A COMPARATIVE STUDY BETWEEN THE EFFECT OF BLEOMYCIN AND CRYOTHERAPY IN THE TREATMENT OF PLANTAR WART

Thesis

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INTRODUCTION

Cutaneous warts are caused by infection of the epidermis with human papilloma virus (HPV). HPVs are divided into separate genotypes depending on the bases of their DNA sequence. Different HPV types may infect either cornified stratified squamous epithelium of skin or uncornified mucous membranes. The appearance of the lesion is influenced not only by viral type but also by environmental and host factors ***(Sterling et al., 2001).***

Plantar warts represent about 30% of the cutaneous warts, they appear as thick, endophytic papules on the sole and lateral aspect of the feet, with gently sloping sides and a central depression. These on the sole are painful to pressure when walking due to deep inward growth ***(Egawa, 2003).***

Multiple modalities are available for the treatment of plantar warts. Authors advise to start with the least painful, expensive and time consuming methods and reserve the more expensive and invasive procedures for refractory extensive warts. Treatment methods include destructive therapy, virucidal therapy, antimitotic therapy and immunotherapy ***(Sterling et al., 2001).***

Bleomycin is a fermentation metabolite of the soil fungus, ***Streptomyces Verticillus***, which was initially discovered in 1962 by *Umezawa*. Intralesional bleomycin has been used for the treatment of warts since 1970. Bleomycin is known to cause single-and double-stranded breaks in DNA, leading to inhibition of DNA synthesis ***(Yamamoto, 2006).***

Bleomycin has antibacterial, antiviral and cytotoxic activity. So, it is used as adjuvant chemotherapy for the treatment of squamous cell carcinomas, lymphomas and malignant pleural effusion.Bleomycin is also used in plantar wart treatment especially those which fail to respond to other modalities of treatment with cure rates ranging from 14% to 99% ***(Abott, 1978).***

Cryotherapy is one of the traditional methods for treatment of warts. Cryotherapy aims to destruction of diseased tissue by application of cold which is an effective and efficient method for treating various skin diseases. Cryotherapy, also known as cryosurgery, is the second most common procedure after skin exision, the mechanism of distruction is necrosis which results from freezing and thawing of cells ***(Zoubouls, 1998).***

It is widely used for the treatment of squamous cell carcinoma, Kaposi sarcoma, cherry angiomas, capillary heamangioma, skin tags, seborrheic keratosis, melasma and

lentigo ***(Gearhart, 2006).*** It is considered one of the most well-established methods of plantar wart treatment. The techniques can vary in application mode, freeze time and interval between treatments. Liquid nitrogen cryotherapy can be performed with a spray gun or cotton-wool pud ***(Bacelieri and Johnson,2005).***

AIM OF THE WORK

Our aim of the work is to compare and assess the therapeutic effects of intralesional bleomycin and cryotherapy as two different methods for plantar wart treatment.

PLANTAR WARTS

Plantar warts are extremely common and very painful. Although they don't cause serious health problems, the pain and cost associated with the treatment of warts can be substantial. Warts are caused by human papilloma virus which is a double-stranded DNA virus with 8,000 base pairs. More than 100 types of human papilloma virus have been identified. Plantar warts are caused by human papilloma virus subtypes 1,2,4 and 63,with types 2 and 4 composing most of the mosaic type plantar warts and type 1 human papilloma virus has been shown to have the highest viral particle density, an important factor in the transmission of plantar warts **(*Sallk and Douglas,2006*).**

Incidence and Prevalence

Plantar warts are estimated to occur in up to 10% in children and adolescents and up to 4.5% in adults aged 25-34 years, the range of greatest incidence is between 12 and 16 years of age. Plantar warts occur with greater frequency in girls than in boys. The peak incidence is at 13 years of age in females and 14.5 years of age in males **(*Plasencia, 2000*).**

Human Papilloma Virus (HPV)

HPV is a double-stranded DNA virus. The virus is 55 nm in diameter and its capsule lacks an envelope, making the virus very stable, infectious for years and resistant to

many therapeutic agents. The HPV ds-DNA genome is composed of 8000 nucleotide base pairs which encode eight gene proteins. E gene ("early", six genes) and L gene ("late" two genes).The E gene interferes with the cell cycle regulation, which is related to tumor formation,genome replication and release of the virus, the L gene interferes with the proteins forming the capsule ***(Brown et al.,1999).***

Pathogenesis of Human Papilloma Virus Infection

The viral replication cycle appears to be linked to epithelial differentiation and keratinocytes maturation. HPV lesions are thought to arise from the proliferation of infected keratinocytes. Infection typically occurs when the basal cells in the host are exposed to infectious virus through a disturbed epithelial barrier after minor skin abrasions or trauma. Following infection, viral genomes are contained in the nucleus as episomes, at approximately 50 to 100 copies per cell, and replicate with cellular DNA replication. The infected daughter cells migrate from the basal cell 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., 2003)*** **(Figure 1).**

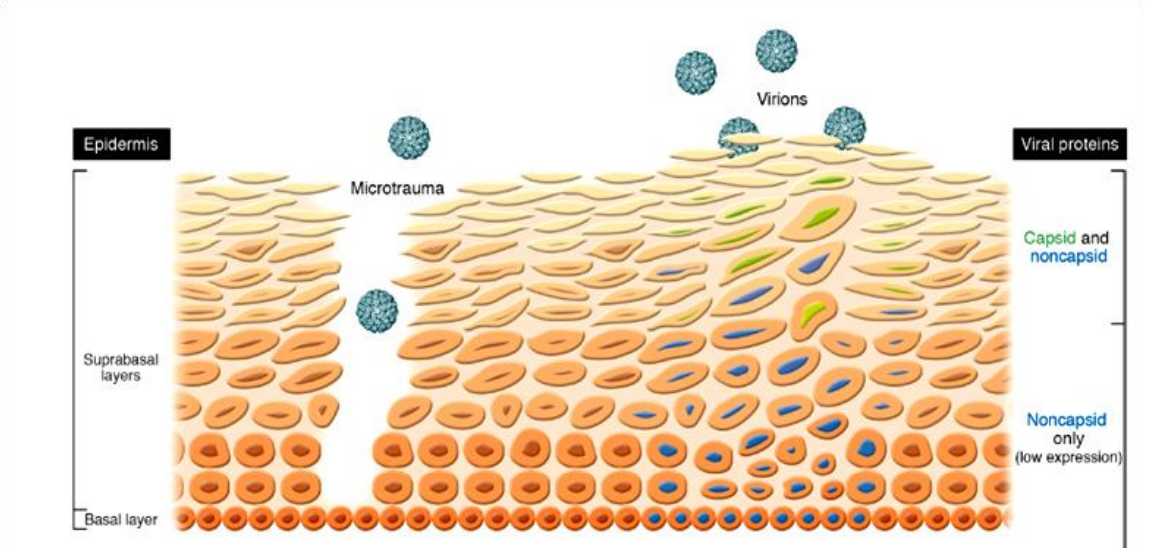

Fig (1): Human papilloma virus life cycle. To establish infection, the virus must infect basal epithelial cells that are long lived or have stem cell like properties. Microtrauma to the suprabasal epidermal cells probably enables the virus to infect the cell within the basal layer. The viral genome maintains 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, 2006).***

The HPV can survive for many months at low temperature without a host, therefore, an Individual with plantar warts can spread the virus by walking barefooted ***(Sanclemente and Gill, 2002).***

Clinical Presentation of HPV infection

Human papilloma viruses (HPVs) produce epithelial tumors of the skin and mucous membranes. More than 100 HPV types have been detected, and the genomes of more than 80 have been completely sequenced. There are three categories used to describe HPV clinically as non genital

cutaneous warts, non genital mucosal warts and anogenital warts **(Table 1)*(Gearhart,2006*).**

Table (1): Diseases and associated HPV subtypes ***(Gearhart, 2006).***

Diseases	HPV Subtypes
Non genital Cutaneous Disease	
Common warts	1,2,4,26,27,29,41,57,65
Plantar warts	1. 2, 4, 63
Flat warts	3, 10,27,28,38,41,49
Butcher's warts	1,2.3,4,7,10,28
Mosaic warts	2, 27,57
Ungual squamous cell carcinoma	16
Epidermodysplasia verruciformis	5,8,9,10,14,17,20,21, 22, 23
Non genital Mucosal Disease	
Respiratory papillomatosis	6,11
Squamous cell carcinoma of lung	6,11,16,18
Laryngeal papilloma	6,11,30
Laryngeal carcinoma	16
Maxillary sinus papilloma	57
Squamous cell carcinoma of the sinuses	16, I8
Conjuctival carcinoma	16
Oral focal epithelial hyperplasia (Heck's disease)	13,32
Oral carcinoma, Oral leukoplakia	16,18
Anogenital Disease	
Condyloma acuminatum	6, 11,30.42,43,44,45,51,52
Bowenoid papulosis	16, 18,34,39,42,45
Buschke-Lowenstein tumors	6, 11
Intraepithelial neoplasia	30, 34,39, 40,53,57,59, 61, 62
Carcinoma of vulva	64,66,37,68,69
Carcinoma of vagina and cervix	6,11,16,18
Carcinoma of penis	16,18,31

Transmission of Plantar wart Infection

Human papilloma virus is transmitted between the hosts through direct contact. For infection and replication to occur, the virus requires a compromised skin surface. The virus attacks the granular and keratin layers of the epidermis, and viral DNA and protein production occur in the upper spinous layer, with final virus assembly occurring in the granular layer. The viral genome does not become integrated with the host cell DNA, instead it remains free in the nucleus of the cell ***(Salk and Douglas, 2006).*** The incubation period of HPV infection can reach up to five years without causing any visible lesions ***(Honor, 2004).***

Symptoms and Signs of Plantar wart Infection

Plantar warts (myrmecia) are usually painful when occur on the bottom of the foot. Patients often feel a 'lump' on the bottom of the foot on standing similar to having a stone in the shoe which enables the patient to walk. In severe cases they cause change in the gait or posture that leads to leg or back pain ***(Brodell and Johnson, 2003).***

On examination, plantar warts are rough, thick, brown or yellow with dark pinpoint centre which represent the tiny thrombosed capillaries that supply blood to the wart. Scraping the wart may cause it to bleed. A plantar wart is similar in its structure to an ice-berg, the part on the surface of the skin is a small part of the entire anomaly, and often

the portion of the wart under the skin is at least twice as big as the part seen on the skin. If plantar warts are left untreated, they can grow up to two inches in circumference and may spread into clusters to form mosaic warts ***(Plasencia, 2000).***

Diagnosis of Planar wart Infection

Diagnosis of plantar warts is based on clinical examination, but can be confirmed by the histopathological appearance of acanthotic epidermis with hyperkeratosis, papillomatosis, parakeratosis with elongated rete ridges often curving towards the centre of the wart. The dermal capillary vessels may be prominent and thrombosed. There may be large keratinocytes with eccentric pyknotic nuclei surrounded by perinuclear halo (koilocytes) which are characteristic of HPV-associated papillomas. HPV-infected cells may have small eosinophilic granules and diffuse clumps of basophilic keratohyaline granules that are not HPV particles ***(Kirnbauer et al., 2003).***

Differential Diagnosis

Plantar warts are simple papillomas that must be differentiated from a callus or a neurovascular corn. The callus and neurovascular corn are hyperkeratotic, waxy, yellowish, ill defined thickening, commonly found over points of constant friction or pressure. They are elevated above the skin surface, with tenderness elicited in the bony prominences under it rather than in the lesion itself. They

have no blood vessels within them and when pared no bleeding occurs, in contrast plantar warts have blood vessels which bleeds when pared. Plantar warts tend to be painful on application of pressure from either side of the lesion rather than direct pressure, unlike calluses which tend to be painful on direct pressure instead ***(Brodell and Johnson, 2003).***

Prevention of Plantar wart Infection

Because plantar warts can spread by contact with moist surfaces, they can by prevented by avoiding walking barefooted in public areas such as showers or communal changing rooms, not sharing shoes and socks, changing shoes and socks daily, keeping the feet clean and dry, checking the feet periodically, observing any growth on, or any changes in the skin, avoiding direct contact with warts on other parts on the body or on other people and regular visiting to a dermatologist as a part of health check-up ***(Micali et al.,2004).***

Treatment of Plantar wart Infection

Treating plantar warts is a challenge. There is no single treatment that is 100% effective and different types of treatment modalities may be combined. The choice of therapy depends on the morphology and extent of the plantar warts and should be guided by the preference of the patient, available resources and the experience of the health care provider ***(Charles and Lacey, 2005).***

The ideal aims of treatment are

- To remove the wart with no recurrence.
- To produce no scars.
- To induce life-long immunity.

Certain general principles in the treatment should be observed

- An immune response is usually essential for clearance as immuno-compromised patients may never show wart clearance.
- The highest clearance rates for various treatments are usually in younger individuals who have a short duration for infection.

***(Sterling et al., 2001*)**

Factors affecting Plantar wart Treatment

They are either factors related to the patients, or factors related to the treatment.

Factors related to the patients

- Age: cure rates are probably higher in young patients.
- Number of lesions: single lesion shows high cure rates in response to treatment than do multiple lesions.
- Duration of the lesion: long-standing warts tend to more resistant to treatment than short duration warts.
- History of previous treatment: warts with previous history of treatment tend to be more resistant to

treatment than warts with no history of previous treatment.

Factors related to the treatment

- Topical treatments: different concentrations, formulations and different methods of applications.
- Intralesional treatments: different concentration, methods of delivery and intervals between number of injections.
- Cryotherapy: different delivery systems, methods and regimens.

(Brodell and Johnson, 2003)

Different types of warts and those at different sites may need different treatments. Multiple modalities are available for plantar wart treatment. Treatment methods include destructive therapy, virucidal therapy, antimitotic therapy and immunotherapy **(Table 2)** ***(Sterling et al.,2001)*****.**

Table (2): Summary of different methods for plantar wart treatment ***(Sterling et al., 2001).***

Treatment	Suggested method to use
Salicylic acid (SA)	Daily application of 25-60% SA in a suitable base for 3 months.
Cryotherapy with liquid nitrogen	15-20 seconds, single or double-freeze thaw cycle every 2-3 weeks for 3-4 sessions.
Bleomycin (Blenoxane)	0.3–0.5 ml bleomycin sulfate injected intralesionally every 2-3 weeks, for one to three injections.
Retinoids	Topical: 0.05% tretinion cream daily for 3 months. Systemic: 1mg/kg/day acitretin for 3 months.
Formaldhyde	Daily application of 0.7% gel or 3% solution as a short soak for mosaic plantar wart.
Gluteraldehyde	Daily application of 10% in suitable base.
Thermocautery	Single surgical removal of the wart, high risk of scarring and recurrence.
Chemical cautery using silver nitrate sticks	Twice weekly application until clearance occurs.
Lasers	▪ Pulsed dye laser is the most commonly used, 4-6 treatments repeated once a month until wart clearance occurs. ▪ Co_2 laser with single treatment. ▪ Er:YAG laser with average of three to four treatments. ▪ Nd:YAG laser with average of three to four treatments.
Photodynamic therapy (PDT)	20% of aminolaevulinic acid (ALA) $\pm$ irradiation for maximum of 3 treatments, one treatment every month.
Topical sensitization	Diphencyprone applied weekly for 8 weeks. Cimetidine orally in a dose of 20-40 mg/kg/ day for 3 months.
Imiquimod (Aldara)	5% imiquimod cream daily application for 4 months.
Mumps or candida antigen	After positive skin test, 0.1 ml of mumps or candida antigen injected intralesionally every 3-4 weeks for a maximum of 3 injections.
Tuberculin antigen	After positive skin test, 0.2 ml of PPD injected intralesionally every 4 weeks for a maximum of 3 injections.