

REVIEWS

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Anal Warts (*Condylomata Acuminata*) – Current Issues and Treatment Modalities

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Abstract

HPV infections are currently the most frequent cause of genital infections in the USA. Risk factors are early onset of sexual activity, multiple sexual partners, a history STDs, an early age of first pregnancy and tobacco use. In the past, HPV viruses were thought to be STDs, but it is now known that penetration is not necessary. Skin-to-skin or mucosa-to-mucosa contact is enough to transmit the virus, which presents high tropism for those tissues. The *Papillomaviridae* family includes over 120 viruses, some of which have high malignant transformation rates. The most common malignancy connected to HPV is uterine cervix cancer and anal canal cancer. The range of morphology of perianal lesions means that a thorough clinical examination is required, including an anoscopy. Therapeutic modalities often seek to eliminate macroscopic changes rather than focus on the cause of the infection, which leads to a high recurrence rate. Externally located changes can be eliminated with patient-applied treatments. Those located in the anal canal and distal end of the rectal ampulla require treatment by a qualified medical provider. Due to the high recurrence rate after standard treatment, special attention has been given to vaccinations. The polyvalent vaccine includes HPV viruses with both low and high malignant transformation risk. This has led to a decrease in the rate of malignancies (*Adv Clin Exp Med* 2014, 23, 2, 307–311).

Key words: *condylomata acuminata*, anal canal, cryotherapy, electro-surgery, vaccination.

The Epidemiology and Biology of HPV Anal Infections

The Human Papilloma Virus (HPV) used to be thought of as one of the most common sexually transmitted diseases (STDs) [1]. However, penetrative sexual contact is not in fact necessary to transmit the virus, which is predominantly transmitted by skin-to-skin or mucosa-to-mucosa contact [2]. The HPV family (*Papillomaviridae*) consists of more than 120 viruses presenting a tropism towards either the cutaneous or mucosa epithelium. The frequency of HPV infection has risen in the past 35 years, and this can be attributed to

a decrease in the age of the first sexual contact as well as an increase in the number of sex partners [3]. HPV is the most common genital infection in the US, and the lifetime risk of at least one HPV infection in women is 75% [1, 4]. The prevalence of anal HPV infection is very high: about 57% in HIV-negative men who have sex with men (MSM) [5]; and among HIV-positive men the infection rate is about 60 times higher than in the general male population [6]. Several risk factors for HPV infection have been identified: early onset of sexual activity, multiple sexual partners, a history of STDs, an early age of first pregnancy and tobacco use [7].

HPV penetrates skin or mucosa up to the basal membrane in search of keratinocytes (basal

epithelial cells). HPV can infect the skin, the uterine cervix, the lower genital region, the anus or the oropharynx. There are more than 40 HPV types that infect the genitourinary tract and anal region [8]. HPVs used to be divided into two subtypes – the high-risk HPV subtype and the low-risk HPV subtype – based on their ability to incorporate the viruses' DNA into the host cells' genome, thus promoting the infected cell's ability to achieve neoplastic transformation. Low-risk subtypes remain separate from the host DNA and replicate separately. In contrast, the high risk subtypes' involvement with the host cell's DNA can result in the binding and inactivation of tumour suppression genes p53 and Rb, and the uncontrolled multiplication of cells with a likelihood of malignant transformation [9].

The vast majority (90%) of anal warts are caused by two low-risk HPV subtypes: 6 and 11. Occasionally they appear in combination with 16, 18, 31, 33 and 35, as well as up to 35 other HPV subtypes, which were identified in 621 subjects with condyloma [10]. The time between infection and the first clinical manifestation of anal warts is usually between three and eight weeks [9]. Typically, anal warts present as flat or elevated flesh-coloured papules or plaques located in the infected areas. The lesions can be moist and either solitary or multiple. The lesions rarely produce severe symptoms, but occasionally are associated with a sensation of anal discomfort or pruritus. Some HPV infections can remain subclinical with the virus dormant within the epithelial cells for years, and the time lag between infection and clinical symptoms can be quite long. On the other hand, most HPV infections can be resolved within one to two years by the person's immune system, and the rate of infection clearance after a 5-year period is about 90% [11, 12].

A diagnosis of anorectal warts is made clinically by visual inspection including anoscopy. The lesions can be dispersed in the anal canal including Morgagni's papillae at the dentate line and the distal part of the rectal mucosa.

Treatment Modalities for Anal Warts

Many treatment modalities for anal warts are primarily focused on destroying or removing the warts locally rather than eliminating the infection [13]. Thus, the recurrence rate varies from 6% to 15% with sinacatechins ointment [14] to 69% after administering local interferon alpha [15].

There are several factors that influence the choice of treatment modality, such as the location

of the warts (all intra-anal or rectal warts should be managed by a specialist), the number of lesions, the patient's ability to apply prescribed creams or gels, the patient's preference, the cost of the treatment and the patient's immunosuppression status.

Treatment plans can be classified either as patient self-administered modalities (for warts located on the perianal skin only) or treatment administered by a professional (for lesions in an intra-anal or rectal mucosa location).

Patient-Applied Treatments

Patient-applied treatment can be chosen from among a couple of options: podophyllotoxin 0.15% cream (Wartec), Imiquimod 5% cream (Aldara) or sinecatechins 15% ointment (Veregen).

Podophyllotoxin is a purified form of a podophyllin resin alcoholic extract from the *Podophyllum* sp. plant. It inhibits mitotic division and thus induces necrosis of the condyloma within a couple of days. The use of podophyllin resin for condyloma treatment was first published in 1942 by Kaplan [16]. Podophyllotoxin 0.15% cream or gel is patient-administered twice daily for 3 consecutive days, followed by a 4-day gap between application sessions, for a maximum of 4 weeks. Some patients complain about the local side effects: skin irritation, itching or a burning sensation. The success rate of the 0.15% podophyllotoxin formulation is 62.2% [17]. The recurrence rate varies from as low as 38% [18] to 55% [17].

Another treatment option available for patient self-administration, is a new local skin immunomodulator, Imiquimod (1-[2-methylpropyl]-1H-imidazo[4,5-c]quinolin-4-amine) 5% cream. Imiquimod activates antigen-presenting cells (APCs). By triggering cytokine production, it enhances the ability of APCs to present viral or tumor antigens to reactive T lymphocytes and amplifies the type-1 helper T cell-mediated immune responses (interferon gamma production as well as other related cytokines). The cellular receptors for Imiquimod and its analogues are toll-like receptors TLR7 and TLR8. These two receptors are part of a larger family of TLRs that are critical components of a person's natural immunity, which evolves to detect dangerous bacterial, viral, fungal, and parasitic infections [19].

Imiquimod seems to be a potent immunomodulator. Systemic immunomodulation and antitumor enhancement activity has been demonstrated in mice following local skin application [20]. It has also been suggested that as a potent TLR7 ligand, Imiquimod administered locally through the skin can modulate human respiratory tract leukocyte

composition as well as general respiratory cytokine responses against *Klebsiella pneumonia* [21].

Imiquimod is applied three times per week for up to 16 weeks. There are many possible local side effects: skin irritation, a burning sensation, pain or skin ulcers. Some patients experience systemic side effects such as headache, muscle ache or fatigue. Unlike the Imiquimod 5% formula, the 3.5% cream has not been known to cause systemic side effects, but there is a substantial difference in the wart clearance rate of the 5% and 3.5% formulations: 56% vs. 36.6%, respectively [18, 22]. The Imiquimod 5% cream has also shown a low recurrence rate of only 13% [18].

Sin catechins (Polypyphenon *E*) 15% ointment is a purified botanical drug isolated from green tea leaves (*Camellia sinensis*). This is actually the first botanical prescription drug that was approved by the FDA [23]. The exact mechanism by which it eradicates anogenital warts has not been fully elucidated. It has been proposed that sin catechins promote the release of cytokine and inhibit cell growth, which is then thought to inhibit transcription factors AP-1 and NF-kappaB [24]. Sin catechins have been shown to modulate apoptosis at various points in the sequence, including altering the expression of anti- and proapoptotic genes. Their anti-inflammatory effects are activated through a variety of different mechanisms, including the modulation of nitric oxide synthase isoforms [25, 26] and the inhibition of several enzymes and kinases involved in generating multiple inflammatory mediators, like proteases and oxygenases [27].

Sin catechins 15% ointment is applied 3 times per week for up to 4 months. The eradication rate is 54.9%, which is similar to other topically applied treatments, and the recurrence rate is 6.5%. The local side effects are also similar to other topical formulations: redness, irritation or a burning sensation, but are reported by only 1 out of 3 treated patients [28].

In conclusion, the available topical treatment options seem to have similar eradication and recurrence rates. The choice of an appropriate treatment should be based on local market availability and price rather than medical or pharmacological factors.

Modalities for Anal Wart Treatment Administered by a Medical Provider

Currently, the Center for Disease Control and Prevention recommendations for specialist-applied treatment of anal warts are 80–90% trichloroacetic

acid (TCA) application, cryotherapy with liquid nitrogen or surgery/electrosurgery [29].

TCA is a potent, erosive and chemically destructive agent that can burn and cauterize skin lesions. Care must be taken during application to avoid staining healthy skin near the anal warts. It is not recommended for intra-anal use. The acid can deeply erode the skin, but the success rates are satisfactory, ranging from 70 to 81% [30, 31]. The reported recurrence rate is high: 36% [31].

Cryotherapy seems to be the best option among the professionally applied techniques. During the treatment, lesions are frozen using a liquid nitrogen cooling probe, which results in necrosis and further clearance of destroyed tissue. Results and complications vary, and can include the destruction of healthy skin, ulcers or scar formation. Cryotherapy is cost effective, minimally invasive, painless and can be applied to intra-anal warts. The eradication rates are similar to TCA: from 81% to 86%, with a recurrence rate of 39% [30, 31].

Surgical excision is the oldest approach, and nowadays seems to be somewhat outdated. However, for patients suffering from a giant condyloma (Buschke-Loewenstein tumor) it may be the treatment of choice [32, 33]. A more contemporary surgical approach, electrosurgery, is a very effective technique with a clearance rate of 94% [34] but can be painful and requires local or intravenous anesthesia.

The specialist-applied modalities are characterized by an eradication rate that ranges from satisfactory to extremely high. However, the high recurrence rate (25–40%) [34] discourages clinical use. The direct-applied modalities that are targeted to remove warts locally do not destroy all the very small or subclinical lesions in the surrounding healthy-looking skin and this may be the cause of recurrence.

Preventive Treatment

In the absence of an ideal treatment for anal warts, prevention could be the best option. The first HPV vaccine (HPV 6, 11, 16, 18) Gardasil was approved by the FDA in 2006 for prophylactic vaccination of girls and young women 9 to 29 years of age [35]. The vaccine is composed of an HPV L1 protein assembled into non-infectious, recombinant virus like particles (VLPs). Gardasil triggers the formation of host antibodies for four HPV subtypes and can provide protection for up to 5 years [36]. The vaccination provides much better protection than a person's natural immunity after an HPV infection. Seroconversion rates were 97.5% or more in multiple studies, compared to a 54% to

69% rate from natural immunity [37]. This quadrivalent vaccine spectrum covers both the high oncogenic risk HPV subtypes (16 and 18) and the low-risk subtypes (6, 11). HPV 16 and 18 are the main pathophysiologic factors that cause uterine cervix cancer and most anal cancers. Furthermore, it has been proven that more than 70% of cervical cancers are caused by those two HPV subtypes [38], while HPV 6 and 11 are etiologic factors in 72% of anal warts [39].

In 2009, the FDA approved the expansion of the therapeutic indications for Gardasil to include boys and young men between 9 and 26 years of

age. Giuliano et al. have reported that the efficacy of Gardasil is 90.4% against external anogenital warts in a group of 4065 healthy males between 16 and 26 years of age [40].

In conclusion, anti-HPV vaccination programs for populations of young women and young men will substantially reduce the incidence of HPV-related diseases: anogenital warts, low-grade cervical dysplasia, cervical cancer, anal cancer and recurrent respiratory papillomatosis (WHO). Widespread HPV vaccination to reduce the viral burden of HPV is critical and necessary to completely eradicate the virus in the population at large.

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