

Non-genital Warts: A Review of Current Treatments

When determining which treatment modality to choose for non-genital warts, there are several factors to consider, including the convenience of the treatment, patient discomfort, location of warts, and potential side effects.

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Warts are one of the most common, benign, persistent and frustrating skin and mucosal conditions encountered in dermatology clinical practice.^{1,3} There are several different forms of non-genital warts, which vary based on location and the human papillomavirus (HPV) type causing the infection. More than 90 serotypes of the human papilloma virus have been identified based on DNA homology.^{6,8} There are several therapies for common warts; none are uniformly effective in eliminating all lesions.⁵ This series will examine the variety of non-genital warts encountered in practice and evaluate evidence of the effectiveness of treatment methods for non-genital warts based on a variety of approaches. Modes of physical destruction will be the focus of this article, while next month's article will analyze the various chemical modes of destruction.

Types and Presentations

Warts account for eight percent of dermatology office visits.⁹ Human papillomavirus (HPV) causes this type of cutaneous infection, which can be inconvenient, disfiguring and recalcitrant to treatment.^{2,5} This benign epithelial proliferation is a source of contention for both the patient and the dermatology provider.¹⁰

The primary clinical manifestations in the skin may vary and include well-demarcated rough, scaly papules, plaques or nodules. The clinical appearance of warts depends on the type of HPV causing the infection and the site of infection. Diagnosis is usually based on clinical examination. One study assessed the diagnostic value of standardized criteria compared with the clinical intuitive diagnosis for verruca vulgaris. The analysis revealed four useful, independent, and strong criteria that include a hyperkeratotic, flesh colored, discrete margin lesion that occurs on any of three sites: fingers and hands, elbows and knees. The criteria in the final list proved to be less discerning than the clinicians who were involved in the study and merely used their clinical intuitive diagnosis.¹¹

Viral warts may occur at any age but are more common in children and adolescents.^{2,12,13} They are

Take-Home Tips. Physical destruction is often the preferred choice of wart removal. Physical modes of destruction—including cryotherapy, electrosurgery, and laser destruction—may each yield different results depending on the specific presentation of each patient. Nevertheless, they represent a wide base of procedures from which physicians can decide on the best approach. ●

seldom seen in infancy, however, there have been several studies on the prevalence of viral warts in school children. While their prevalence in the general population is unknown, they can affect up to 20 percent of children and adolescents.^{3,14} Some reports indicate an estimated incidence of 10 percent in children and young adults.^{7,12} Common warts occur in five percent to 10 percent of all pediatric patients.⁴ In 1998, the overall prevalence of warts was 22 percent among school children in the Australian state of Victoria.¹⁵ In a study of 3,029 primary school children in Taiwan, the incidence of viral warts was 6.9 percent.¹⁶ The range of greatest incidence is between 12-16 years of age, with the peak incidence at age 13 in females and age 14.5 in males.^{4,17} There also appears to be an increasing trend with age and the greatest number of warts occurring in children aged 12 years.

Although the prevalence of HPV in the adult population is not known, various diagnostic techniques, including serology and DNA hybridization, suggest that exposure to the virus, and subclinical as well as latent infection, may be very common. Infection occurs as a result of person-to-person spread, including that of sexual transmission, vertical transmission, and from exposure to virus in the environment.¹²

The course of the disease is unpredictable. Sometimes disease progression is self limited, though not always, making treatment necessary.⁷ Another study examining the natural progression of warts showed that after two years without treatment approximately 40 percent of children experienced complete resolution.¹⁷ Two-thirds of all warts in children will resolve spontaneously without treatment, usually within two years.⁴ Many warts regress spontaneously over several years in some adults. Many patients seek treatment, because the warts are unsightly, tender or painful.^{4,8,9,12,17} There is considerable social stigma associated with warts on the face and hands, and they can be painful on the soles of the feet and near the nails.⁸ They can be a source of physical discomfort and psychological trauma, as well as contagion.¹² The authors of several studies state that children with treatment-resistant warts potentially may be reservoirs for HPV transmission.¹⁷ Patients frequently request treatment to hasten the resolution.^{4,8,9,12}

In many cases, warts are recalcitrant despite the large array of therapeutic options.⁶ Because of the chronic nature of warts, patients often require several office visits for treatment, which will vary depending on multiple factors, such as clinical variant, severity and treatment modality. Extragenital warts in people who are immunocompetent are harmless and usually resolve spontaneously within months or years owing to natural immunity.⁸

It would appear that the immune system plays a significant role in the ultimate expression of HPV.¹² The lesion is self-innucleated and the incubation time is variable, ranging from a few weeks to more than one year. They can decrease spontaneously or increase in number and size according to patient's immune status.¹³ Latent infection also exists in which viral DNA is present in tissue but where complete virus particles are not assembled. Recognition of this state is only possible using certain diagnostic techniques (e.g., DNA hybridization or polymerase chain reactions). The degree to which contagion is possible in latent and subclinical infection is not known. It is possible that many individuals may never be cured of this virus and may "express" at various times the spectrum of HPV from clinically obvious lesions to latent infection. Whether it is possible to eradicate the virus completely is unresolved. The issue does not primarily lie with the otherwise healthy individual with warts on the finger, but rather with the patient who has HPV of the genital area and/or mucous membranes, as well as within the immunocompromised patient.¹²

Treatment aims to cure the patient's physical and psychological discomfort, and to prevent the spread of the infection.⁵ Cosmetic embarrassment and risk of self-innucleation are indications for treatment, which can be challenging. Effective therapy must provide reduction in pain and improvement in quality of life.⁷ Major goals of treatment are to increase the clinical disease-free-interval, decrease the bulk of clinically diseased tissue in an effort to "assist" the immune system in dealing more effectively with this virus, and decrease transmission of HPV to adjacent or distant body sites or to other persons by decreasing clinically infected HPV tissue.¹² Although there are several treatment options available, there is no single treat-

ment that evokes complete remission every time for 100 percent of patients.

Human papillomavirus (HPV) is a non-enveloped, double-stranded DNA virus which preferentially infects basal epithelium through microabrasions and tissue disruption. Warts may be divided into vulgaris (most common), filiform, plantar, periungual, flat, genital, and oral.¹³ Bacelieri, et al. report that warts typically continue to increase in size and distribution and may become more resistant to treatment over time.¹⁷

Cell mediated immunity has been shown to be important for controlling HPV infection and HPV associated tumors in experimental models. T helper (Th) 1 cells are effective in the host defense against viral infections and tumors.³ Cell immunity is very important, and warts are particularly exuberant in patients who have Hodgkins disease, AIDS, and also in patients taking immunosuppressant agents. It is reported that 55 percent of the immunosuppressed patients submitted to renal transplantation have warts, especially vulgaris and plantaris, up to five years after the transplantation. Humoral immunity seems to be less important, because patients with multiple myeloma are not particularly prone to have them.¹³

Modalities of therapy for human papillomavirus include physical destruction (i.e. cryotherapy, surgical removal, electrodesiccation, carbon dioxide or pulsed dye laser therapy), chemical destruction (i.e. salicylic acid, 80 percent phenol in solution, podophyllin, cantharidin), immunomodulator therapy (i.e. imiquimod, interferon, bleomycin, candida, retinoids, cimetidine, contact immunotherapy), tape occlusion and no treatment.^{4,6,7,10} The choice of therapy is guided by considering the side effects, such as pain and scarring, the rate of response, and the expense. Treatment usually begins with the more simple methods that have fewer side effects, then progresses to more complicated modalities if earlier treatments have failed.¹⁰ Invasive methods have the drawbacks of pain and long recovery periods. Topical management requires the application of drugs for long durations and treatment success is, therefore, highly dependent on patient compliance.⁸ Focht et al. reviewed a variety of therapies that had been studied for the treatment of warts, with success rates ranging from 32 percent to 93 per-

cent.⁴ Most of the therapies are either expensive, painful, or labor intensive.⁵

Methods of Physical Destruction

Methods of physical destruction have short-term efficacy and have been established in multiple clinical trials. Only a few trials have examined their long-term clinical responses. Methods of physical destruction include cryotherapy, electrosurgery and laser removal.

Cryotherapy. Cryotherapy, which generally uses liquid nitrogen to freeze tissues and destroy warts, is one of the most common and effective treatments.¹⁷ Liquid nitrogen cryotherapy involves freezing a wart with liquid nitrogen for 10 to 20 seconds every two to three weeks. Precisely how cryotherapy destroys warts is not well understood, but the prevailing theory is that freezing causes local irritation, leading the host to mount an immune reaction against the virus.⁴

Cryotherapy is widely used as an accepted mode of treatment with relative safety and moderate discomfort for patients. However, effectiveness is variable. In one retrospective study of 302 cases of viral warts in children 12 years of age and younger, liquid nitrogen was used as the first-line modality treatment of viral warts. They used liquid nitrogen to treat 267 cases. In 48.3 percent, the warts cleared completely. In 9.4 percent there was partial clearance, and in 1.9 percent there was no documented improvement. A total of 42.3 percent of the patients treated with liquid nitrogen defaulted on subsequent follow-ups. The number of treatments required to clear the warts ranged from one to 29 treatments, with a mean of 4.3 treatments. For patients who had complete clearance of viral warts, the average number of treatments required according to wart location was as follows: face (4.1), trunk (3.0), upper limbs (4.0), lower limbs (3.2), hands (5.2), and feet (5.4).¹⁸

A review of 16 trials assessing cryotherapy treatment found that most of these trials studied different cryotherapy application regimens rather than comparing cryotherapy with other treatments or placebo. Two smaller trials did not show any significant difference in cure rates, while two larger trials also showed no significant difference in efficacy between cryotherapy and salicylic acid.

The author pooled the data from four trials, which showed “aggressive” cryotherapy (various definitions) to be significantly more effective than “gentle” cryotherapy, with cure rates of 52 percent and 31 percent respectively. Pain and blistering seemed to be more common with aggressive cryotherapy, although reporting of side effects was less complete. Pain and blistering were noted in 64 percent of participants treated with an aggressive (10 second) regimen compared with 44 percent treated with a gentle (brief freeze) regimen. Five participants withdrew from the aggressive group and one from the gentle group due to associated pain and blistering.⁸

Cure rates for cryotherapy vary widely, depending on the treatment regimen. In general, the wart is frozen for 10 to 30 seconds until a 1- to 2-mm iceball halo surrounds the targeted area.¹⁷ One study found cryotherapy to have a wart clearance rate equal to 72.3 percent.²⁰ In another study, clearance rates at three months were 47 percent with cryotherapy with cotton wool bud and 44 percent in the cryospray group. That study found that the use of a double-freeze-thaw cycle confers little or no advantage over a single freeze in the treatment of hand warts, but may be considerably more effective for plantar warts.¹⁹ Bacelieri and Marchese Johnson report the highest cure rates are achieved when treatment occurs at a frequency of every two to three weeks. Benefit from therapy continuing for more than three months was not documented.¹⁷

In order to determine the optimum treatment interval, Gibbs, et al. examined three trials. They found no significant difference in long-term cure rates between treatment at two, three and four weekly intervals in reviewed trials. In one trial, pain or blistering was reported in 29 percent, seven percent and zero percent of those treated at one, two, and three weekly intervals, respectively. The higher rate of adverse effects with a shorter interval between treatments might have been a reporting artifact due to participants being seen soon after each treatment. Only one reviewed trial examined the optimum number of treatments. This trial showed no significant benefit of applying cryotherapy every three weeks for greater than three months to the warts on hands and feet.⁸

A major drawback to cryotherapy for many children is the fear and discomfort they experience with the procedure. Other potential complications of cryotherapy include blistering, infection, and dyspigmentation of the skin. Cryotherapy is also inconvenient because it requires frequent clinic visits for success. When the freezing interval is increased from three to four weeks, there is a decrease in the cure rate from 75 percent to 40 percent.¹⁷

Cryotherapy is easy to apply and doesn't require patient adherence with topical applications at home. However, scarring can occur, discomfort can be moderate in intensity and usually a minimum of three to four treatments are needed. Cost can also be an issue, especially if several return office visits are warranted.¹⁷ Most of the trials of cryotherapy studied different regimens rather than comparing cryotherapy with other treatments or placebo. Although there is more controversy about its efficacy, most of the studies show lower cure rates for cryotherapy when compared with other studies done on bleomycin.²⁰

No published study was found to compare the efficacy of bleomycin with cryotherapy on the same patients or the same study group.²³ Adalatkah, et al. found that bleomycin had 1.23 times more clearance efficacy than cryotherapy. Pain was the main problem both in cryotherapy and intralesional bleomycin; analgesia was helpful in both groups. Pain management seemed to be easier for bleomycin; the pain period was shorter compared with pain and discomfort that may continue for several hours after cryotherapy.²⁰

Clinical efficacy of cryotherapy in the Banihashemi, et al. study was relatively similar to other studies. Their study showed phenol was an effective form of treatment for warts. However, both methods must be used by a physician, but phenol needs more attention due to its toxicity and should not be used in extensive areas. It can be used when cryotherapy is not available.⁵

Electrosurgery. Electrosurgery involves either thermal coagulation or electrocautery to destroy HPV affected lesions. In the direct-current form of electrosurgery, termed electrocautery, electricity flows only through the instrument producing heat that is applied to the lesion. In the alternating-current form of elec-

troscopy, electricity flows from the instrument through the patient to a grounding plate.²¹ The goal is to destroy the virus in the epidermis and to not harm the underlying dermis, to minimize risk of scarring. Local anesthesia is needed to perform electrosurgery.

Electrocautery with curettage is an alternative treatment option for viral warts. It usually requires only a single treatment, and the clearance rate seems to be high. Patients selected by Mitsuishi, et al. for electrocautery had solitary or few warts (less than three). Eleven patients were treated with electrocautery, all above eight years of age. Complete clearance was documented in eight of 11 patients. One child had partial clearance and two children defaulted on follow up. This method is probably less suitable for younger children, who may be unable to cope with the trauma of pain from the injections of local anesthesia and treatment.³

There are no recent studies of electrosurgical methods for genital wart treatment. Older studies show a 61-94 percent clearance within three to six weeks of treatment. Despite its effectiveness, electrosurgery should be considered second-line treatment. Scheinfeld reviewed two randomized trials which showed slightly greater efficacy for electrotherapy compared with cryotherapy; however, the differences in outcomes are only short term and do not persist after three months of follow-up.²¹

Laser Destruction. Laser destruction of warts is based on the principle of photodermal or photomechanical destruction of the target tissue.⁷ Treatment with a vascular lesion laser, also known as pulsed dye laser therapy, can selectively target hemoglobin contained in blood vessels within the warts.¹⁷ Target structures absorb monochromatic coherent light of specific wavelength and fluence.⁷ As the hemoglobin heats up, thermal energy is dissipated to surrounding tissues, leading to cauterization of blood vessels. Depending on the pulse duration and energy density, this may result in the coagulation (photodermal effect) or blasting (photomechanical effect) of these structures. The result is a necrotic wart that eventually sloughs off.¹⁷ A wart is a lesion characterized by proliferation and dilation of vessels, making this treatment effective.⁷

Studies examining the effectiveness of pulsed dye laser therapy after an average of two or three treatments have reported overall cure rates of 48 percent to 93 percent for warts located at various sites. One study demonstrated an overall clearance rate of 72 percent. The highest clearance rate was 85.7 percent for periungual warts, and the lowest clearance rate was 50 percent for plantar warts.¹⁷

A separate study compared pulsed dye laser therapy with cryotherapy and cantharidin. Of the patients treated with cryotherapy or cantharidin, 70 percent demonstrated clearance after two treatments, whereas 66 percent of the patients treated with pulsed dye laser demonstrated clearance following two treatments. Therefore, no statistically significant difference was noted in the treatment modalities. Pulsed dye laser therapy is recommended as second-line therapy for plantar warts and third-line therapy for common warts and flat warts. However, another review found poor evidence to support the use of a single pulsed dye laser treatment because of problems with study methodology and listed it for the treatment of warts located on the hands and feet only.¹⁷

In another study the average number of treatment sessions required with long pulsed Nd:YAG laser for clearance was 1.49 (range, 1-4 sessions); 64 percent of warts were clear by the end of the first treatment, while 96 percent of warts were cleared after the fourth. *Verruca vulgaris* responded better than other types of warts and required fewer treatments for clearance (mean, 1.35 sessions). Deep palmoplantar warts required a mean of 1.95 sessions for clearance. The clearance rate after the first treatment was also higher in the *verruca vulgaris* group (72.6 percent) than in the periungual warts group (64.7 percent) and in the deep palmoplantar warts group (44.1 percent).⁷

Gibbs, et al. reviewed four trials that reported varying success with different types of photodynamic therapy (PDT). The heterogeneity in methods and variations in trial quality precluded firm conclusions. One well-designed trial in 40 adults reported cure in 56 percent of warts treated with aminolevulinic acid PDT compared with 42 percent treated by placebo photodynamic therapy. Topical salicylic acid was also used for all participants as combination therapy.⁸

Pain was a common side effect, as was transient numbness, hemorrhagic bulla, hyperpigmentation and hypopigmentation. In addition, patients with periungual warts experienced nail dystrophy. During a median follow-up period of 2.24 months (range, 2-10 months), 11 relapses were seen (recurrence rate, 3.3 percent).⁷ In one trial, reviewed by Gibbs, burning and itching during treatment, and mild discomfort afterwards were reported universally with aminolevulinic acid photodynamic therapy. All participants with plantar warts were able to walk after treatment. In another study, severe or unbearable pain during treatment was reported in about 17 percent of warts with active treatment and about four percent with placebo photodynamic therapy.⁸

Pulsed dye laser therapy usually requires fewer office treatments and no home treatments, unless adjunctive treatment is desired. Discomfort and scarring may be issues for pulsed dye laser therapy.¹⁷

Han, et al. concluded that long-pulsed Nd:YAG lasers are a safe and effective treatment for warts, with response rates higher than those obtained with conventional therapies. No single optimal treatment has been indicated for warts therefore, long pulsed Nd:YAG lasers should be considered a reasonable addition to the therapeutic options available. Future studies examining optimal laser parameters and treatment intervals would enhance our knowledge of how best to use long-pulsed Nd:YAG laser therapy in managing warts.⁷

The CO₂ laser has been shown effective for the destruction of warts,²⁵ including in immunocompromised individuals.²⁶ However, the cost of therapy and limited access to lasers may limit clinical utility.²⁵

Papillomavirus DNA has been detected in the vapor from warts treated with CO₂ lasers and with electrodesiccation, with

Tape Occlusion

Despite the lack of data, occlusion therapy with duct tape has been endorsed at dermatology meetings as a safe and effective therapy. The mechanism of action of duct tape on warts is unknown, but, as with other therapies, it may involve stimulation of the patient's immune system through local irritation. Tape occlusion, if proven effective, could be an inexpensive, convenient, and painless alternative to cryotherapy in the treatment of pediatric warts.⁴

The first randomized, prospective study examined the efficacy of tape occlusion therapy for warts. They found that the warts that ultimately responded to tape therapy typically showed at least partial resolution after two to three weeks of treatment. Warts unchanged in appearance by the three-week mark were unlikely to respond.⁴

Another study evaluated 80 immunocompetent adults with at least one wart measuring 2 to 15mm. The researchers concluded no statistically significant differences in the proportions of patients with resolution of the target wart (eight [21 percent] of 39 patients in the treatment group vs. nine [22 percent] of 41 in the control group). Of the patients in the treatment group, 75 percent of treated patients and 33 percent of controls who had complete resolution experienced recurrence of the target wart by the sixth month. No statistical difference between duct tape and moleskin for the treatment of adult warts was found.¹⁴

There are anecdotal reports in the literature of tape occlusion therapy for treatment of common warts. Although there have been no randomized, prospective trials of tape occlusion versus standard therapies in the treatment of warts, one report indicates a success rate of approximately 80 percent using adhesive tape.⁴

Some reports indicate that duct tape occlusion therapy of warts was significantly more effective than cryotherapy. Patients in the duct tape arm who had complete resolution of their warts were 85 percent versus 60 percent of patients in the cryotherapy arm. The exact time to disappearance of the warts was not accurately recorded due to variability in when patients were contacted for follow-up or returned for more cryotherapy or wart measurements.⁴ The majority of warts that resolved with tape occlusion therapy were unlikely to resolve if no response was seen by two weeks. The majority of warts responding to cryotherapy (60 percent) resolved after only two treatments spaced two weeks apart. Based on this information, average time to resolution between the two treatments was comparable.⁴

Prior to the aforementioned study, few anecdotal reports existed in the literature for use of tape occlusion therapy in the treatment of warts and no prospective, randomized, controlled trial had yet been performed. This study shows that duct tape occlusion therapy is not only equal to, but exceeds the efficacy of cryotherapy in the treatment of the common wart. Tape occlusion therapy can now be offered as a nonthreatening, painless, and inexpensive technique for the treatment of warts in children.⁴

Wart Therapy: Physical Destructive Modalities

higher quantities of DNA derived from the laser vapor. However, a surgical mask was found to block virtually all virus,²⁷ suggesting that proper precautions limit risk of viral transmission to the clinician.

Conclusion

The physical modes of destruction presented here may each yield different results depending on the condition of each patient. Nevertheless, they represent a wide base of procedures from which physicians can survey the literature to decide on the best approach. While physical destruction might be the preferred choice of wart removal, physicians will often resort to other means of destruction out of necessity.

In a follow-up article next month, we will discuss chemical means of destruction, including salicylic acid, phenol, and cantharidin. It will also explore the possible roles of immune modulators and intra-lesional immune modulators. ■

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