

Current Treatment Options for Cutaneous and Plantar Warts: A Literature Review and Update

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ABSTRACT

Warts are a generally benign and common finding in patients worldwide, with an estimated prevalence of 10–20%. Discussing treatment options for warts is a complicated subject as numerous options exist, but no one treatment modality has satisfying efficacy and recurrence rate. Furthermore, current guidelines for treating warts are outdated, with the latest one published in 2014. Since then, numerous research has yielded new data and evidence with regards to various aspects of warts. Hence, this evidence-based literature review aims to provide an update to these previous guidelines. Literature search was conducted to collect latest evidence regarding to warts and their treatment. The main keywords used to conduct the literature review are “treatment”, “cutaneous wart”, and “plantar wart”, and “verruca vulgaris”; these keywords are adjusted for each treatment modality. As of date, the best-studied treatments are salicylic acid and cryotherapy. Both therapies are still the primary treatments for warts, though their efficacy are not very high. Pulsed-dye laser and photodynamic therapy with aminolevulinic acid have promising success rates and can be considered alternative treatments. Surgical excision remains the treatment of choice for advanced and warts refractory for treatment. With regards to the small number of novel studies found from the literature search, we highly support more studies to be conducted with regards to wart treatment. Furthermore, we also urge for existing guidelines to be updated to current available evidence.



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1. INTRODUCTION

Warts, also known as verruca, have been afflicting mankind for quite some time. In the first century, the Roman physician Aulus Cornelius Celsus wrote of three types of wart-like lesions in his medical treatise “De Medicina”. The first lesion was “acrochordon”, which manifests in children and disappeared on their own. The second lesion was called a “thymion” and the third “myrmecia”, with the description of the former resembling that of genital warts and the latter of plantar warts [1], [2]. Yet, warts are still a common finding worldwide, affecting approximately 10% of the population; these numbers are even higher in school-aged

children, wherein the prevalence is estimated at 10–20% [3].

While generally benign and commonly regarded as a purely cosmetic blemish, a 2003 quality-of-life study found that warts bring a notable impact on patients' life. Around 81.2% of the subjects were moderately to extremely embarrassed by warts and 70.5% were moderately to extremely concerned of stigmatization by others. Others also complained of extreme difficulty in playing sports (27.4%), moderate to severe discomfort (51.7%) and moderate to severe pain (35.4%) [4]. As such, this widespread condition also has the potential to cause a high degree of patient morbidity.

Furthermore, available guidelines online are scarce and relatively outdated. From a literature search, the author found only a total of three warts treatment guidelines published within the last 15 years. The earliest guideline the author found was written by [5] published in 2006, another by [6] published in 2011, and the latest guideline written by the British Association of Dermatologists [7] in 2014. Since then, numerous research has yielded new data and evidence with regards to various aspects of warts. Hence, this evidence-based literature review aims to provide an update to these previous guidelines.

2. Methods

A literature search was conducted to collect the evidence presently available with regards to the epidemiology, pathogenesis, and diagnosis of warts. Additionally, the efficacy, safety, and costs (if available) of each treatment modality is also investigated. As means of quality control, only credible references published later than 2014 used. Journal articles and institutional or organizational websites are also used as reference. The main keywords used to conduct the literature review are “treatment”, “cutaneous wart”, and “plantar wart”, and “verruca vulgaris”; these keywords are adjusted for each treatment modality. Due to linguistic barriers, articles not written in English are excluded from this review. Anogenital warts (condyloma acuminata) are also no included in this review.

3. Discussions

3.1 Warts (*Verruca*)

Warts are an extremely common finding which are usually benign and self-limiting. They are caused by an infection of the epidermal cells by human papillomavirus (HPV) which results in cellular proliferation and a thickened papule on the skin [8]. The HPV is an icosahedral non-enveloped virus with circular double-stranded DNA. Around 280 types of papillomaviruses have been documented in vertebrates, more than 200 of those infect human. Of the various types, there are 12 which are closely associated with malignant neoplasms and classified as high-risk. The most prevalent HPV types are the HR-HPVs-16, 18, 31, 33, 45 and the low-risk-HPVs 6 and 11 [9].

Being widespread in the general population, warts are estimated to affect 7–12% of people worldwide. Cutaneous warts are more frequently found school children, meat handlers, and immunocompromised patients. Race-wise, warts occur approximately twice as frequent in people of white race in comparison to blacks or Asians, while sex-wise there is no remarkable difference in the male-to-female ratio. Warts can occur at any age but are unusual in infancy and early childhood. The incidence increases among school-aged children and peaks at 12–16 years of age [3], [10].

Warts are more commonly found at sites of trauma such as the hands and feet. This is probably due to inoculation of the virus into areas where the epithelium is slightly damaged. Transmission of warts by walking barefoot in places where others also walk barefoot is also possible [8]. Being less than 14 years old, having

lower education, sharing personal items, having a large family size and unhealthy behaviours such as alcohol consumption and smoking are also found to be risk factors for cutaneous warts [11], [12]. There also seems to be an occupational risk for warts, as one survey found out that the prevalence of warts on the hand was 34% in slaughterhouse butchers and 33% in retail butchers. Another important risk factor is immunosuppression, wherein a study found out that 90% of patients had warts after 5 years of receiving renal transplantation [8].

Transmission of warts necessitates direct skin contact with viral particles. This contact may happen directly with a wart, or indirectly via fomites such as flooring, towels, and sports equipment. The HPV itself is able to survive for months to years on surfaces. In the case of HPC infection, there is no systemic dissemination nor viremia. As such, of HPV is not transmissible via contact with bodily fluids, except from fluids produced by the warts themselves. The pathogenesis of HPV infection is entry of virus upon contact with a pre-existing disruption in the epidermis. Afterwards, HPV enters the basal epithelial layer, binds to cellular receptors, and is taken up actively dividing stem cells. After an incubation period of 1–20 months, the viral DNA is established within the host cell [13].

Once infection occurs, there are 3 possible outcomes: clearance of infection with subsequent immunity to that particular HPV type, latent infection, and clinical manifestation in the form of warts. The pathogenesis of warts starts when the virus is not cleared and begins to stimulate the basal cells to proliferate and replicate viral proteins, which leads to the formation of the wart. About 65–78% of cutaneous warts resolves on their own within 2 years. However, in those older than 12 years, the rate of spontaneous resolution decreases. The regression of warts relies heavily on an effective cellular immune response. In the healthy patient, viral antigen is taken up by Langerhans cells of the epidermis, which is then transported to lymph nodes via regional lymphatic drainage. They are then presented to T cells, which proceed to produce an antigen-specific immune response towards infected keratinocytes. Eradication of the infection and regression then follows. However, if this process fails, a persistent infection is established [13].

Currently, numerous treatments are available for warts. However, no one treatment is considered effective in all cases. Furthermore, evidence for almost all treatments is still lacking [6], [7], [13]. Hence, this study reviews the available treatments for warts and revisits them to reevaluate them with updated evidence.

3.2 Current and future potential treatments modalities

No Therapy (Watchful Waiting)

As warts are of minor severity in most people who are immunocompetent, watchful waiting is an acceptable option [7]. Expectant management is also an option for new warts due to their self-limiting nature [6]. In immunocompetent individuals, these warts resolve in months to years, with the spontaneous clearance of warts occurring in approximately two-thirds of children. Clearance in adults may be much slower though, with warts lasting for 5–10 years. A number of factors come to play with regards to the rate of wart resolution, such as host immunity, HPV type, and the site of the lesion [7], [14]. Some people also experience discomfort, social stigmatization, and functional interference due to their warts. In these cases, an inexpensive and safe treatment is warranted.

While numerous treatments are available, no one treatment is an absolute cure for warts. This is also complicated by the lack of quality evidence from previously conducted research [14]. As Indications for treatment as set out by the American Academy of Dermatology include patient desire for therapy; symptoms of pain, bleeding, itching, or burning; disfiguring or disabling lesion; lesions of large sizes or large numbers; and an immunocompromised condition [15].

The recurrence of warts is a source of frustration for patients and physicians alike. HPV may remain dormant in the epithelial cells, not showing any apparent signs. The effect of the patient's natural immunity and previously administered treatment may delay the redevelopment of wart [14]. This temporary clearance may give false sense of remission. One survey found that 83% of respondents believed themselves to be cured of warts at the end of their treatment, but 43% of respondents were not cleared of warts upon follow-up in 19 months [16].

Destructive Treatments

Salicylic Acid

Salicylic acid (SA) is a keratolytic which works by chemically exfoliating epidermal cells and keratin. It is also thought to induce a local inflammatory response and stimulate local host immunity. Current evidence seem show that treatment with SA usually yields an effect on warts though the effect is mostly moderate. Irritation of surrounding skin from treatment with SA affects patient compliance [6], [7], [13]. A 2021 systematic review [17] found the cure rate of SA to be 13.6% in plantar warts, much lower than that reported in a previous systematic review by [14]. Advantages of SA therapy include its low cost, over-the-counter availability, and minimal adverse effects [6]. While still lacking solid evidence, SA is a mainstay in the treatment of warts along with a handful of other modalities. Novel research on SA in the treatment of warts is limited. One single-center randomized controlled trial (RCT) protocol published in 2020 planned to study the efficacy of salicylic acid combined with AV2, a broad-spectrum antiviral drug [18].

Cryotherapy

Cryotherapy involves the application of low temperatures to deliver cold injury, inducing cellular damage and local inflammatory response to the warts. A 2022 meta-analysis found cryotherapy to be neither superior nor inferior to other treatments. However, there were evidence which showed antivirals and chemotherapy to be superior to chemotherapy in treating plantar warts [19]. The same 2021 systematic review we mentioned before also reported that along with SA, cryotherapy also has a low cure rate. The review also found that liquid nitrogen cryotherapy is not very convenient, more painful, and more expensive. A more aggressive approach in cryotherapy—which is associated with greater risk of adverse effects such as pain, blisters, and scars—is also found to be more effective than gentle cryotherapy [17]. Despite its low cure rate, cryotherapy seems to still be the primary treatment for plantar wart, as pointed in a review by [20].

Novel combinations of cryotherapy in the treatment of warts are currently being studied, such as cryotherapy with tuberculin immunotherapy for better response and less sessions [21], [22] or cryotherapy with 40% trichloroacetic acid for less adverse effects [23]. Others compare cryotherapy with thermotherapy [24], [25], imiquimod-SA [26], or intralesional chemotherapy [27]. Overall, the efficacy of cryotherapy and the compared treatment are similar. However, most of the comparison treatments have less adverse effects than cryotherapy.

Silver Nitrate

Silver nitrate is conventionally used to treat chemically cauterize epithelial tissues as in the case of epistaxis. Silver nitrates are more popular in the United Kingdom (UK) and among podiatrists. This may be due to caustic applicators containing 95% silver nitrate being available over-the-counter in the UK [5], [14]. However, evidence to support the use of silver nitrate in the treatment of warts are inadequate. No study was found to be documented in PubMed comparing the efficacy of silver nitrate with other treatments since 2007. Along with another study from 1997, there were only 2 studies catalogued in the literature. One advantage of silver nitrate is its convenience, as pointed out by a 2017 randomized trial which found no significant difference in the efficacy of self-applied and professional-applied silver nitrate treatment of plantar warts

[28].

Surgical and Laser Treatments

Surgical excision is the treatment of choice for warts refractory to treatment and advanced diseases. These therapy options include electrosurgery, curettage, and scissors excision. Only surgical therapies have clearance rates near one hundred percent [29]. The method of excision involves scraping or cutting warts off. Before the warts are excised, a salicylic acid solution or plaster usually is applied to the lesions [30]. Electrosurgery involves the insertion of an active electrode in warts to induce tissue destruction. Singh et al. found that the complete resolution rate achieved by electrosurgery was 75% versus 73.3% in patients treated with cryotherapy [31]. Another study conducted by Dalimunthe et al. showed cure rate was higher in electrosurgery with curettage than in the application of 80% phenol solution [32]. Up to this date, there is still limited evidence concerning these therapies. Some adverse effects of surgical excision include pain in the local site, wound infection, delayed wound healing, postinflammatory dyspigmentation, and scarring [31], [32].

Pulsed-dye Laser

Pulsed-dye laser (PDL) radiates a 585 to 595 nm wavelength, which is hypothesized to destroy the superficial capillaries that supply warts, thus starving the host cells of viral molecules [33]. Another study also suggested that PDL destructs the HPV virus as a result of the virus' heat-sensitive properties [34]. PDL has been used as a therapy for simple and recalcitrant warts, with remission rates ranging from 47 to 100%. Palmar warts have higher response rates than plantar warts. This therapy can also treat warts in the face and other cosmetically sensitive areas, with remission rates ranging from 41 to 100% [33]. Usually, warts were trimmed to enhance light penetration. Side effects of this therapy include local pain during and after the procedure, crusting, bullae, scarring, and temporary pigment changes. However, a study reported that PDL has a lower bulla formation and pain incidence than cryotherapy [35]. To conclude, current literature supports that PDL is an effective option for wart treatment.

Photodynamic Therapy with Aminolevulinic Acid (ALA-PDT)

Aminolevulinic acid is a photosensitizer that induces photooxidation in the abnormal cells after irradiation with visible light. This agent is usually applied to the wart for three to eight hours after exposure to the light. This treatment destroys warts by blocking microvessels in tissues which cause a lack of oxygen and nutrition and enhances immune response. Some advantages associated with ALA-PDT include minimal damage to the surrounding tissues, avoiding side effects caused by conventional physical therapies, and treating the deep lesions. This therapy effectively treats male urethra warts, with a 95% complete remission rate and 5% recurrence rate in a large-scale clinical trial. Another study also reported complete resolution in 97.3% and recurrence in 2.7% of patients. Adverse effects include local ulcers, erosions, redness, swelling, scars, painful irritation, and mild tingling sensation [36], [37].

Virucidal and Antiproliferative Agents

Formaldehyde

As a disinfectant with antibacterial, antifungal, and antiviral properties, formaldehyde (formalin) has been used to treat warts. This agent works by thickening, whitening, and removing the epidermis that contains the virus. In addition, thickened and hardened epidermis induces paring down the parts affected by lesions [38]. A study conducted by Mapar et al. showed that formalin application was practical in 83.3% of patients. However, only 11.1% reached complete disappearance of warts [39]. Ahmad et al. compared the effects of formalin 10% twice daily with cryotherapy every two weeks for three months [40]. The researcher concluded that formalin is preferred to cryotherapy due to its lower cost and no need for follow-ups. The most common

side effects caused by formalin are redness, irritation, and dryness of the skin. Severe allergic reactions are rare [39].

Vitamin D Analogues

Vitamin D3 currently shows favorable rates for treating warts as an innovative approach. Vitamin D3 is thought to regulate proliferation and differentiation of epidermis and modulate cytokine production. In addition, some researchers suggest immunomodulatory effects by inhibiting IL-6, IL-8, and other cytokines through a vitamin D receptor-dependent pathway. However, the exact effect is not known [41]. [42] reported complete clearance in 80% of patients using intralesional vitamin D3 at the end of 8 weeks. Kavya et al. showed similar results; 78.57% of patients achieved complete response, 14.28% showed a moderate response, and the rest showed a mild response [41]. Several side effects of vitamin D include swelling at the injection site and dyspigmentation. Severe systemic and local complications are infrequent.

Podophyllin and Podophyllotoxin

Podophyllin is a cytotoxic agent which is commonly used as a treatment for warts. Podophyllotoxin inhibits the formation of microtubules, thus interrupting the cell cycle. It also has an antiviral effect. This therapy is done directly to warts with a cotton swab weekly for four to six weeks or until the lesion is fully healed. Podophyllin resin is currently used as a topical treatment for anogenital warts [43]. A network meta-analysis by Bertolotti et al. reported that the most effective patient-administered treatments were podophyllotoxin 0.5% solution (63.5%) and podophyllotoxin 0.5% cream (62.2%) [44]. However, this agent is ineffective in treating cutaneous warts because of less drug penetration due to the thick layer. Side effects include acute inflammatory reaction with necrosis, erythema, edema, and skin ulcer. Systemic adverse effects, such as headache, fever, ileus, and gastrointestinal symptoms, can also occur due to the antimitotic effects of podophyllotoxin [45].

5-Fluorouracil

Five-fluorouracil (5-FU) is an antitumor agent which blocks DNA synthesis by inhibiting pyrimidine and thymidine. 5-FU inhibits cellular proliferation and causes cell cycle arrest, which is beneficial for treating warts. However, topical 5-FU is not very efficacious. Intralesional injection of 5-FU enables higher drug concentrations within the lesion and effectively treats warts. Three trials showed remission rates of warts by using intralesional 5-FU ranging from 60-74%. Potential adverse effects of 5-FU include pain at the injection site, burning sensation after injection, onycholysis, erythema, hypopigmentation, hyperpigmentation, ulceration, and scarring [46], [47].

Bleomycin

Bleomycin is a cytotoxic agent that inhibits protein and DNA synthesis. It also possesses antibacterial and antiviral properties. This agent has been used to treat warts for over five decades. Bleomycin for injection is available in vials that contain 15 mg of powder, which is then reconstructed with 5 ml of water for injection. The injection took place at the base of each wart until the lesion was blanched. Recent reports showed promising results, with a complete remission rate ranging from 69.3% to 96.47%. Dhar et al. found a higher clearance rate (94.9%). In treating recalcitrant warts, a 19.35% recurrence rate was reported. Adverse effects of this treatment include pain during injection for a few days, transitory perilesional hyperpigmentation, tissue necrosis, nail dystrophy, loss of fingernail due to matrix destruction, and erythema [48], [49].

Occlusal therapy (Duct tape)

Duct tape is a convenient alternative therapy for warts, despite the lack thereof solid evidence. The therapy involves applying a small piece of duct tape on warts with tape once every 4 to 7 days and paring down to

remove dead skin cells using an emery board for 4 to 6 weeks. Some studies suggested that the tape can heal warts by creating a keratolytic and macerating environment, stimulating an immune response. A study conducted by Focht et al. showed that 21 of 26 (85%) children treated with duct tape vs. 15 of 25 (60%) children treated with cryotherapy achieved complete resolution of their warts [50]. However, Abdel-Latif et al. found that cryotherapy has higher efficacy than duct tape in treating plantar warts in adults [51]. Adverse effects of this therapy include skin irritation from the glue, poor stickiness of duct tape, or bleeding associated with the paring-down process. Albeit the therapy is not recommended as a monotherapy, this treatment is painless, inexpensive, and convenient.

Immunological Agents

Imiquimod

Imiquimod is one of the most used therapies for warts, enhancing the immune response to viral infection. This agent is a toll-like receptor 7 (TLR-7) analog that stimulates inflammatory cytokines production, such as interferon-alpha, tumor necrosis factor, and interleukin-12. Imiquimod also enhances antigen presentation to T cells. A case series found that imiquimod 5% daily for five days per week can treat 30% of patients entirely and reduce wart size >50% in 26%. Another case series reported that 90% of patients achieved complete remission with imiquimod applied daily for four weeks under occlusion. Topical imiquimod shows a promising successful rate for treating warts in immunocompromised patients. Imiquimod 5% also can be used in children, as young as five years old, with good safety and success. Commonly reported side effects are burning, erosion, itching, erythema, and scabbing in local areas. Severe systemic side effects are infrequent [52].

HPV Vaccine

HPV vaccine is a potential treatment for patients with recalcitrant cutaneous warts [53]. The quadrivalent HPV vaccine works against HPV types 6, 11, 16, and 18 and is generally indicated to prevent anogenital cancers and genital warts. The HPV vaccine can provide cross-protection of extragenital strains, which is beneficial in eradicating extragenital warts. Some studies in adults and children suggested that recalcitrant warts achieved complete resolution after treatment with the HPV vaccine. A study conducted by Waldman et al. showed that 7 of 16 (44%) patients achieved complete clearance while treated with the HPV vaccine. This therapy is promising for recalcitrant warts, as these patients previously have failed other therapies such as imiquimod [54]. Common side effects associated with the HPV vaccine include redness, swelling, itching, or pain at the injection site. Headaches, nausea, and shivering are also reported.

3.3 Constraint

The limitation of this study manifests from not all treatment options included in this study and the limited optimal evidence and controlled trials available. Larger-scale controlled trials and meta-analyses are needed to compare and determine the most effective treatment.

4. Conclusion

The current treatments for warts can be classified into no therapy, destructive method, surgical and laser treatment, virucidal and antiproliferative agents, and immunological agents. As of date, the best-studied treatments are salicylic acid and cryotherapy. Both therapies are still the primary treatments for warts, though their efficacy are not very high. PDL and ALA-PDT have promising success rates and can be considered alternative treatments. Vitamin D3, 5-FU, bleomycin, formaldehyde, and imiquimod have shown high complete resolution rates and can be an option if available. Despite the lack of evidence, duct tape can provide 'placebo' effects and be combined with other therapies considering its minimal side effects. Surgical excision remains the treatment of choice for advanced and warts refractory for treatment. The HPV vaccine can be an

innovative option for recalcitrant warts. With regards to the small number of novel studies found from the literature search, we highly support more studies to be conducted with regards to wart treatment. Furthermore, we also urge for existing guidelines to be updated to current available evidence.

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