

New Lines in the Treatment of multiple Warts: Review Article

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ABSTRACT

Background: Warts are a widespread, benign, and typically self-limiting cutaneous ailment that is exceedingly prevalent. They might be as small as a few millimeters or as large as several centimeters. Papillomaviruses, which cause warts, are transmitted via contact with infected skin. Epithelial lesions ranging from benign to malignant may be caused by human papilloma virus (HPV), which are two-stranded DNA viruses. Due to the absence of an envelope, HPV is extremely persistent and resistant to a wide range of treatment drugs. HPV genotypes that cause both skin and genital warts have been completely classified to date. Trauma sites like the hands and feet are the most prevalent locations for them to occur. Treatment options for warts include various forms of destructive methods such as cryotherapy, electrocoagulation, topical salicylic acid, topical 5-fluorouracil, laser surgery, and others. A viable treatment option in these situations appears to be immunotherapy. As evidence of the importance of immunity, immunosuppressed persons are more likely to develop and maintain warts.

Objective: To review different lines in management of different types of warts.

Methods: Multiple warts, new lines, and treatment were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from January 2008 to May 2021 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: Immunotherapeutic modalities are effective in wart therapy with the advantage of avoiding scarring of destructive therapies and acting on injected and non-injected warts.

Keywords: Warts, Immunotherapy.

INTRODUCTION

It's common to encounter verrucae, or harmless growths on the skin and mucosa, after infection with the Human papilloma virus (HPV) ⁽¹⁾.

Typically, warts are little growths that are rough and hard to the touch and have a similar hue to the rest of the skin. Unless they are located on the soles of the feet, where they can be unpleasant, they rarely cause any symptoms. Hands and feet are the most common sites, although they are not the only ones that might be affected. The number of warts may vary. Because they aren't malignant, they are safe ⁽²⁾.

Prevalence and incidence:

There is likely a considerable range in prevalence among different age groups, populations, and time periods. Despite the lack of epidemiological data, they are extremely common among youngsters ⁽³⁾. In the general population, the prevalence of warts is stated to be between 1% and 24% ⁽⁴⁾.

HPV causes warts. In addition, immunosuppression is a risk factor. According to an observational study of immunosuppressed kidney transplant recipients, 90% of those patients had warts five years or more after their donation ⁽⁵⁻⁷⁾.

Diagnosis:

The typical clinical appearance of cutaneous warts is typically used to make a diagnosis.

1) Characteristics of the histopathology sample:

Acanthosis, papillomatosis and hyperkeratinization can be seen in a variety of warts, depending on their location.

Dermoscopic examinations reveal reddish or black spots or hairpin or coiled arteries, as well as hemorrhages/extravasation of erythrocytes and elongated and tortuous vessels ^(8,9).

2) Dermoscopy:

Vesicular, yellowish, structureless regions with many irregularly dispersed red-brown to black spots or linear streaks are the hallmarks of palmoplantar warts, which are the result of blood vessel hemorrhages. Palmoplantar warts are characterized by a lack of smooth skin lines ⁽¹⁰⁾.

Management of cutaneous warts:

Wart prevention guidelines have been established by official dermatological, primary care, and public health groups ⁽⁸⁾. An overview of the best practices for avoiding warts include: Avoidance of going barefoot in public places, as this might cause warts to develop ⁽⁹⁾. Ensure that your feet are kept dry at all times. Avoid sharing shoes, socks, or towels, if at all possible. Every day, change your socks. Also, do not touch someone else's wart ⁽¹¹⁻¹²⁾.

HPV cannot currently be cured with a particular antiviral medication. The viral life cycle can be disrupted by some of the treatments that are now on the market. Some warts can cause discomfort or interfere with daily activities, or they can be a severe cosmetic nuisance and embarrassment if they appear on the face or other prominent parts of the body. As a result, a variety of therapy options are available ⁽¹³⁾.

A- Destructive treatments

There are a plenty of wart treatments available, many of which have little or no evidence to support their utility. In an ideal world, therapy would leave no visible scars, however many patients would rather have a lifelong scar than a bothersome, unpleasant wart ⁽¹⁾.

The diseased epithelium is typically damaged or destroyed as part of the therapeutic process. This can also lead to cell death and the presentation of antigens, which could lead to an immunological reaction. When DNA replication is reduced, the wart will become less dense and new viruses won't be able to infect the skin ⁽³⁾.

Warts can be effectively treated if the immune system is stimulated directly in the area where the wart is located. Immune response is unknown, but the poor or non-existent response to treatments in immunosuppressed patients would indicate that it is crucial for wart clearance following destructive or inflammatory treatment ⁽¹⁾. Epidermal injury can be caused by a variety of different methods, including chemical, physical, and those listed below ⁽¹⁾.

B- Virucidal agents

- **Formaldehyde:** It has been claimed that 80% of youngsters with verrucas were cured by using formaldehyde soaks. Saturation levels of formaldehyde range from 3-10%. Allergy to formaldehyde is a known problem ⁽⁹⁾.
- **Glutaraldehyde:** A glutaraldehyde-based paint with a 10% glutaraldehyde concentration was found to be as effective as SA paint in treating plantar warts. Repeated usage of glutaraldehyde, especially at concentrations greater than 10%, has been linked to profound necrosis, as evidenced by some reports ⁽¹⁰⁾.
- **Occlusotherapy:** Treatment of cutaneous warts with occlusion has been used for some time, with a recommendation of 47% of patients cleared at 2 months, the exact mechanism is restriction of the blood supply ⁽¹¹⁾.

C. Antiproliferative agents:

1- Vitamine D analogues ⁽¹²⁾.

2- Podophyllin and podophyllotoxin:

By interfering with the mitotic spindle, podophyllotoxin can damage both normal skin and warts. If applied in high quantities or across broad areas, it can cause serious systemic effects and is contraindicated during pregnancy. There has been insufficient research on podophyllotoxin's efficacy in treating cutaneous warts, despite its widespread use in treating anogenital warts. According to this theory, cutaneous warts' low penetration compared to mucosal sites is due to their thick, cornified coating. But the negative effects of this medication include blistering and a strong inflammatory reaction ⁽¹³⁾.

3- Fluorouracil:

Both plane warts and common warts on the hands and feet have been successfully treated with topical 5-FU. Inhibiting DNA synthesis, 5-FU damages basal layer cells that are in the process of mitosis. It causes irritation and, on rare occasions, erosion when used topically or intra-lesion if it is taken for a lengthy period of time, hyperpigmentation or hypopigmentation can occur ⁽¹⁾.

4- Bleomycin:

Bleomycin has been recognized and utilized as a wart treatment for 40 years as a cytotoxic agent in systemic chemotherapy. Small needles and syringes can be used to inject the bleomycin solution into warts, or it can be put to the wart and 'pricked' into the wart with a needle ⁽¹⁾. This technique can be made more comfortable by administering local anaesthesia prior to or concurrently with bleomycin injection. Bleomycin causes some pain for a few days before necrosis sets in, and the necrotic tissue falls apart after some days ⁽¹⁴⁾.

5- Retinoids:

▪ Topical retinoids:

The proliferation and differentiation of the epidermis are affected by retinoids, which can lower the size of warts and modify the composition of the stratum corneum. Skin dryness and irritation are the most common adverse effects, both when administered topically and systemically, and these side effects may influence inflammatory reactions in the skin and contribute to the immunomodulatory effects of the drug ⁽¹⁵⁾.

▪ Systemic retinoids:

Several cases of severe warts being treated with oral retinoid, including immunosuppressed patients, have been reported. This medication works by cutting off the blood supply to the wart. There is a high probability of recurrence after withdrawal of acitretin 0.5–1 mg/kg daily for up to 3 months, however the mass of lesions is usually reduced ⁽¹⁶⁾.

6- Cidofovir:

DNA polymerase is competitively inhibited by cidofovir, a powerful nucleoside analogue, which stops cidofovir-incorporated viral cells from replicating ⁽¹⁷⁾. The parenteral form of cidofovir is reconstituted as either a 1% or 3% cream for use on the skin. Five days of treatment under occlusion, followed by a week without treatment, can be repeated. In a case series of seven children, cidofovir 1% cream was used to treat long-standing warts, with four of the children attaining complete eradication after eight weeks of treatment, lasting up to a year in 75% of patients ⁽¹⁸⁾.

D- Immunotherapy:

Cell-mediated immunity (CMI) plays a significant role in wart resolution, highlighting the need for immunological protection against HPV infections and

increasing focus to stimulation of the patient's immune system, specifically CMI, to destroy the virus. That's why, wart therapy challenges can be overcome by using treatment techniques such as immunotherapeutic approaches to treat warts⁽¹⁹⁾. An antigenic activation of the host-cell-mediated immune system by intralesional Candida, mumps and tuberculin antigens has been employed to induce wart elimination. However, reported clearance rates for this type of intralesional immunotherapy range from 47 percent to 87 percent⁽²⁰⁾.

1- Imiquimod:

Imiquimod, a well-known treatment for genital and perianal warts, is widely available. Interferon alpha (IFN- α), tumour necrosis factor-alpha (TNF- α), and interleukin 12 (IL-12) are produced, released, and induce a proinflammatory response as a result. Additionally, natural killer (NK) cells are activated⁽²¹⁾. Immunocompetent as well as immunocompromised people have benefited from imiquimod, as evidenced by several case studies. The most commonly reported negative effects are mild-to-moderate local discomfort⁽²²⁾.

2- Contact immunotherapy:

Diphenylcyclopropenone/diphencyprone or squaric acid diphencyprone elicit a local delayed hypersensitivity reaction at the wart site that triggers a local immune response during contact immunotherapy. Retrospective analysis of patients treated with DPC for palmoplantar warts over an eight-year period found that 88% of patients had complete clearance of all warts. There were no recurrences during a two-year follow-up after a median treatment time of five months⁽²³⁾. Pruritus, desquamation, erythema, as well as oedema and the possibility of cancer are only a few of the negative effects. The medication should be terminated if a patient develops autoeczematization or extensive urticaria⁽²⁴⁾. Bacille Calmette–Guerin (topical) and other allergens, such as those used in immunizations, have been suggested as potential therapy. Plane warts can be treated with topical medicines, which may be especially beneficial for children⁽²⁵⁾.

3- Intralesional immunotherapy:

Through the antigenic activation of the host-cell-mediated immune system, intralesional Candida, mumps, and tuberculin antigens have been employed to promote wart clearance. Intralesional immunotherapy has no solid evidence to support its use, however claimed clearance rates range from 47% to 87%^(26, 27).

4- Zinc oxide and zinc sulfite^(28, 29):

Ionic contra-viral therapy:

Combination of Digoxin and Furosemide:

HPV 1, 2, 27 and 57 are the most common causes of verrucae in the general population (more than 80%). Papillomaviruses depend on the infected host cell's environment to multiply, as is well known. DNA

viruses like HPV, for example, require potassium ion influx for replication⁽³⁰⁾.

Diuretic furosemide and cardiac glycoside digoxin both block K⁺ influx by interfering with Na/K ATPase (NaKATP) and NaK-KCL (NaKCL). For the treatment of HPV-induced illnesses, such as cutaneous warts, these two chemicals may be useful. Digoxin and furosemide were reported to have the strongest inhibitory effect on DNA replication in an in vitro study conducted in 2006⁽³⁰⁾.

Ionic contraviral therapy (ICVT) is a new method that combines two well-known, well-established medications. It has been shown to be most effective when applied locally⁽³¹⁾.

CONCLUSION

Immunotherapeutic modalities are effective in wart therapy with the advantage of avoiding scarring of destructive therapies and acting on injected and non-injected warts.

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