Introduction

Warts are the cutaneous manifestations of human papillomavirus (HPV) infection. They may exist in different forms. Common warts (verruca vulgaris), plantar warts (verruca plantaris), flat or plane warts (verruca plana), and genital warts (condyloma accuminata) are some of the clinical manifestations of HPV infection ***(Bacelieri and Johnson, ٢٠٠٥).***

Plantar warts are hyperkeratotic lesions on the plantar surface. They tend to develop over areas of pressure such as the heel. Plantar warts are often endophytic (ie, they grow into the deeper layers of skin because of pressure). Although they are generally self-limited, plantar warts should be treated to lessen symptoms, decrease duration, and reduce transmission ***(Rinker and Shenefelt , ٢٠٠٥).***

Papillomaviruses are small (٥٥ nm) double-stranded DNA viruses. Papillomaviruses are widely disseminated in the animal kingdom, and more than ٢٠٠ genotypes of human papillomaviruses that infect the skin and mucosal surfaces have been characterized. These viruses are highly species specific. Papillomaviruses have never been grown in vitro but have been characterized by molecular methods ***(Gearhart, ٢٠٠٦).***

Treating warts is a therapeutic challenge for most physicians. No single therapy has been proven effective at achieving complete remission in every patient. As a result, many different approaches exist, including observation and treatments that can be combined for greater effectiveness ***(Sterling et al., ٢٠٠١).***

The most frequently used topical methods include salicylic acid which is safe and effective ***(Gibbs et al., ٢٠٠٢)***. Another line of treatment is cryotherapy. Cure rates for cryotherapy vary widely, depending on the treatment regimen. In general, the wart is frozen for ١٠ to ٣٠ seconds until a ١- to ٢-mm iceball halo surrounds the targeted area ***(Bacelieri and Johnson, ٢٠٠٥).*** The highest cure rates are achieved when treatment occurs at a frequency of every two to three weeks. Optimal cure rates for plantar warts have been demonstrated by paring the hyperkeratotic surface and using two freezes with a complete thaw in between ***(Berth-Jones and Hutchinson, ١٩٩٢).***

Lasers have also been used to treat warts. Complete clearance rate with the CO_2 and pulsed-dye lasers for warts has been reported in ٤٧-٩٠٪ of patients. However, scarring and pain are well known side effects of the CO_2 laser, whereas the pulsed dye laser is less painful ***(Robson et al., ٢٠٠٠).***

The Er:YAG (wavelength ٢,٩٤ um) laser is a solid-state laser containing a YAG crystal doped with erbium gas and excited by a pulsed flash lamp to emit laser pulses by a gas discharge tube ***(Cantatore and Kriegel, ٢٠٠٤).*** It is ten times more selective for water than the CO_2 laser, thereby causing less thermal damage. The associated thermal relaxation time is in the order of microseconds. Thus, there is minimal heat transfer to adjacent tissue during the laser pulse. The Er:YAG laser is therefore a useful instrument in laser surgery, especially when aiming at careful ablative removal of superficial lesions with maximum sparing of adjacent tissue ***(Alster, ١٩٩٩).***

The Er:YAG laser seems to be comparable with the pulsed dye laser, achieving a clearance rate of ٧٢,٥٪ after a single application of the Er:YAG laser for common warts ***(Wollina et al., ٢٠٠١).*** Another interesting feature of the Er:YAG laser is that HPV-DNA is completely destroyed during treatment, which is in contrast with both cryotherapy and CO_2 laser ***(Hughes and Hughes, ١٩٩٨).***

Many studies have been published regarding different therapeutic modalities of warts. Most of these, however, have focused on treatment of common, not plantar warts. Comparative studies, in general are lacking. No studies have compared cryotherapy with Er:YAG laser treatment for plantar warts.

Aim of the Work

The aim of this work is to compare the effect of cryotherapy versus Er:YAG laser on plantar warts as regards the clinical response, number of sessions, recurrence rate, side effects, and feasibility of either technique.

I. Warts

History

Cutaneous warts (verrucae) were known to the ancient Greeks and Romans in the ١st century AD. Until the ٢٠th century, genital warts were believed to be a form of syphilis or gonorrhea. ***Ciuffo in ١٩٠٧*** established the viral nature of warts. In ١٩٤٩, the viral particle was observed using an electron microscope. Since ١٩٧٦, ٨٣ types have been isolated and characterized in a defined manner, but more than ١٣٠ human papillomaviruses (HPV) types have been identified based on polymerase chain reaction (PCR) amplification products. Distinctions between HPV types include the type of epithelium typically infected (cutaneous or genital/mucosal) and the most serious anticipated outcome (benign proliferation or malignancy) ***(Nebesio et al., ٢٠٠١).***

The Virus

Papillomaviruses (from the Latin *papilla*, 'nipple or pustule' and the Greek suffix-*oma*, which is 'tumour') are members of the Papovaviridae family ***(Zheng and Baker, ٢٠٠٦).*** HPV is a double-stranded (ds) DNA virus that causes cutaneous viral warts, most commonly located on the skin and genitalia ***(Rivera and Tyring, ٢٠٠٤).*** The HPV virion is ٥٥nm in diameter. The HPV capsid lacks an envelope, making HPV very stable, infectious for years, and resistant to many therapeutic agents. The HPV ds-DNA genome is composed of ٨٠٠٠ nucleotide base pairs, which encode eight gene proteins: E ("early", six genes,) and L ("late", two genes, L١, L٢). The E genes interfere with cell cycle regulation, which is related to tumor formation/malignant phenotypes, genome replication/ expression, and release of the virus. The L genes encode the proteins forming the capsid. HPVs are epitheliotrophic and

host-specific, each infecting only its natural host. HPVs do not infect laboratory animals and do not propagate in tissue culture ***(Brown et al., ١٩٩٩).***

The viral replication cycle appears to be linked to epithelial differentiation and also to keratinocyte maturation. HPV lesions are thought to arise from the proliferation of infected basal keratinocytes. Infection typically occurs when basal cells in the host are exposed to infectious virus through a disturbed epithelial barrier as would occur during sexual intercourse or after minor skin abrasions ***(Sanclemente and Gill, ٢٠٠٢).*** Following infection of the basal layer of epithelium, viral genomes are contained in the nucleus as episomes, at approximately ٥٠ to ١٠٠ copies per cell, and replicate with cellular DNA replication.The infected daughter cells migrate from the basal layer to suprabasal layer and begin differentiation, remain active in the cell cycle and enter into S-phase, while uninfected cells exit the cell cycle as they detach the basement membrane. So, viral genomes are amplified to thousands of copies per cell, late genes are expressed and production of mature virions is induced ***(Fehrmann et al., ٢٠٠٣).***

Human papillomaviruses (HPV) infections have not been shown to be cytolytic, rather viral particles are released as a result of degeneration of desquamating cells. The HPV can survive for many months and at low temperatures without a host; therefore, an individual with plantar warts can spread the virus by walking barefoot ***(Sanclemente and Gill, ٢٠٠٢).***

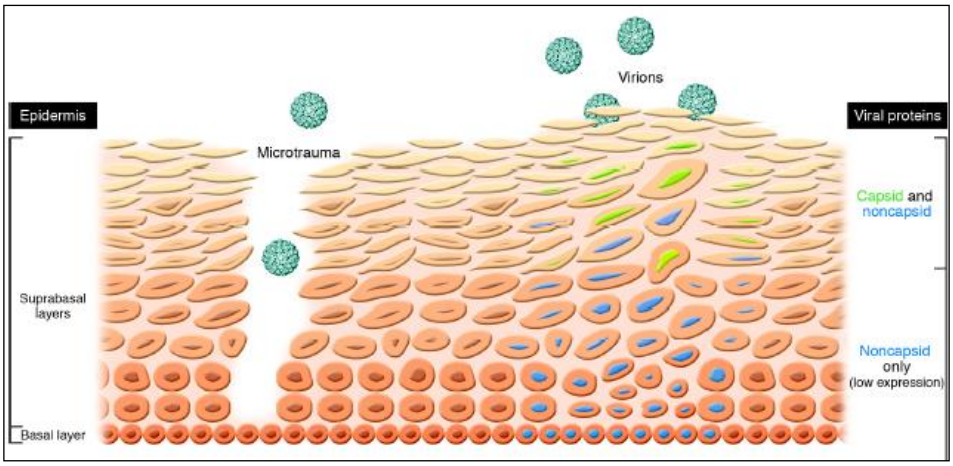

Fig. (١): Papillomavirus life cycle. To establish infection, the virus must infect basal epithelial cells that are long lived or have stem cell–like properties. Microtrauma to the suprabasal epidermal cells probably enables the virus to infect the cell within the basal layer. The viral genome maintains itself as an episome in basal cells, where the viral genes are poorly expressed. Viral replication takes place in suprabasal layers and is tied to the epidermal differentiation process. The presence of the virus causes morphological abnormalities in the epithelium, including papillomatosis, parakeratosis, and koilocytosis. Progeny virus is released in desquamated cells ***(Lowy and Schiller, ٢٠٠٦).***

Histopathology

Warts are usually diagnosed by their clinical appearance. Histologically, a wart demonstrates acanthotic epidermis with papillomatosis, hyperkeratosis and parakeratosis with elongated rete ridges often curving towards the center of the wart. Dermal capillary vessels are prominent and may be thrombosed, and mononuclear cells may be present. HPV-associated papillomae are characterized by large keratinocytes with an eccentric, pyknotic nucleus surrounded by a perinuclear halo (koilocytes). HPV infected cells may have small eosinophilic granules and diffuse clumps of basophilic keratohyaline granules and are not

HPV particles. Flat warts have less acanthosis and hyperkeratosis and do not contain parakeratosis or papillomatosis, but they do have abundant koilocytes. Anogenital warts may express slight to extensive acanthosis and parakeratosis since they are within or adjacent to a mucosal surface and do not have a granular layer. Koilocytes are often observed in anogenital warts, and the rete ridges often form thick bands extending extensively into the underlying, highly vascular dermis ***(Kirnbauer et al., ٢٠٠٣).***

Classification

Human papillomaviruses (HPVs) produce epithelial tumors of the skin and mucous membranes. More than ١٠٠ HPV types have been detected, and the genomes of more than ٨٠ have been completely sequenced. The current classification system, which is based on similarities in their genomic sequences, generally correlates with the ٣ categories used to describe HPV clinically: nongenital cutaneous warts, nongenital mucosal warts and anogenital warts (Table ١) ***(Gearhart, ٢٠٠٦).***

Table (١): Diseases and Associated HPV Subtypes.

Diseases and Associated HPV Subtypes	HPV Type
Nongenital Cutaneous Disease	
Common warts (verrucae vulgaris)	١, ٢, ٤, ٢٦, ٢٧, ٢٩, ٤١, ٥٧, ٦٥
Plantar warts (myrmecias)	١, ٢, ٤, ٦٣
Flat warts (verrucae plana)	٣, ١٠, ٢٧, ٢٨, ٣٨, ٤١, ٤٩
Butcher's warts	١, ٢, ٣, ٤, ٧, ١٠, ٢٨
Mosaic warts	٢, ٢٧, ٥٧
Ungual squamous cell carcinoma	١٦
Epidermodysplasia verruciformis	٥, ٨, ٩, ١٠, ١٤, ١٧, ٢٠, ٢١, ٢٢, ٢٣, ٢٤, ٢٥, ٣٧, ٣٨
Nongenital Mucosal Disease	
Respiratory papillomatosis	٦, ١١
Squamous cell carcinoma of the lung	٦, ١١, ١٦, ١٨
Laryngeal papilloma	٦, ١١, ٣٠
Laryngeal carcinoma	١٦, ١٨
Maxillary sinus papilloma	٥٧
Squamous cell carcinoma of the sinuses	١٦, ١٨
Conjunctival carcinoma	١٦
Oral focal epithelial hyperplasia (Heck's disease)	١٣, ٣٢
Oral carcinoma, Oral leukoplakia	١٦, ١٨
Anogenital Disease	
Condyloma accuminatum	٦, ١١, ٣٠, ٤٢, ٤٣, ٤٤, ٤٥, ٥١, ٥٢
Bowenoid papulosis	١٦, ١٨, ٣٤, ٣٩, ٤٢, ٤٥
Bowen's disease	١٦, ١٨, ٣١, ٣٤
Buschke-Löwenstein tumors	٦, ١١
Intraepithelial neoplasia	٣٠, ٣٤, ٣٩, ٤٠, ٥٣, ٥٧, ٥٩, ٦١, ٦٢, ٦٤, ٦٦, ٦٧, ٦٨, ٦٩
Carcinoma of vulva	٦, ١١, ١٦, ١٨
Carcinoma of vagina & cervix	١٦, ١٨, ٣١
Carcinoma of penis	١٦, ١٨

(Gearhart, ٢٠٠٦).

Transmission of Human Papillomavirus

The incubation period of human papilloma virus can reach up to ٥ years without causing visible lesion ***(Honor, ٢٠٠٤).*** As mentioned before, the virus requires infection of the basal layer of epithelium for successful infection, either in cutaneous or mucosal skin ***(Egawa, ٢٠٠٣).*** Infection is transmitted directly or indirectly as follows:

١. In non-genital infections, abrasions and trauma are the most common way of infection. Other causes predispose to warts are swimming pools, shower rooms, nail bitting, occupational trauma, hyperhidrosis, athletic injuries, unsuitable footwear and trauma of shaving. Contaminated fomites like clothes, medical instruments and gloves also transmit infection ***(Roden et al., ١٩٩٧).*** Children may acquire the infection also by contact with members of the family who have hand warts or by autoinoculation from their own hand warts ***(Sonnex et al., ١٩٩٩).***

٢. In genital infections, sexual intercourse is the most common way of infection ***(Honor, ٢٠٠٤).*** Contaminated fomites, medical instruments as laser plumes used in wart treatment, contaminated underwears account for infection, even after cleaning in ethanol ***(Roden et al., ١٩٩٧).*** Patients with genital warts can transmit infection to their sex partners by finger genital contact ***(Sonnex et al., ١٩٩٩).***

Sexual abuse must never be eliminated when considering possible modes of transmission of HPV to children. Caretakers can also transmit the infection to children through their hand warts. Changing baby diapers or helping a child in bathing or

toileting, may transmit the infection to child's genitals ***(Honor, ٢٠٠٤).***

Vertical transmission of human papilloma virus from infected mother to her infant can occur, either through blood stream prior to birth, or during passing birth canal, so caesarean section reduces but doesnot eleminate the possibility of infection ***(Honor, ٢٠٠٤).***

Clinical Presentation of HPV Infection

١. Cutaneous forms:

- *Common warts:*

They are hyperkeratotic, exophytic and dome-shaped papules or nodules associated with HPV-١, ٢ or ٤. They are most commonly located on fingers, the dorsal surfaces of hands and other sites prone to trauma such as knees or elbows, but may occur at any anatomical location. Autoinoculation by scratching may cause a linear arrangement of warts. Involvement of the nail fold (eponychium) and ablative therapy may destroy the matrix resulting in onychodystrophy ***(Kirnbauer et al., ٢٠٠٣).***

Characteristic features are punctuate black dots representing thrombosed capillaries and capillary bleeding that follows shaving of the hyperkeratotic surface ***(Kirnbauer et al., ٢٠٠٣).***

- *Palmar and plantar warts*:

Appear as thick, endophytic papules on the palms, soles and lateral aspects of the hands and feet, with gently sloping

sides and a central depression, resembling an anthill (hence the term ***myrmecia,*** meaning anthill). On the sole, these are painful to pressure when walking due to deep inward growth. Plantar warts that coalesce into large plaques are referred to as *mosaic warts* ***(Egawa, ١٩٩٤).***

The majority of palmoplantar warts are caused by the closely related HPV types ٢, ٢٧ and ٥٧, and they occur most commonly in patients ٦-١٠ years of age. Although a higher incidence of HPV-٢ related warts was reported in atopic children, other investigators have failed to find such an association ***(Kirnbauer et al., ٢٠٠٣).***

● *Butcher's warts*:

These earn their name from their occurrence in meat processing professionals. They appear as extensive verrucous papules or cauliflower-like lesions on the dorsal, palmar or periungual aspects of the hands and fingers and are associated with HPV-٧. They are not caused by animal papillomavirus types ***(Keefe et al., ١٩٩٤).***

● *Flat warts*: or *verrucae planae:*

Flat warts (verrucae planae) are smooth, flat-topped variants of common warts that are ٢ to ٤ mm in diameter. They most often occur on the face and extremities of children and on the lower legs of women, where they may be spread by shaving ***(Stulberg and* Hutchinson, ٢٠٠٣).** They are usually caused by HPV types ٣ or ١٠ and less often by ٢٨ and ٢٩ ***(Kirnbauer et al., ٢٠٠٣)***.

● *Epidermodysplasia verruciformis (EDV):*

Epidermodysplasia verruciformis (EDV) is an inherited disorder in which there is a mild defect of cell-mediated immunity and widespread and persistant infection with HPV. The lesions vary considerably and may be flat, wart-like lesions, often pigmented, red or atrophic macules or branny pityriasis versicolor-like plaques. The flat, wart-like lesions are frequently localized to the extremities and the face and thicker plaques may resemble seborrhoeic keratoses. EDV-specific HPV types have been described, as HPVs ٥,٨,٩,١٢,١٤,١٥, ١٧,١٩,٢٥,٣٦ and ٣٨, but mainly types ٥ and ٨ are detected in EDV-associated skin cancers. There is a risk of development of squamous cell carcinoma on sun-exposed skin ***(Sterling et al., ٢٠٠١).***

٢. Mucosal forms:

More than ٢٥ HPV types infect the mucosa of the anogenital, the upper respiratory and the digestive tracts. Subclinical infections are much more common than visible warts. Application of ٥٪ acetic acid (aceto-whitening) may aid in the identification of subclinical lesions as white areas ***(Kirnbauer et al., ٢٠٠٣).***

• *Condylomata acuminatum:*

Condylomata acuminatum classically are soft, fleshy, and vascular. They usually appear on moist surfaces, such as the vaginal introitus, preputial sac, or perianal area. These lesions typically have a distinct clinical appearance marked by a raised, granular surface, often with multiple small fingerlike projections. With magnification, a central venule can be seen within each projection. Multiple and coalescing lesions are common ***(Oriel, ١٩٩٠)***.

Several kinds of anogenital warts have been described. (١) Classical "pointed" warts (condylomata acuminata) are cauliflower-like lesions that are most commonly found on moist surfaces. (٢) Keratotic genital warts have a thickened, horny surface; they resemble common skin warts and are most often found on dry surfaces. (٣) The third type is the smooth papular wart, an exophytic lesion without the cauliflower appearance of condylomata acuminata; these are usually found in relatively dry locations, such as the shaft of the penis. (٤) Flat condylomata are subclinical lesions that are difficult to detect without the benefit of special techniques, such as treatment of the epithelial surface with ٣–٥٪ acetic acid solution ***(Handsfield, ١٩٩٧).***

• *Bowenoid papulosis:*

Bowenoid papulosis is a neoplasia that occurs predominantly in young, sexually active adults. Men and women present with multiple, verrucous, brown red papules (average, ٧mm in diameter) in the anogenital region, histologically resembling squamous cell carcinoma in situ. The lesions may become confluent and coalesce. Commonly, Bowenoid papulosis can be mistaken for lichen planus, psoriasis, seborrheic keratoses, or condylomata acuminata. HPV ١٦ has been detected in the majority of cases. In men, lesions appear on the glans or shaft with a benign clinical course, often regressing spontaneously despite marked histologic atypia. In women, lesions are found around the labia minora and majora, inguinal folds, and perianal areas. Because women are at risk of developing cervical dysplasia and neoplasia, the preferred treatment consists of superficial excision of the lesions. Recurrence rates of ٢٠٪ have been reported ***(Nebesio et al., ٢٠٠١).***

• *Oral warts:*

Appear as small, soft, pink or white, slightly elevated papules and plaques on the buccal, gingival or labial mucosa, the tongue or hard palate. *Oral condylomata* are associated with HPV types ٦ and ١١ and may result from digital or oral-genital sexual transmissions. In HIV-positive patients, oral papillomas are frequently detected and may contain unusual types such as HPV-٧, -٧١, -٧٢ and –٧٣**.** In *focal epithelial hyperplasia* or Heck's disease, multiple circumscribed papules are found on the gingival, buccal or labial mucosa resembling flat warts or condylomata. This disorder is rare in Caucasians but relatively common in children who are South American Indians, Greenlander Eskimos or are from South African communities and is associated exclusively with HPV-١٣ or –٣٢ ***(Kirnbauer et al., ٢٠٠٣).***

- *Oral florid papillomatosis: (Ackerman tumor).*

These are multiple, confluent warty or verrucous lesions associated with HPV types ٦ or ١١ which are found in the oral cavity or the nasal sinuses. The development of these lesions is believed to be promoted by smoking, irradiation and chronic inflammation. Patients with oral papillomas need frequent examinations and repeated biopsies for early diagnosis of progression to a well-differentiated verrucous carcinoma ***(Kirnbauer et al., ٢٠٠٣).***

- *Buschke-Löwenstein tumor:*

Buschke-Löwenstein is a rare tumor of the anorectum and the external genitalia associated with the low-risk HPV types ٦ or ١١ that usually cause condylomata acuminata, but the basis for the difference in biological behavior between these two entities has not been established. In rare cases, pre-existing anogenital condylomata may progress into large exophytic cauliflower-like tumor masses that infiltrate deeply into