INTRODUCTION

Verrucae are benign proliferations seen in skin and mucosae due to infection with papillomaviruses ***(Sterling, 2014).***

There are about 130 known types of HPV. HPV infects the squamous epithelium, usually of the skin or genitals, but each HPV type is typically only able to infect a few specific areas on the body. Many HPV types can produce a benign growth, often called a "wart" or "papilloma", in the area they infect ***(Ting & Manos, 1990).***

Warts are typically small, rough, and hard growths that are similar in color to the rest of the skin. They typically do not result in symptoms except when present on the bottom of the feet where they may be painful. While they usually present on the hands and feet they can also affect other locations. One or many warts may appear. They are not cancerous ***(Rollins, 2017).***

There are different treatment strategies for warts, they can be treated by destructive modalities namely cryotherapy, electrocoagulation, topical salicylic acid, topical 5-fluorouracil, laser surgery etc. All of these treatments are essentially painful, time consuming, expensive, recurrence is common and none of them give complete clearance ***(El-Mohamady et al., 2014).*** Therefore, immunotherapy seems to be a promising modality in such cases. The role of immunity is documented by the appearance and persistence of warts in immunosuppressed individuals ***(Atherton et al., 2017).***

Immunotherapy agents that have been tried include cimetidine, imiquimod, interferons, Candida albicans antigens, measles, mumps, rubella (MMR) vaccine, tuberculin (purified protein derivative) ***(Meena, 2013).***

Zinc, elemental or in its various forms (salts), has been used as a therapeutic modality for centuries. It was used for a number of dermatological conditions including infections (warts, leishmaniasis) ***(Gupta, 2014).***

Zinc sulfate has an immunomodulatory function and plays a role in enhancing cellular and humoral immunity ***(Gupta, 2014).***

Zinc sulfate has been used successfully in the treatment of common warts and genital warts orally and topically in plane warts ***(Sharquie et al., 2007).*** A few studies have utilized intralesional injection of 2% zinc sulfate solution for the treatment of common wart ***(Mohamed et al., 2016).***

The mechanism of action of zinc sulfate in viral warts cannot be speculated but is probably similar to the action of zinc sulfate in cutaneous leishmaniasis and bleomycin in viral warts, as both induce necrosis and inflammation. When zinc sulfate is injected intradermally, it causes a marked infiltration of inflammatory cells (first a wave of eosinophils then lymphocytes, and finally fibroblasts) towards the injection site ***(Najim et al., 2006).***

Topical vitamin D has been used successfully for wart treatment in some cases. The effect of vitamin D derivatives on warts is speculated to be derived from its potential to regulate epidermal cell proliferation and differentiation and to modulate cytokine production ***(AlGhamdi, 2013).***

Aktaş (2016), clearly demonstrates that recalcitrant plantar warts can be treated successfully with intralesional vitamin D3 injection. This treatment caused minimal side effects, and there was no evidence of wart recurrence during the follow up period.

AIM OF THE WORK

The aim of this work is to evaluate and compare the clinical efficacy of intralesional 2% zinc sulfate solution vs intralesional vitamin D in the treatment of planter warts as well as reporting the side effects.

Chapter 1

WARTS

Definition:

Warts (verrucas) are an extremely common, benign, and usually self-limited skin disease. Their size ranges from a few millimetres to several centimetres. The normal skin lines are interrupted by skin coloured to brownish-grey tumours, the diagnosis is established clinically; no supplementary histologic or virologic investigations are needed ***(Bacaj and Burch, 2018).***

Incidence and Prevalence:

Prevalence probably varies widely between different age groups, populations, and periods of time ***(Lacarrubba et al., 2018).***

They are very common in children although limited epidemiologic data exist ***(Lacarrubba et al., 2018).***

The prevalence of warts in the general population is reported to range from 1- 24% ***(Chen et al., 2008).***

Etiology/ Risk Factors:

Warts are caused by HPV. They are most common at sites of trauma, such as the hands and feet, and probably result from inoculation of virus into minimally damaged areas of epithelium. Warts on the feet can be acquired from walking

barefoot in areas where other people walk barefoot. One observational study (146 adolescents) found that the prevalence of warts on the feet was 27% in those that used a communal shower room and 1.3% in those that used the locker (changing) room ***(Finley et al., 2016).***

Warts on the hand are also an occupational risk for butchers and meat handlers ***(Bacaj and Burch, 2018).***

Immunosuppression is another important risk factor. One observational study in immunosuppressed renal transplant recipients found that, at 5 years or longer after transplantation, 90% had warts ***(Reusser et al., 2015).***

1. Cutaneous Warts:

Lesions are caused most frequently by the cutaneous HPV types 1, 2, 3, 4, 7, 10, 27, and 57. Infection is predominantly by direct skin-to-skin contact but may be indirect through contaminated surfaces and objects ***(SyrjÄnen, 2010).***

2. Anogenital Warts:

HPV-6 and 11 are typically associated, but HPV-16, 18, 31, 33, and 35 are found occasionally. Similarly, to cutaneous warts, transmission occurs via skin-to-skin contact; therefore, in children, the possibility of sexual abuse should always be excluded. Vertical transmission has also been suggested including antenatal, perinatal, or postnatal route ***(Bussen et al., 2012).***

3. Oral warts:

Lesions are most frequently associated with HPV types 6 and 16, high risk HPV especially type 16 have been detected in more than 80% of cases of leukoplakia, HPV is strictly epitheliotropic, infecting stratified squamous cutaneous and mucosal epithelial cells. Oral HPV infection may be subclinical or putatively associated with benign or malignant oral neoplasms. The benign HPV-associated oral lesions, focal epithelial hyperplasia (Heck disease), oral squamous cell papilloma, oral verruca vulgaris (common wart) and oral condyloma acuminatum, are collectively referred to as oral warts. Oral warts are usually asymptomatic, may be persistent or uncommonly, may regress spontaneously ***(Bharadwaj et al., 2014).***

Pathophysiology:

Infection of epidermal cells with HPV results in cell proliferation and a thickened, warty papule on the skin. The appearance of warts is determined by the type of virus and the location of the infection ***(Lacarrubba et al., 2018).***

The full complexity of the relationship between warts, HPV and patient immunity is not yet fully elucidated ***(Doorbar, 2016).***

Once in contact with a host, HPV gains entry to the basal epithelial layer, where actively dividing stem cells are located. In the basal epithelium, the virus binds with cellular receptors and is subsequently taken up by the now-infected cell. After an

incubation period of 1 to 20 months, viral DNA is then established within the host cell, usually without integration into the host cell genome ***(Witchey et al., 2018).***

Once infection occurs, outcomes are possible: clearance of the infection with resultant immunity to that particular HPV type, latent infection, or clinically manifested infection as a wart. After infection, if the virus is not cleared, the host basal keratinocyte is stimulated to divide and replicate viral DNA via HPV E1 and E2 proteins ***(Sudhakar et al., 2013).***

This process produces numerous stem cells that each contain 20 to 100 copies of the viral DNA. The basal stem cells contain very low levels of viral proteins, which enhances the virus's ability to evade the host's immune response ***(Krishna and Jethwa, 2013).***

As the basal cells undergo normal differentiation into keratinocytes, they progress toward the outer surface of the epithelium. At the same time, the viral genome promoter region is activated, leading to increased production of viral proteins that enhance HPV genome amplification within each differentiating cell. It is thought that E5, a membrane protein produced via the viral DNA template, serves to enhance signaling from growth factor, which in turn maintains the cell's capacity for DNA replication ***(Witchey et al., 2018).***

Once viral DNA copies are sufficient, L1 and L2 viral coat proteins are expressed by surface keratinocytes. Protein E2 recruits viral DNA copies to the host cell nucleus, where the viral DNA is packaged into capsids composed of proteins L1 and L2. The infectious viral particles can then be released in high numbers from desquamated keratinocytes on the surface of the wart ***(Sanclemente and Gill, 2002).***

The induction of cellular replication throughout the process of viral genome amplification leads to the hyperkeratinized papule that constitutes a wart ***(Doorbar et al., 2015).***

As a result of normal sloughing of the epithelium, viral particles are released and may be transmitted to surfaces where the virus will lie until picked up by a new host or spread to adjacent sites (autoinoculation). Thus, once one wart develops, the host is susceptible to additional warts developing ***(Stiebing et al., 2018).***

Warts and malignancy:

Benign warts in immunocompetent individuals almost never undergo malignant transformation. There are a small number of reports of lesions that have initially appeared as warts and later become invasive squamous cell carcinomas (SCC) ***(Grulich and Vajdic, 2015).***

Nearly all cases of cervical cancer are associated with HPV infection, with two types, HPV types16,18,31,33,45 (high risk types), in contrast infection with HPV types 6,11 occur

mainly in benign and low grade intraepithelial lesions and very rarely associated with the development of anogential malignancy, HPV types 5,8 frequently associated with SCC associated with epidermodysplsia verruciformis (EDV) ***(Berman and Schiller, 2017).***

Progression of HPV infection to invasive cancer typically requires several decades and is related to persistent HPV infection, accumulation of additional genetic mutations and the oncogenic proteins E6 and E7, E6 facilatates destruction of the tumor suppressor protein p53 and E7 binds to the retinoblastoma tumor suppressor protein inhibiting its function. The oncogenic mechanisms for the virus is entering a lesion, altering the epithelium characteristics, and suppressing local immunity, thereby resulting in an increased likelihood of harboring oncogenic HPV types have been established. Some reports have also reported that infection with non-oncogenic HPV types 6 and 11, which cause condyloma acuminata, may facilitate coinfection with the oncogenic types of HPVs and the subsequent pathologic changes ***(Cho et al., 2017).***

Sun exposure increases the incidence of warty lesions and also acts as a cocarcinogen. Dysplastic change is quite common and there is frequently poor correlation between clinical and histological appearances. The lesions may appear typical of virus warts, solar or Bowenoid keratoses or keratoacanthomata or occasionally frank SCC. Numerous HPV

types have been found in benign and malignant squamous lesions in immunocompromised patients and the precise role they play in initiation and progression of malignancy is yet to be elucidated ***(Witchey et al., 2018).***

Clinical Features:

A range of types of wart have been identified, varying in shape and site affected, as well as the type of HPV involved. According to shape **(Table 1)** ***(Micali and Lacarrubba, 2018).***

Table (1): Morphology of warts ***(Silling and Akgül, 2018)***.

Clinical type	Appearance	HPV type
Common warts	Firm, rough keratotic papules and nodules on any skin surface. May be single or grouped papules.	1, 2, 57
Plane warts (flat warts)	2-4 mm in diameter, slightly elevated. Most commonly flat topped papules with minimal scaling.	3, 10
Intermediate warts	Features of common and plane warts	2, 3, 10, 28
Myrmecia	Deep burrowing wart	1
Plantar warts	May start as sago grain-like papules which develop a more typical keratotic surface with a collar of thickened keratin.	1, 2, 4, 57
Mosaic warts	Occur when palmar or plantar warts coalesee into large plaques	2
(Ano) Genital warts (Condyloma acuminate	Epidermal and dermal nodules and papules in the perineum and on the genitalia	6, 11
Oral warts	Small white or pink elevated papules on the oral mucosa. (HPV 16 has been detected in 80% of cases of oral leukoplakia)	6, 11, 32
Filiform or digitate	Thread- or finger-like warts, most common on the face especially near the eyelids and lips	

According to site:

Cutaneous lesions are classified according to anatomic localization. Common warts (verrucae vulgaris) are exophytic papules or plaques of variable size with hyperkeratotic surface They are usually located in sites prone to trauma, i.e., on the hand and fingers, but they may occur anywhere ***(Micali and Lacarrubba, 2018)***. In periorificial areas, they appear pedunculated and filiform **(Fig 1b)** ***(Micali and Lacarrubba, 2018)***. Palmar and plantar warts are endophytic/exophytic papules often painful at pressure **(Fig 1c)**. They may coalesce into large plaques named as mosaic warts **(Fig 1d)** ***(Lacarrubba et al., 2018).*** Flat warts (verrucae planae) are often multiple, pinkish, brownish, or skin-colored slightly elevated papules sometimes in a linear array that commonly involve the face, hands, and arms **(Fig 1a)** ***(Hogendoorn et al., 2018).***

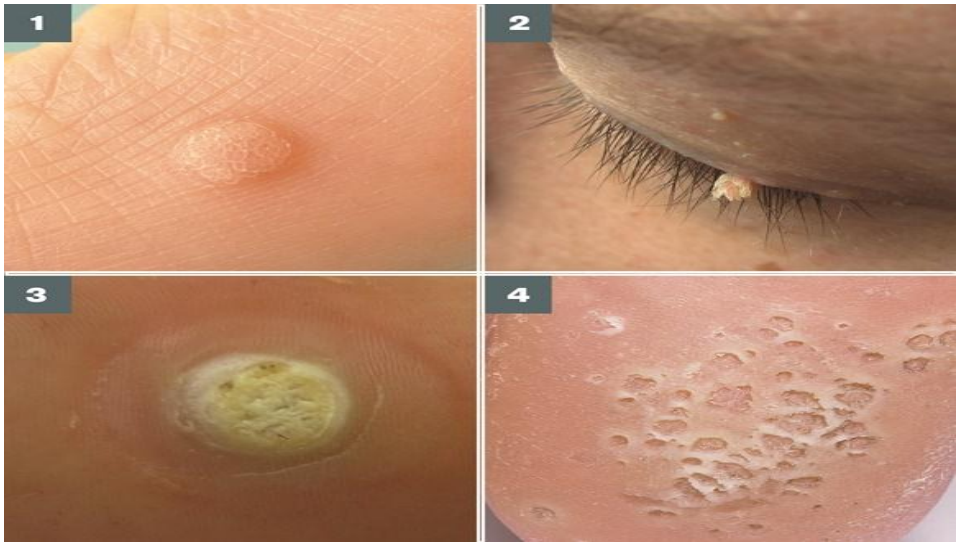

Figure (1): Different types of warts. a) Plane wart b) Filiform wart c) Plantar war d) Mosaic wart ***(Zaman, 2018).***

Anogenital Warts: Lesions in the anogenital region are also known as condylomata acuminata. They appear as exophytic, cauliflower-like, pedunculated, or broad-based papules or plaques with brownish or skin-colored surface and bleed easily **(fig 2)** (DD. Condyloma lata of syphilis) ***(Gross et al., 2018).***

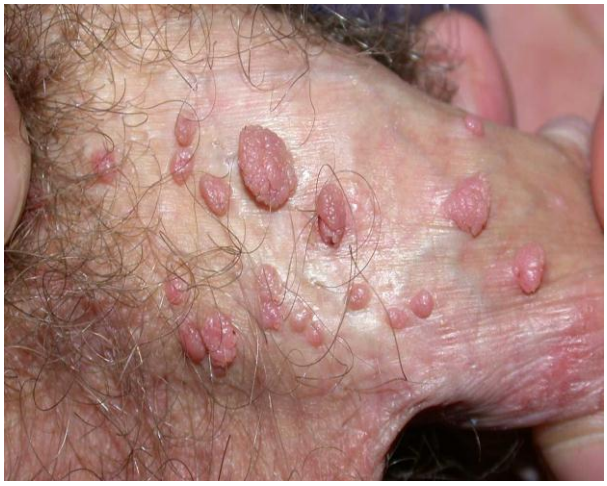

Figure (2): Genital warts ***(Lacarrubba et al., 2018).***

Variants of cutaneous warts:

1- Verruca planae:

Verruca plana, also known as a "flat wart", is a reddish-brown or flesh-colored, slightly raised, flat-surfaced, well-demarcated papule of 2 to 5 mm in diameter. Upon close inspection, these lesions have a surface that is "finely verrucous" ***(Pavithra et al., 2011).***

HPV type 3 and, less often, types 10, 27, and 41 most often causes flat warts. They generally occur in multiples and are grouped on the face, neck, dorsa of the hands, wrists, or the knees. In rare instances, there is extensive involvement with lesions on the extremities and trunk as well **(Fig 3)** ***(Masatkar et al., 2018).***

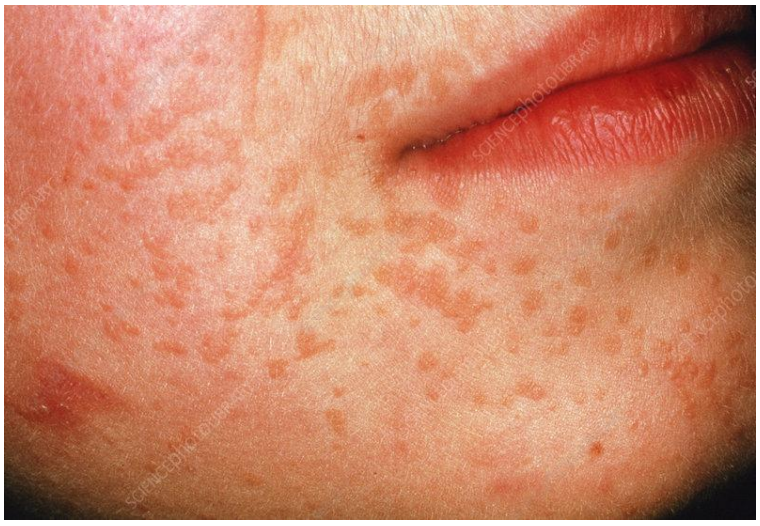

Figure (3): Plane wart**s** ***(Pavithra et al., 2011).***

2- Periungual wart:

Periungual warts are warts that cluster around the fingernail or toenail. They appear as thickened, fissured cauliflower-like skin around the nail plate **(Fig 4)**, Periungual warts often cause loss of the cuticle and paronychia. Nail biting increases susceptibility to these warts. Warts of this kind often cause damage to the nail either by lifting the nail from the skin or causing the nail to partially detach. If they extend under the nail, then the patient may suffer pain as a result. Sometimes periungual wart infections resemble the changes that are found in onychomycosis. In worst cases, if the infection causes injury or damage to the nail matrix, deformity in the nail may become permanent ***(Ham et al., 2017)***.

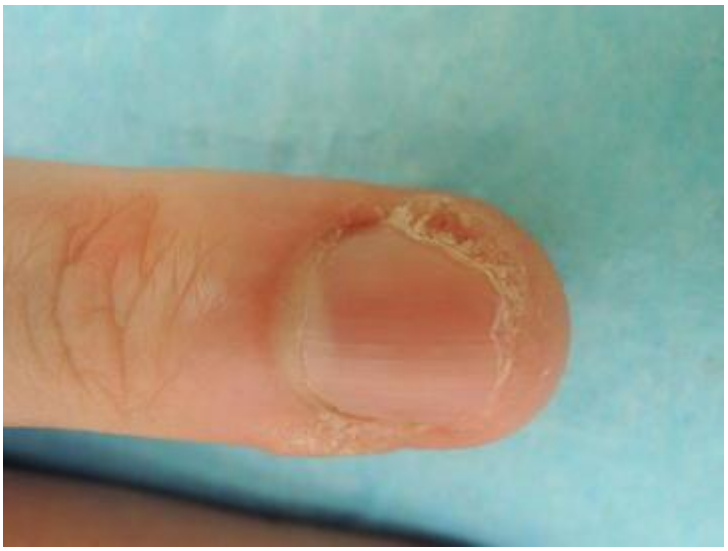

Figure (4): Periungual warts ***(Schroeter et al., 2007).***