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Progress in the treatment of Cutaneous warts

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ABSTRACT

Viral warts are caused by HPV infection and result in the formation of benign proliferative lesions in humans. The diagnosis of viral warts is relatively simple and can be made on the basis of lesion characteristics, physical examination, laboratory tests and histopathology. Clinically, warts can be classified as common warts, flat warts, plantar warts, condyloma acuminatum and epidermodysplasia verruciformis. As warts tend to recur during treatment, a combination of treatments is more likely to prevent recurrence. This article is a review of advances in the treatment of warts. The aim of this article is to provide guidance to more dermatology clinicians to better understand the optimal choice of clinical treatment for warts.

KEYWORDS

Warts; HPV; Treatment

1. INTRODUCTION

Viral warts are associated with HPV infection of keratinocytes and the incidence of viral warts is approximately 7-12% [1]. HPV is a double-stranded DNA virus and there are more than 200 subtypes [2]. HPV viruses can be classified according to their oncogenicity into high-risk types (HPV-16 and HPV-18) and low-risk types (HPV-6 and HPV-11), of which high-risk HPV infections can lead to squamous cell carcinoma [1-3]. Skin HPV infections can lead to the formation of the following types: common warts, flat warts, plantar warts and condyloma acuminatum. It is important for dermatologists to tailor treatment to the clinical characteristics of the different types of warts [4].

This article describes current advances in the treatment of warts in the light of recent expert consensus, reviews and meta-analyses on the treatment of warts.

2. DIAGNOSIS AND TRANSMISSION OF VIRAL WARTS

Typical viral warts can be diagnosed by visual examination [1]. Dermatopathological examination and HPV genotyping can be performed for skin lesions suspected of being precancerous or carcinogenic. 3-5% acetowhite is useful in aiding the diagnosis of early condyloma acuminatum. A case series study showed that 51 patients with suspected condyloma acuminatum were examined by skin histopathology and colposcopy, and the positive rates of the two methods were 95.60% and 88.20%, respectively [4]. A case series study showed that 116 viral warts hyperplasia lesions were found positive by using 5% acetowhite test, 57.70% of viral warts in moist area and 0% of viral warts in dry area [5]. The study showed that 5% acetowhite test was accurate in the subclinical stage of warts infection. Acetowhite test had an accuracy, sensitivity and specificity of 55.30%, 92.30% and 58.20% respectively [6].

The main routes of transmission of common warts, plane warts, and plantar warts include skin and hand contact and indirect contact [7]. Sexual and vertical transmission are the main routes of HPV infection leading to warts. The formation of an HPV-containing laser plume during carbon dioxide laser treatment of viral warts can also lead to medical transmission of HPV [8].

There are more than 200 subtypes of HPV that can cause viral warts, cervical cancer and anal cancer [1, 4, 9]. A cross-sectional study found that 64.29% of sexual partners (N=263) had at least one person with HPV infection and 42.01% had two persons infected with the same subtype of HPV [10]. These findings suggest a high likelihood of HPV transmission through sexual contact [11]. A cohort study found that the probability of vertical transmission of HPV from mother to child was 27.66% and there was no significant difference between vaginal and caesarean delivery (25.71% vs. 28.81%). A systematic review found that the use of carbon dioxide laser for the treatment of viral warts resulted in a significantly higher probability of HPV infection in the upper respiratory tract (nose, mouth, and throat) [1, 3, 5, 10, 11]. Therefore, carbon dioxide laser treatment should be accompanied by exhaust ventilation.

3. LABORATORY TESTS FOR VIRAL WARTS

For warts, we recommend the acetowhite test to aid diagnosis [12]. If HPV typing of infected tissue is required, samples can be obtained by excision or clamp of infected tissue. Dermoscopy can also aid in the clinical diagnosis of viral warts [1]. Although the clinical use of the acetowhite test is controversial, it is still considered an inexpensive and simple adjunctive test [1, 2].

4. PRINCIPLES OF TREATMENT FOR VIRAL WARTS

Remove or debride viral warts or subclinically infected tissue in the skin as early as possible [1, 11]. If the warts are co-infected, it is recommended that the infection should be controlled before the warts are removed. For pregnant women with warts, the treatment plan will depend on the size of the warts and the effect of treatment on the foetus [3]. When cauterising warts, it is important to avoid contact with flowing particles.

The main aim of current treatment is to remove the warts and improve the patient's clinical symptoms [3-5]. The likelihood of recurrence is high even after removal of visible warts during clinical treatment. Holistic treatment of warts can reduce the extent of HPV infection in the skin, but it is difficult to completely remove HPV infection from the body. To prevent or treat subclinical infection of warts, laser, photodynamic and imiquimod application can be used for warts over 1cm in diameter to reduce the likelihood of recurrence [13, 14].

There are currently no effective anti-HPV drugs that can clear HPV infections completely. Physical therapy or surgery can remove any visible warts. For vaginal or cervical warts, the physician should identify the specific type of HPV [15]. And if necessary, colposcopic biopsies can be done to check for precancerous or cancerous lesions in the vagina and cervix [16]. In pregnant patients with condyloma acuminatum, the number and size of the warts may increase [4]. Podophyllotoxin and imiquimod are not safe for pregnant women. Warts in pregnant women can be treated with cryotherapy, trichloroacetic acid, or surgery. It is currently recommended that pregnant women with warts be treated as soon as possible. However, it has been suggested that treatment of small, slow-growing warts in pregnant women may be considered after delivery [4].

4.1. Progress In The Treatment Of Common Warts

Common warts are predominantly caused by HPV-2, and local injections of bleomycin, 5-fluorouracil (5-FU) and cidofovir can be used to control recurrent and recalcitrant common warts, with local adverse effects such as pain, burning, erythema or post-inflammatory hyperpigmentation around the

injection site [5]. A prospective clinical trial showed a cure rate of 64.70% with a mixture of 5-FU (40 mg/ml) and lidocaine [2]. A case series study found that cidofovir (15 mg/ml) was administered once a month to localised lesions, with 276 patients (N=280) requiring an average of 3.2 treatments for cure [15]. A meta-analysis showed that liquid nitrogen cryotherapy in combination with topical trichloroacetic acid or intradermal injection of Candida antigen increased the cure rate of common warts. A case series study of patients with common warts who received local hyperthermia (hand 43.5℃, foot 45.3℃) for 30 minutes each time for 5 consecutive days found a cure rate of 53.85% after 3 months of follow-up [11, 12].

4.2. Progress In The Treatment Of Flat Warts

10% 5-aminolevulinic acid photodynamic therapy (5-ALA-PDT) has been suggested for the treatment of flat warts [11]. Carbon dioxide laser, pulsed dye laser (PDL) and YAG laser may also be considered for multiple flat warts. Local injections of bleomycin or Candida albicans antigen may also be considered for the treatment of flat warts [3, 9].

Flat warts are common on the face in adolescents and are mainly caused by HPV-3, 10, 28 and 41 [11]. A systematic review found that ALA-PDT was more effective than carbon dioxide laser in treating flat warts, but also had a higher incidence of side effects. ALA-PDT treatment was also superior to liquid nitrogen cryotherapy [1, 4, 11]. One RCT found that 10% ALA-PDT was superior to 5% ALA-PDT or 20% ALA-PDT, and a systematic review showed that carbon dioxide lasers, PDLs, and Nd:YAG are the main types of laser used to treat viral warts (other than condyloma acuminatum), with response rates of 50.00-100.00%, 47.10-100.00%, and 47.10-100.00%, respectively. Laser combined with topical medications such as (bleomycin, salicylic acid or cantharidin) may also be effective in improving response rates [2, 11, 15]. One guideline suggests that intradermal injection of Candida albicans antigen is significantly more effective than other treatment modalities (oral isotretinoin, local injection of 5-FU or other microbial antigens into skin lesions) in the treatment of flat warts. Adverse effects include local pain, local erythema and oedema or flu-like symptoms [16].

4.3. Progress In The Treatment Of Plantar Warts

Topical hyperthermia can be recommended for the treatment of plantar warts [11, 13, 14]. Cryotherapy can also be used to treat plantar warts. Long-pulsed 1046nm Nd:YAG laser in combination with topical moisturising emulsion or carbon dioxide laser may also be an option for the treatment of plantar warts [17]. Local injection of recombinant human IL-2 in combination with carbon dioxide laser may also be a new option for the treatment of plantar warts. Local injection of bleomycin can also be used to treat plantar warts.

Plantar warts are mainly caused by HPV-1, 2, 4, 27 and 57 and are more difficult to treat because of the higher likelihood of recurrence [1]. One RCT showed that liquid nitrogen cryotherapy for plantar warts had a cure rate of 82%. Patients in these trials were free of the disease for more than 6 months [1, 3].

A cohort study found that long-pulsed 1046nm Nd:YAG laser treatment after topical moisturising cream treatment in patients with plantar warts could achieve a cure rate of 97.08% (mean treatment duration 1.3) [1, 18]. In one RCT, patients with plantar warts treated with local injection of recombinant human IL-2 in combination with carbon dioxide laser were found to have significantly higher success rates than those treated with carbon dioxide laser, liquid nitrogen freezing, topical fluorouracil ointment, and local injection of recombinant human IL-2 alone (94.00%, 78.00%, 56.00%, 32.00%, and 44.00%, respectively). One RCT found that local injection of bleomycin (63.02%) had a significantly higher cure rate than cryotherapy (48.82%) [1, 2].

4.4. Progress In The Treatment Of Condyloma Acuminatum

5% imiquimod in combination with physical therapy protocols (liquid nitrogen freezing, carbon dioxide laser, etc.) can be used to treat CA [6, 8]. Topical medications can be used to treat CA if the single lesion is less than 5 mm, the confluent lesion size is less than 10 mm, or the total number of lesions is less than 15. ALA-PDT can be used for lesions less than 5 mm in diameter. ALA-PDT in combination with physical therapy may be effective in reducing recurrence rates. Surgical excision may be considered for larger diameter CA lesions, with pedicles, or for persistent recurrent CA lesions. Physical therapy regimens combined with immunomodulators (e.g. imiquimod or recombinant human interferon alpha 2b) or photodynamic therapy may also be an option for the treatment of CA. For CA patients co-infected with HIV, topical imiquimod combined with photodynamic therapy may be considered [1, 18, 19].

The current principles of treatment for CA are early removal of warts, improvement of clinical symptoms and prompt removal of potentially infected tissue to try to prevent recurrence of CA. A systematic review found that topical application of 5% imiquimod combined with carbon dioxide laser had a higher clearance rate of CA than carbon dioxide laser alone [13, 20]. A review found that podophyllotoxin ointment or solution was most effective in removing warts or preventing recurrence. A systematic review found that ALA-PDT, which directly inhibits HPV replication, was significantly more effective than carbon dioxide or liquid nitrogen freezing in treating CA recurrence rates [13, 21].

4.5. Progress In The Treatment Of Epidermodysplasia Verruciformis

5-FU and imiquimod can be used for topical treatment of EV (low wart size and number) [1, 4]. If EV warts are generalised, topical or systemic application of Tretinoic acids may be considered [22]. For recalcitrant EV warts, electrocautery or cryotherapy can be used [1, 2]. Surgical excision may be considered for severe keratinised lesions, precancerous lesions or lesions that form squamous cell carcinomas. All patients with EV should be protected from the sun. EV is a rare chronic disease caused by a high genetic susceptibility to HPV, and its main clinical manifestation is widely distributed lesions. Patients with EV are susceptible to solar keratosis and squamous cell carcinoma after the age of 30 years. A case report of a 16-year-old female patient with EV was treated with systemic application of ganciclovir, BCG polysaccharide nucleic acid, and electrocautery and cryotherapy for skin lesions.

5. CONCLUSION

This article reviews the diagnosis and transmission of viral warts and advances in the clinical management of common warts, flat warts, plantar warts, CA and EV.

CA and EV. Viral warts have a high incidence of clinical morbidity and are associated with treatment irregularities and a high recurrence rate. This article may provide guidance and ideas for dermatologists in the management of viral warts in clinical practice.

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