

Contact Immune Sensitizers in Treatment of Verrucae Vulgaris

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Abstract

Background: Verruca vulgaris is commonly associated with human papillomavirus (HPV) subtypes 2 and 4 and affects approximately 10% of the population. In adults, warts are less likely to resolve spontaneously and are more resistant to treatment. Moreover, immune-suppressed individuals have an increased burden of warts compared with immune-competent patients. The first-line treatment for warts includes salicylic acid and cryo-therapy; however, their efficacy rates range from 0% to 80% and 14% to 90%, respectively objectives. This article aims to demonstrate efficacy and safety of contact immune sensitizers in treatment of verrucae vulgaris. **Conclusions:** Dinitrochlorobenzene, squaric acid dibutylester and diphenylcyclopropanone are three substances that have demonstrated efficacy in the treatment of wart. Diphenylcyclopropanone provides a good option for the treatment of warts, and this treatment could be considered as an initial treatment option for patients who wish to avoid treatment-related pain and subsequent side effects, especially children or patients with large numbers of warts

Keywords: Verrucae Vulgaris, Immune Sensitizers, Diphenylcyclopropanone, Squaric Acid Dibutylester

Introduction:

Verrucae are benign proliferations seen in skin and mucosa due to infection with HPV. More than 200 types of HPV have been reported to date and have been associated with various dermatological diseases, but each HPV type is typically only able to infect a few specific areas on the body^[1]. Many HPV types can produce a benign growth, often called a "wart", in the area they infect. Verrucae are considered to be a popular skin disease that show an incidence of about 33% in children aging between 6 and 12 years and about 3.5% between adults^[2].

Patients may suffer from substantial negative psychological impacts, therefore, treatments with lower side effects and low recurrence rate are required. Various treatment modalities are available for cutaneous verrucae, including topical therapies (such as trichloroacetic acid, salicylic acid, podophyllotoxin, and 5-fluorouracil), electrocautery, cryosurgery, surgical excision, carbon dioxide laser, and immunotherapy^[3].

Topical, intra-lesion, and systemic immunotherapeutic modalities have been widely used for the treatment of verrucae because of their non destructive action, high safety profiles, promising results, and low recurrence rates^[4].

Diverse immunomodulators, such as dinitrochlorobenzene (DNCB), squaric acid dibutylester (SADBE), and diphenylcyclopropanone (DPCP), have been used for treating warts. Among them, DPCP is the most widely used for its outstanding safety^[5].

Etiology and Risk Factors:

Warts are caused by HPV infection. Warts on the hand are also an occupational risk for butchers and meat handlers. Immunosuppression is another important risk factor. One observational study in immunosuppressed renal transplant recipients found that, at 5 years or longer after transplantation, 90% had warts^[6].

HPV comprise a group of non enveloped double-stranded DNA (dsDNA) viruses that belong to the Papillomaviridae family. They infect keratinocytes and induce hyperplasia and hyperkeratosis and hence forming warts^[3].

Types of HPV: Most HPV types trigger specific types of warts and show a predilection for certain anatomical sites. Extra-genital cutaneous warts can present as common warts (verrucae vulgaris), plane warts or plantar warts. Common and plantar warts are predominantly caused by HPV types 1, 2, 4 and 7, whereas types 3, 10, 27 and 41 usually give rise to plane warts^[3].



Fig. (1) Different types of warts ^[7].

Clinical features:

Cutaneous lesions

Common warts (verrucae vulgares):

They present as skin-colored or gray-brown papules, with a rough (hyperkeratotic) surface. The dorsal surface of the hands and fingers are the main predilection sites. HPV-1, -2, -4, -27, and -57 are the most prevalent types ^[8].

Periungual warts: Due to the special location of periungual warts, they are difficult to access. In addition to causing major cosmetic disfigurement of the nail, periungual warts are a therapeutic challenge that are characterized by resistance to various treatments and frequent recurrence ^[9] (fig 1).

Plantar warts (verrucae plantares): may appear as a singular rough, flesh-colored to yellow or grey-brown, hyperkeratotic papule, or a thickened termed a mosaic wart and characterized by the presence of verrucous, yellowish structureless areas with multiple irregularly distributed red-brown to black dots or linear streaks due to hemorrhages ^[10] (fig 1).

Filiform warts: These are most commonly found on the face and neck in men, but they can occur on any part of the body. It is a morphological variation of the common wart and the detected HPV types are the same as common warts, especially HPV 2 ^[11].

Plane warts: are primarily caused by cutaneous HPV types 3, 10, 28, and 29. Lesions appear as smooth, flat, or slightly elevated papules, usually skin colored or may be pigmented. The most common sites affected are the face, dorsa of the hands, and forearms ^[12].

Epidermodysplasia verruciformis:

Epidermodysplasiaverruciformis (EV) is a rare inherited dermatologic condition mainly autosomal recessive demonstrating an

increased susceptibility to specific HPV genotypes 3, 5 and 8 resulting in both benign and malignant skin lesions ^[12].

Mucosal lesions

Benign mucosal lesions

Condyloma accuminata: is the most common sexually transmitted disease found in young and sexually active population ^[14] (fig 1).

Multifocal epithelial hyperplasia (Heck's disease) is a benign, rare, familial disorder, characterized by soft circumscribed multiple sessile papular elevations of the oral mucosa, primarily associated with HPV types 13, 32 ^[15].

Recurrent respiratory papillomatosis (RRP): is generally a benign and self-limited disease caused by HPV and characterized by the appearance of papillomatous lesions anywhere in the aero-digestive tract ^[16].

Inverted papillomas (Schneiderian papillomas): are benign epithelial neoplasms arising from Schneiderian mucosa. There are three subtypes exophytic, oncocyctic, and inverted papillomas ^[17].

Other rare benign lesions as oral and Conjunctival papillomas: Oral squamous papillomas are common lesions of the oral mucosa of squamous epithelial origin presenting as a papillary or verrucous exophytic mass ^[18].

Premalignant mucosal lesions

Bowenoid Papulosis: is triggered by HPV infection and manifests clinically as solitary or multiple verrucous papules and plaques that usually are located on the genitalia. Most lesions are associated with HPV type 16; however, HPV types 18, 31, 32, 35, and 39 were also detected ^[19].

Erythroplasia of Queyrat (Bowen's disease of the glans penis): is a rare in situ squamous cell carcinoma (SCC) of the glans penis, which typically appears as one or more

well-margined erythematous velvety plaques^[20].

Malignant Mucosal Lesions

Vulvar cancer: Invasive vulvar cancer is usually preceded by vulvar intraepithelial neoplasia (VIN) or cervical carcinoma and often develops from chronic genital warts^[21].

Buschke-Löwenstein tumor (giant condyloma acuminatum or verrucous carcinoma of the anogenital region): It is a clinically aggressive tumor, with ulcerated cauliflower-like lesions, often associated with fistulas and abscesses^[22].

Penile cancer: Clinically, the lesions are hardened, nodular, ulcerated or erosive and may present with verrucous surface. HPV can be detected in lesions of penile cancer in a percentage reaching 40-70% and the most frequent type is HPV 16^[23].

Treatment of Warts

The primary reasons for treating warts are to:

Alleviate symptoms associated with the warts.

Prevent spread of the virus to adjacent anatomical sites or other people; and

Removal of the wart usually for aesthetic reasons

Treatment modalities are generally either immune modulating or ablative^[24].

Contact immunotherapy

Contact immunotherapy is classically performed with contact sensitizers Such as diphenylcyclopropenone (also known as diphenylcyclopropane DPC) or squaric acid dibutylester (SADBE). These agents act through activation of the host adaptive immune system with a resultant antiviral state inducing clearance of the wart (table 1). Also the presence of an immune response at both the site of treatment and at untreated wart sites provides some evidence of a systemic reaction in addition to the local immune reaction^[25].

To initiate contact immunotherapy, the patients first received the contact allergen topically at a concentration much higher than that actually used during subsequent treatment with gradual up-titration. Traditionally, a stronger inflammatory reaction was linked to a higher chance of treatment success, since the strong reaction indicates stronger stimulation of the immune system. However, some research did not show a correlation between the inflammatory reaction and the therapeutic results. Instead, it is the severity of the disease that predicts the outcome of the treatment^[26].

Topical immune sensitizers

Contact immunotherapy is classically performed with contact sensitizers such as DNCB, DPC, or SADBE. These agents are

thought to act through activation of the host adaptive immune system producing clearance of the wart. Furthermore, the systemic reaction provides the treatment of untreated wart sites^[25].

Dinitrochlorobenzene (DNCB):

DNCB or 1-chloro-2,4-dinitrobenzene was the earliest contact allergen introduced in 1912. It used to be popular for the treatment of extensive or recalcitrant AA, with hair re-growth ranging around 25–89% and complete re-growth rates being 6.7–25%. However, in 1985, DNCB was found to be mutagenic and carcinogenic in Ames test and had to be discontinued thereafter^[27]. It is rapidly absorbed after topical application and its excretion is primarily by kidneys. It contains contaminants that are mutagenic and carcinogenic to animals, so it is no longer used in clinical settings^[28].

Diphenylcyclopropenone (DPCP):

It is a topical sensitizer, efficacy of which was primarily reported by Happle et al in 1983.89 Currently, DPCP is the most commonly used substance owing to the following reasons:

First, it is non mutagenic in Ames assay, with no report of systemic absorption^[29].

Second, no long-term adverse effect has been documented yet.

Finally, it is less expensive and more stable in acetone solution compared to SADBE.

Diphenylcyclopropenone is a more potent contact sensitizer than DNCB at the same concentration. However, DPC may be a safer option, as unlike DNCB it is not mutagenic and not detectable in serum or urine after topical application^[28].

Squaric Acid Dibutylester (SADBE):

SADBE or 3, 4-dibutoxycyclobut-3-ene-1,2-dione is a sensitizing agent. Its efficacy in AA treatment was first reported in 1980, SADBE is an ideal sensitizing agent due to its absence in the environment and lack of cross-reaction with other agents. However, it is unstable in acetone solution and can degrade within a few hours at room temperature. To circumvent this issue, a light-resistant temperature-controlled container is used for sustaining its maximum effect. SADBE induce a type IV delayed hypersensitivity reaction, stimulating a cell-mediated response against the hapten-bound viral proteins on antigen-presenting cells resulting in wart resolution^[27].

Distant warts can also resolve, suggesting stimulation of a systemic immune response as well. Adverse effects of SADBE include redness, swelling, and itching at the application site. However, some patients might

experience more severe reactions, such as blistering, burning of the skin, and spreading of rash to other areas. Uncommon adverse effects reported include spread of generalized

eczema, persistent contact dermatitis, and severe angioedema^[30].

Table 1: Use of Contact Immunotherapy in the Treatment of Skin Diseases^[31].

Author s	Participant number	Agent s	Sensitization protocol	Intervention	Dropouts	Outcomes
Moore	12 (DNCB) + 11 (5-FU)	DNCB or 5- FU	No	0.2% of DNCB or 5% 5-FU ointment, frequency undocumented	6 (DNCB) + 7 (5-FU)	5 (83%)/6 received complete clearance in DNCB group; compared to 2 (50%)/4 in 5-FU group
Georga la	15	DNCB	0.15 ml of 2% in acetone on the right arm	0.5 or 1% of 2 DNCB weekly for 6–8 weeks	2 (1 discontinued treatment, 1 due to side effects)	Lesions all cleared in other 13 patients
Dall' Oglio	7 (adults) + 2 (children)	SADB E	3% in acetone to the lesion (adult) or dorsum of hand (children)	0.0003–0.3% of SADBE twice a week	1 (lost to follow-up)	Lesions all cleared in 8 patients without recurrence in 18 months
Miyata	3 (children)	DPCP	0.1% to the left arm for 24 h	0.5 or 0.05% of DPCP to the lesion twice a week	0	All the lesions regressed completely in 6 months
Yen	1	DPCP	1% to the left upper arm for 24 h	0.1% of DPCP to the lesion every 2 weeks for 2 months	0	The lesion disappeared completely after 6 months

Mechanism of Topical Immunotherapy

An ideal agent for topical immunotherapy meets the following requirements: safe, reliable sensitization, absent from the environment, and not cross-reactive with other chemicals. Only DNCB, SADBE, and DPCP are currently used. It is believed that these chemicals induce type 4 hypersensitivity and affect self-immunity in various ways, even though the precise mechanism is still speculative. For instance, some researchers found that polymorphisms in tumor necrosis factor- α and interleukin-1 receptor antagonist genes have been linked to the severity of alopecia areata, which could also influence topical immunotherapy-induced inflammation, affecting the clinical outcome^[32].

Moreover, serum levels of interleukin-4 and interleukin-12 are shown to be predictive for the clinical outcome of AA, suggesting the involvement of humoral immunity. As for warts, it is shown that CD4-to-CD8 ratio is reversed during immunotherapy^[33].

Furthermore, nonspecific antiviral reaction by activation of antiviral cytokines such as interleukin-2 and interferon- γ is suggested to be a mechanism for treating warts. It is also hypothesized that the agents act as a hapten to bind to an antigen associated with the viral warts, and thus help epidermal Langerhans cells or dermal dendritic cells process the complex and present to the naïve T-helper cells in the lymph nodes. In melanoma, peritumoral tumor-infiltrating lymphocytes and PD-1 expression predict better response to DPCP, indicating the immune-modulating effect of the chemical agent^[34].

The Relationship between Sensitization and Prognosis

To initiate contact immunotherapy, the patients first received the contact allergen topically at a concentration much higher than that actually used during subsequent treatment with gradual up-titration. Traditionally, a stronger inflammatory reaction was linked to a higher chance of treatment success, since the

strong reaction indicates stronger stimulation of the immune system^[35].

Topical Immunotherapy in the Treatment of Warts

In 1973, the first use of DNCB contact immunotherapy for resistant warts was reported with a cure rate of 91%. Now, contact immunotherapy plays an important role in treating warts, when other options such as chemical destruction (salicylic acid and/or lactic acid topical paints) or physical destruction (liquid nitrogen cryotherapy) show unfavorable results. It is a relatively painless treatment method, compared with traditional treatment modalities mentioned above that are destructive to tissues^[36].

Unlike cryotherapy or salicylic acid, which imposes direct destruction of the lesion including peripheral normal tissue, the “innocent bystander” hypothesis exist the contact allergens work by enhancing systemic immunization, as shown by a higher rate of spontaneous resolution of warts to which topical agents were not applied. moreover, it is also safe and effective in children, with the time required for complete cure shorter than adults^[37].

In immunosuppressed patients, there is a lower clearance rate, requiring a greater number of treatments over a longer time period, but contact immunotherapy still remained a useful option. Duration, number of warts, and new warts adjacent to prior ones have been shown to be negatively associated with response to therapy. Some studies also found the location of the warts to influence the resolution time, with plantar and periungual warts requiring the longest time. There is also a case report documenting a patient with epidermodysplasia verruciformis treated with SADBE successfully without recurrence. Aside from monotherapy, there are also trials or case reports to combine conventional therapy with topical immunotherapy^[38].

Limitation: The evaluation of skin lesions needs standardization for the comparison of efficacy. For patients who were treated effectively, long-term follow-up and subsequent regiment for maintenance may be needed. The mechanisms of topical immunotherapy were poorly studied outside alopecia areata and verrucae.

Conclusion: Topical immunotherapy is currently considered as the first-line treatment. The use of contact immunotherapy with DNCB, DPCP, and SADBE has declined in part owing to the emergence of more effective treatment, and also owing to the restriction of self-compounding by the health authorities in many countries. DPCP and SADBE have

already been officially approved as compounded chemicals that can be used for treatment for warts, also are currently prescribed as sensitizing agents with appreciable tolerability. In our opinion, topical immunotherapy, when used with caution, is an effective and safe treatment.

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