "mosaic" plaques on the heel

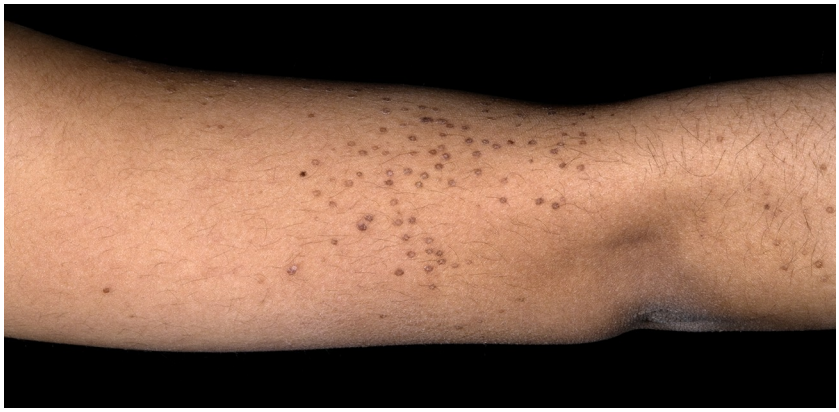

Fig 2 Grouped planar warts showing flat topped hyperpigmented papules