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Review Article

Review of treatment modalities in the management of genital warts

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Abstract Genital wart is one of the most commonly found human mucosal viral infection caused by the Human Papillomavirus (HPV). Genital warts can present as papules, plaques or blisters that look like a pink, brown cauliflower, or flesh-coloured mass. The treatment modalities for genital warts that are currently available are focused on eliminating the genital warts growth instead of addressing and controlling the underlying HPV infection. A little evidence has been provided regarding the existing treatment modalities in terms of their effectiveness in eliminating genital warts in the long term or that they have a key role in the prevention and development of malignant genital warts. Moreover, the treatment modalities that are currently used are different in terms of price, side effects, dosing regimen, treatment duration, and efficiency for managing genital warts. However, it is important to consider that the treatment modalities are often tailored to each patient depending on the level of HPV spread, areas that have been infected, and other comorbid chronic diseases.

Key words
Genital warts, treatment modalities, human papillomavirus.

Introduction

Genital warts are one of the most commonly found human mucosal viral infection caused by the Human Papillomavirus (HPV). Genital warts can present as papules, plaques or blisters that look like a pink, brown cauliflower, or flesh-coloured mass. They usually affect part of the keratin-containing epithelium, such as the frenulum, crown, and glans. In men, the foreskin, penis, and scrotum are affected whereas in women, the labia, periurethral area, clitoris, perineum, and vulva are affected. However, in most of the cases, the cervix, perineum, perianal canal, anal canal, rectum, urethra, urethra, bladder and oropharynx can also be affected.[1] Genital warts fall in the spectrum of sexually transmitted diseases which make the patient mentally burdened and in the meantime also increase the chances of developing other sexually transmitted diseases. They may be asymptomatic or symptomatic and they can either appear as intermittent lesions or confluent lesions, depending on the HPV species. Genital warts are usually benign, however, in people with compromised immune systems, they may become malignant. Whereas in people with strong immune systems, warts may go away on their own or upon treatment.[2]

There are various modalities of treatment for genital warts. Treatment options for genital warts include topical immunotherapy,

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intralesional systems, surgery, and intra-lesional immunotherapy. All of these treatment modalities have shown promising effects in treating virus-infected genital warts. However, management of genital warts is difficult in terms of the patient's cooperation, acceptance, and consent.[3] It is observed that most of the patients are often treated incompletely as they are either reluctant or over-worried about their sexuality. There are many topical treatment options including trichloroacetic acid podophyllotoxin solution, imiquimod cream and sinecatechins cream. On the other hand, cryosurgery, electrocautery and many other surgical techniques are also available. It has been observed that genital warts can recur after topical treatment and surgery is the only method with a cure rate approaching 100% where the recurring rate is almost negligible. Therefore, the most critical element in the management of genital warts is patients' need to be informed about treatment modalities.[4] The aim of this paper is to review the epidemiology and virology of genital warts so that effective treatment modalities can be identified.

Epidemiology

In the United States, it is estimated that 500,000 to 10,00,000 new cases of genital warts are diagnosed each year. The clinical evidence shows that genital warts develop in approximately 1% of the population that is sexually active by the end of year 2018. The global HPV report of 2017 estimated the economic burden of HPV at $4 billion in US alone whereas the global economic burden of HPV was estimated to be $29 billion.[5] However, this included the direct costs of treating genital warts and metastatic cervical cancer.

Genital warts are usually associated with high-risk sexual behaviour and activities. They are less common in the heterosexual population as compared to the homosexual population.[6] The hospital admission data of genital warts also indicated that genital warts are most commonly found in men sex men (MSM) and women sex women (WSW) population as compared to men sex women (MSW) population, during the same period.[1,7] A cross-sectional survey of approximately 500 MSMs who attended the GUM (genitourinary medicine) Clinic in London was conducted to identify the prevalence of genital warts among MSMs. It was found that nearly one-third of MSMs had been diagnosed with genital warts representing 30.3% of the recruited population. Whereas 1 in 10 MSMs had genital warts in the past years representing 9.8% of the recruited population. However, recurrent episodes of genital warts were also observed in MSMs. The findings also indicated that MSMs require extensive awareness and education regarding the prevalence and risk factors of genital warts and other sexually transmitted diseases.[8] The 2016 Joint Vaccination and Immunization Committee (JCVI) recommended that MSMs and WSWs should undergo sexual health screening and HIV clinics for effective interventions of HPVs and STDs. Following this recommendation, HPV vaccination was treated among MSMs who attended sexual health education sessions, HIV clinics and a vaccination schedule so that the prevalence and incidence rates of genital warts could be reduced.[9]

In the general population, the estimated prevalence of genital warts among MSM was found to be 11% in 2017 which is the same as that of the prevalence of genital warts in WSW. It has been observed among women who have sex with men have a lower prevalence of genital warts because of the reduced engagement in high-risk sexual behaviour.[10] Therefore, it is recommended that prevention programs, promotion messages, awareness and education sessions, and vaccination coverage for the

MSMs and WSW because of the higher prevalence of genital warts among them.[11]

Virology of HPV

About 40 subtypes of HPV can infect sexually reproductive pathways and can generally be divided into the three categories including low-risk, medium-risk, and high-risk HPVs. However, depending on the probability of epithelial dysplasia, types 6 and 11 of HPV rarely cause cervical cancer therefore, these are considered low-risk HPVs. It has been observed that infections of low-risk genotypes of HPV account for approximately 90% of genital warts, while types 16 and 18 of HPV are linked with cervical dysplasia.[12] Therefore, these types are considered the most common cancerous HPVs. Evidence-based research mentioned that HPV infection with these subtypes of HPV is found in 70% of cervical squamous cell carcinoma (SCC) cases. Moreover, other subtypes such as 31, 45, 51, 56, 58, and 59 of HPV are generally considered moderate-risk HPVs. The reason behind this is that it is often associated with squamous cell tumours, but rarely with cervical cancer. Patients with genital warts can be infected with many strains of HPV although the specificity of the virus plays a significant role in diagnosing the progression of warts. Hence, it has little effect on the diagnosis, management, or treatment of genital warts in both men and women.[13]

HPV can be grouped into two non-enveloped deoxyribonucleic acid (DNA) viruses which belong to the family of Papoviridae. The replication of this virus is confined to the basal layer in a cell that is on the surface tissues. The virus infiltrates the skin epithelium as well as mucous membranes in search of a suitable host cell. Then keratinocytes infiltrate the base of the epidermis and infect mucous membrane at any part of the reproductive system, such as the vagina, vulva, cervix, and around the anus in women. And around the shaft, scrotum, urethra and periphery in men. The site of infection is characterized by the spread of the DNA of the virus and the development of warts, papules, or plaques.[14]

The genome of HPV consists of six early-open-read frames that are named E1, E2, E4, E5, E6, and E7 and two slow-open-read frames that are named L1 and L2. The former is important for regulating and coding proteins that are involved in the replication of HPV and transformation at the cellular level. On the other hand, the slow-open-read frames of L1 and L2 encode the capsid protein of the virus.[6,15] Moreover, differences in the genotype of L1 led to small changes in the DNA replication patterns of viruses that are believed to be responsible for the formation of 12 different HPV subtypes that are usually remained isolated from the DNA of the host cell and then replicate. Furthermore, the high-risk subtypes of HPV combine their own DNA directly with the genetic material of the host cell. The combination of the DA of the host cell and the virus often activates the genes of non-E6 and E7. This is because these genes promote the RNA transcription in cancer proteins and inactivate the tumour cells by binding and suppressing genes of p53 and Rb. This results in enhanced cell proliferation as well as an increased risk of progression of genital warts into cancer.[4,9,16]

Treatment Modalities

The treatment modalities for genital warts that are currently available are focused on eliminating genital warts growth instead of addressing and controlling the underlying HPV infection. A little evidence has been provided regarding the existing treatment modalities in terms of their effectiveness in eliminating genital warts in the long term or that they have a

key role in the prevention and development of malignant genital warts. Moreover, the treatment modalities that are currently used are different in terms of cost, side effects, dosing regimen, treatment duration, and efficiency for managing genital warts. It is important to consider that treatment modalities are often tailored to each patient depending on the level of HPV spread, areas that have been infected, and other comorbid chronic diseases.[17]

The most common treatment modality for managing genital warts is the 0.05% solution of podophyllotoxin or 0.15% gel and cream (Class A). It is a pure extract from the genus Podophyllum that binds to the microtubules of cells, inhibiting cell division and causing necrosis of genital warts within 3-5 days of its administration. Superficial erosion occurs when the wound becomes necrotic and heals within three to four days. This regimen is generally considered safe, efficient, and suitable for self-administration.[18] The topical solution, cream, and gel of podophyllotoxin is available which should be used twice a day for more than 3 consecutive days a week and continued for up to 4 weeks. This treatment is generally recommended for genital ulcers while the carrier formulations in cream or gel are considered more suitable for lesions in anal or vaginal areas. However, randomized placebo-controlled trials showed cure rates ranging from 45-77% when Podophyllotoxins were used for treatment. On the other hand, it was also found that the topical use of Podophyllotoxins is associated with a high recurrence rate of 38%. Warts that persist after four courses of treatment should be treated in other ways.[19]

Imiquimod 5% Cream or imidazoquinoline amine Cream 5% (class A) is another topical treatment modality for genital warts which is used as an immune-stimulating drug for patients with genital warts. It is used to treat various skin diseases such as basal cell carcinoma and cutaneous keratin.[20] Furthermore, patients treated with imiquimod showed a reduction in the infection burden as measured by HPV DNA. For the treatment of genital warts, imiquimod should be used three times a week at bedtime for consecutive 16 weeks. Common local side effects include inflammation, itching, burning, redness, irritation, eczema, soreness, and pain. Patients sometimes experience various side effects such as fatigue, body aches, headaches, and general malaise. In a pivotal clinical study, 56% of patients were able to remove warts and the mean time to eliminate genital warts was found to be 8 weeks in women which was shorter than in men which is 12 weeks, while a low recurrence rate of 13% was also observed with the use of this product.[21] Clinical research has confirmed the effectiveness, safety, and efficacy of imiquimod cream at 5% for treating genital warts. The prolonged duration of application of the imiquimod cream and sporadic frequency may impact the patients' response to treatment.[22]

Another topical treatment is done by Imiquimod Cream 3.75% (class A) and the Food and Drug Administration (FDA) has recently approved imiquimod 3.75% to be used as a topical cream for the treatment of genital warts and HPV. Furthermore, the relapse rate was relatively low. It was also found that up to 85% of patients received full treatment as recognized at the 12-week follow-up evaluation, indicating that the patients are willing to use this treatment modality.[23] This product is believed to offer several important benefits in terms of patient compliance as the imiquimod 3.75% regimen is significantly cost-effective, feasible, convenient, and acceptable to be used every day for up to eight weeks.[24] The imiquimod 3.75% cream is believed to have significantly lesser side effects.[25]

Sinecatechins 15% (Class A) is another topical treatment modality that is available in the form of cream, Sinecatechins is a herbal extract that has been approved by the FDA in 2006 due to its effectiveness in the healing effect of genital warts. The active ingredient in Sinecatechins 15% is the green tea extracts which have antioxidant, antibiotic, anticancer, and antiviral properties. It is recommended that sinicatechin 15% cream should be applied to the topical surface of warts for up to four months and three times a day.[26] A randomized controlled trial found Sinecatechins 15% to be more effective for treating genital warts as compared to the controlled group with a clearance rate of up to 58%. The relapse rate was relatively low, that is 6-9% after the 12th follow-up week. The herbal extract of Sinecatechins has been reported with some adverse or harmful reactions by less than 20% of its users. Although the reported side effects are usually mild to moderate including itching redness, pain, and burning at the application site. However, more serious reactions have also been reported by 3% of its users which include lymphadenitis, vaginitis, balanitis and blistering associated with topical use of the product.[27]

Trichloroacetic Acid 80-90% (TCA) Solution (class B) is a harmful chemical that can burn, corrode, and damage skin and mucous membranes. It is usually manufactured as an 80-90% solution due to which it becomes harmful acid with multiple side effects. Therefore, TCA must be used upon recommendation or prescription by a doctor. However, usually, a single dose can successfully treat a wart, but it may be needed several times depending on the growth of genital warts.[28] TCA is recommended because it is an economical and convenient treatment that requires short-term use and adherence. This product is more effective for superficial warts whereas lesser effective for major viral infections. It has a cure rate of approximately 70-80% and a high recurrence rate of 36% in both males and females.[29] However, there are several side effects of TCA therapy such as burning and pain at the site during injections and damage to healthy tissues around genital wart. Burning can be reduced by washing with cold water, soap, and baking soda after excessive use. Skin damage, scars, tissue damage, blisters, and scabs are rare. The success rate of TCA is high due to which TCA therapy is considered an effective treatment modality for genital warts.[30]

Cryotherapy (Class B) is a procedure for freezing abnormal tissues using certain cooling agents including liquid nitrogen or nitrous oxide. The temperature of the cooling agent is kept too low to avoid permanent damage to the skin and blood vessels. The application of the cooling agent is done in multiple sessions that initiate an immune repair process which leads to the removal of damaged cells and necrosis.[31] A cross-sectional study found that cryotherapy works best on small warts and it is a cost-effective treatment modality with a high success rate. The cure rates ranged from 79-88% in the first three sessions. This indicates that the results are more effective than TCA. Cryotherapy has several limitations including variable dosage, maintaining the temperature of the cooling agent, and time of exposure which can affect the effectiveness of treatment modality. The relapse rate of cryotherapy is found to be ranging from 25-40%.[32] Furthermore, some side effects of cryotherapy have also been reported which include damage to tissues, painful blisters, infections, permanent scarring, and loss of skin colour. Comparing cryotherapy with other treatment modalities, cryosurgery does not cure asymptomatic genital warts. Another disadvantage of cryosurgery is that it requires multiple sessions and visits to the dermatologists due to which most of the patients quit this treatment without completing the recommended

sessions.[25]

Electrosurgery (Class B) is based on high-frequency electrical current through electrocoagulation, which is a thermal coagulation process that burns or eliminates warts. Then the burnt skin tissue is scrapped to be removed. This treatment modality is effective in treating small warts found on the penis shaft, vagina, or rectum. However, electrosurgery is usually not recommended for large warts because it can cause permanent scarring. Electrosurgery is a very effective technique as a randomized controlled trial showed a 94% cure rate after 6 weeks of treatment. Electrosurgery is a rather painful process hence, it is usually done by giving localized or general anaesthesia. It has been identified that side effects of electrosurgery are generally mild and are limited to post-surgical pain.[34]

Surgical excision with scissors (class B) is one of the oldest methods of removing genital warts. Surgery has been a basic option for many years. It involves removing the tissues of warts from the genital area with the use of a scalpel or scissors, then the surrounding healthy skin is stitched. A clinical assessment based study found that the elimination rate of surgical excision is relatively high i.e. 72%, which appears instantly and usually lasts for a year.[23] Although this treatment option is considered somewhat out-dated, its effectiveness for very large genital warts is proven and it is still recommended by the doctors. Moreover, surgery is still the best way to remove genital warts that are suspected to have developed into cancer. Surgery to remove large genital warts is a painful procedure that often causes bleeding and scarring in the affected area.[35]

The newest and relatively complex surgical excision procedure used to treat genital warts is the Mohs procedure. But it is a highly specialized technique for removing a thin layer of genital warts analyzed immediately with a microscope.[36] The skin of the surrounding areas of warts is removed in such a way that all warts are removed and only healthy tissues remain intact. The most significant benefit of a surgical procedure is that it can keep the skin as healthy as possible. However, this treatment modality is expensive and complicated process that may result in scarring.[37]

Potassium hydroxide (KOH) is a strong alkaline agent with mild irritant properties. KOH has been shown to be an efficient, well tolerated, cost effective and safe option in the management of genital warts[38] KOH has a keratolytic effect and causes destruction of virus when applied over the affected skin. KOH 5% aqueous solution should be applied over genital warts using a cotton swab tip daily till mild inflammation is observed. Side effects like erythema, edema, pain, or stinging sensation, superficial erosions and post inflammatory hypopigmentation have been reported.[39] Camargo CLA *et al.* conducted a comparative study between KOH and cryotherapy for genital warts which showed that KOH has comparable effective results as cryotherapy while offering a better safety profile.[39]

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