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Review

Topical Treatment Options for Extragenital Verrucae

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Abstract

Background: Verrucae are benign proliferations seen in skin and mucosae due to infection with papillomaviruses. They may present differently according to clinical appearance and localization. In time, about 60% of verrucae spontaneously resolve. Since there is no single effective treatment method, a few different methods may be combined or sequentially applied. Local treatment methods of verrucae will be discussed in this paper.

Definition

Verrucae are benign proliferations seen in skin and mucosae due to infection with papillomaviruses. These viruses cause slow growing lesions that do not cause acute symptoms or signs [1, 2].

Historical Aspect

Verrucae have been known since ancient Greece and Rome. Up until the 19th century, verrucae were believed to be a form of syphilis or gonorrhea [2]. An infectious etiology was first questioned by Payne when he contracted verrucae after treating a patient. Viral etiology was first proposed by *Ciuffo* in 1907 and Strauss et al. isolated the small DNA virus in 1949. *Joseph Melnick* used the term papovavirus in 1960. The virus was characterized by following research and it was named human papilloma virus (HPV) [3]. In 1974, *Zur Hausen* proposed that there may be different types of virus and 4 types were identified in 1976 [4]. Today, due to advanced recombinant DNA technology, over 100 different genotypes of HPV have been identified [2].

Incidence/Prevalence

HPV infections are seen widespread. Nongenital verrucae are most frequently seen in children and young adults. Most people develop lesions at some point in their lifetime. Verrucae are seen twice more frequently in Caucasians [5]. In a survey conducted among school children, prevalence of verrucae was found to be 12% in children aged 4 -6 and 24% in children aged 16-18 [6].

Epidemiology

The virus is spread among humans via contaminated people [3]. Conditions where the epidermal barrier is lost such as little abrasions or maceration facilitate viral spread. Frequent hand washing is a risk factor for simple verrucae. Spread from the hands to small abrasions on the face, elbows and knees are common in children.

Spread of the virus depends on factors such as localization, infectious inoculum, period of contact, type of virus, immunologic status of the person and trauma [7].

Etiology / Pathogenesis

Papovaviruses are slow-growing, double stranded, naked DNA viruses [7]. HPVs are divided into two: Cutaneous and mucosal types. The mucosal types HPV 16, 18, 45 and 56 especially pose high risk for anogenital cancer [8]. In addition to this, studies have shown that especially immunosuppressed patients show traces of HPV in premalignant and malignant skin tumors.

The incubation period of the virus varies between 1-8 months and is around 4 months [3]. HPV inoculates in epithelial cells and causes proliferation of squamous cells. It can also remain subclinically or latent in skin or mucosae [7].

Clinical Findings

Clinical findings depend on the type of HPV, anatomic region and immunologic status of the host. There are several clinical presentations. These are: Vulgar (common) verrucae, plantar verrucae, plane (flat) verrucae, filiform verrucae, anogenital verrucae and epidermodysplasia verruciformis. They are characterized by papules, plaques and nodules with distinct borders. Sometimes changes in color may be seen. *Köbner* phenomenon can be observed. Diagnosis is made clinically [7]. Verrucae are commonly seen in traumatized areas such as the hands and feet and the virus probably enter the skin via areas of minor trauma. Many studies have shown that severe verrucae are common among professions dealing with butchery and meat [6].

Treatment

60% of verrucae spontaneously resolve in 2 years [9]. Since there is no totally effective treatment method, different methods may be combined or used sequentially [7].

Salicylic Acid: Salicylic acid is an agent with keratolytic and local irritant effects. It is used for the treatment of verrucae with 10-40% concentrations in cream, gel, paint, ointment formulations and with 40-60% concentrations in plaster and special gel formulations. Treatment under occlusion should be preferred for verrucae localized in the hands and feet. Protection of normal skin areas around the lesion is advised to prevent dermabrasion and further spread of the virus [7]. Lower concentrations of salicylic acid should be preferred in children in order to prevent potential systemic toxicity [3].

Placebo-controlled clinical trials have shown that salicylic acid cures 73% of verrucae [6]. When compared with cryotherapy, neither have shown a significant difference [6, 10]. Comparison with other topical agents (gluteraldehyde, dinithranol) has also shown no difference.

It has been stated that salicylic acid is a good treatment option in the treatment of uncomplicated verrucae and it is advocated for first-line treatment. It has also been shown that topical agents containing salicylic acid are safe and effective [6].

Cryotherapy: Liquid nitrogen is the most commonly used cryogen [11]. It effects through intracellular and extracellular formation of ice, which leads to cell death. The virus is not eliminated by cryotherapy but an immune response forms against viruses which are released from the damaged cells [7]. Cryotherapy should be applied within periods of 1-3 weeks, 5-20 seconds each, with a freezing margin of 1-2 mm. The application may be done via a cotton tipped or spray applicator [3]. In a study where 363 patients were treated with either cryospray or cotton tipped applicators, no significant difference in effect was observed between the two methods of application [11].

17 randomized controlled clinical studies have shown cure rates ranging between 9-87% with cryotherapy [6]. When compared with salicylic acid, no significant difference in cure rates has been observed [6, 10]. When salicylic acid and cryotherapy are combined, higher cure rates have been attained [10]. In 4 controlled clinical trials where 592 patients were included, 52% cure rate was attained when treatment period was longer (10 seconds). The cure rate declined to 31% with a shorter period of application [6]. Longer duration of treatment resulted in more pain and blister formation as side effects.

In 3 randomized controlled clinical trials

where cryotherapy was applied with intervals of 2, 3 and 4 weeks, no significant difference was found. Nevertheless, it is widely believed that shorter intervals between applications results in increased cure rates [6].

Addition of 5fluorouracil to treatment with cryotherapy has resulted in no additional cure in a randomized controlled clinical trial on 80 patients with verrucae [12].

When cryotherapy is applied correctly, it causes limited tissue damage and less pigmentation and scar formation. The disadvantages of cryotherapy are the need for more than one application and pain during and after application. It is advantageous in that it is blood-free and can be used on pregnant subjects [3].

As a result, cryotherapy is an effective and safe first-line method in the treatment of verrucae.

Dinitrochlorobenzene (DNCB): Topical immunotherapy has been in use for the treatment of verrucae for the last 30 years. DNCB was the first immunotherapeutical agent to be used but its mutagenic effects limit its usage. Other contact sensitizers are diphenylcyclopropenone and SADBE. The mechanism of effect in treatment of verrucae is unknown. Some authors claim that topical immunotherapeutical agents cause a type 4 hypersensitivity reaction in infected tissue and cause damage [13].

Since DNCB is a potent contact allergen and causes local irritation, it should be applied to less than 10 lesions. 2% concentration diluted in acetone is used for sensitization. Thereafter, it is used in 0.05-0.1% concentrations for treatment [3]

Placebo-controlled randomized trials have shown 80% cure rates with DNCB. DNCB is a promising method of treatment especially for treatment of resistant warts [6].

Diphenylcyclopropenone (DPCP): Diphenylcyclopropenone is a contact immunotherapeutic agent and causes type 4 hypersensitivity. It is usually used for resistant verrucae. It is used at a concentration of 1-3% on the arm for sensitization [14]. Two weeks later, it can be used in concentrations of 0.004-0.01%, depending on the area applied. Every 2 weeks, it is reapplied in increased concentrations. Treatment should remain in the highest concentration the patient is able to tolerate [3].

Patients with palmoplantar verrucae resistant to treatment DPCP has been used with 87.7% success [15]. In a study where 72 patients with verrucae were recruited, topical DPCP was compared with cryotherapy. At the end of 12 months, 93.3% cure was achieved with DPCP, whereas the cure rate for cryotherapy was 76.3%. This study reported a long period of immunity to HPV with DPCP treatment [16].

In a study where 6 patients with resistant facial verrucae were treated with DPCP, complete remission was seen at the end of 10 weeks. This study concluded that DPCP is a safe, effective and well-tolerated method of treatment for chronic resistant facial verrucae [17].

In 211 patients with resistant palmoplantar verrucae, a cure rate of 87.7% was reported with diphenylcyclopropenone [18].

Squaric Acid Dibuthylesther (SADBE): It is an agent causing hypersensitivity just like DNCB and DPCP but is less commonly used. Cure rate is reported to be 10-69%. Sensitization is achieved with 1% concentration. Treatment is initiated with 0.01% and increased to 0.1% gradually, with weekly applications lasting 2-12 (mean: 6) weeks. Another method advocates the use of 0.5-5% concentrations every 2-4 weeks, without causing any reaction. Its most common side effect is contact dermatitis [3].

In a study where 188 pediatric patients with resistant verrucae were included, SADBE was used at concentrations of 0.03-3%, two times per week. Complete remission was achieved in 84% of patients in less than 10 weeks and no side effects were observed. Relapse was seen in 16% of patients at the end of a 24 month follow up period [13].

In a retrospective study where 598 patients' records were analyzed, 86% complete remission was noted with SADBE [19].

According to these studies, SADBE is especially effective and may be used as an alternative treatment method for patients with resistant and multiple verrucae.

Photodynamic Therapy: Hematoporphrin de-

rivatives such as 5-aminolevulinic acid are used systemically or topically in photodynamic therapy (PDT). These substances are metabolized to protoporphirin and activated by light to cause cell damage [7].

Randomized controlled clinical trials conducted using different photodynamic therapy modalities found 8-75% cure rates [6, 20, 21, 22].

In a placebo-controlled study of PDT where 52 patients were recruited, 40% showed resolution of lesions [6]. In another study, 40 patients were treated using either PDT or PDT with 5-aminolevulinic acid. Cure rate in the latter group was reported to be 56% [20].

In a study where a total of 28 patients were included, 4 different types of PDT were compared with cryotherapy. Cure rates for PDT were reported to be 28-73% and 20% for cryotherapy [21].

As a result, PDT is not routinely recommended for treatment of verrucae since it does not cause much additional effect compared with simpler and cheaper methods [6].

Bleomycin: Bleomycin is an antineoplastic and antibiotic causing necrosis in infected tissue. A 0.2-1 ml (200-1000 IU/ml) solution of 1 mg/ml bleomycin is directly injected into the lesion. Large verrucae may require more than one injection. A few days after the injection, the area is necrosed and heals by scarring [3].

In 5 randomized controlled clinical trials using bleomycin, the results were conflicting. Cure rates were 16-94%.

In 2 placebo-controlled studies of bleomycin where a total of 40 patients were included, bleomycin was found to be more effective. In another study of 62 patients, placebo was found to be more effective. Yet another study of 31 patients showed no difference between the two.

A randomized controlled trial where different concentrations of bleomycin (0.25-0.5 and 1.0 units/mL) were used showed cure rates of 73-88% and 90%. According to this study, increasing concentrations of bleomycin lead to increased cure rates.

The most common side effect of intralesional bleomycin is pain. This can be reduced by use of local anesthetics prior to injection [6].

Laser: Carbon dioxide lasers are the most ablative approach in the treatment of verrucae. With cohort and case-control studies, the carbon dioxide laser has been shown to be 75% successful in the treatment of resistant verrucae. Side effects have been reported to be bleeding and pain.

Pulse dye laser is the most suitable amongst the non-ablative lasers. Less side effects have been noted [23]. In a nonrandomized study conducted on 120 patients, cure rate of 49.5% has been reported with pulse dye laser. It has been emphasized that the pulse dye laser has especially been effective for the treatment of flat verrucae. [24] In another study where 73 patients with resistant warts were included, 89% cure was reported after 10 applications of pulse dye laser [25].

In a study where 40 patients were recruited and a total of 4 applications of pulse dye laser were performed monthly, cure rates compared to cryotherapy or cantharidine were not different [3].

According to these studies, laser treatment of verrucae is safe and effective but since it is costly, it is recommended for the treatment of resistant verrucae.

Tretinoin: There is no controlled study on local tretinoin. It is reported to be effective in concentrations of 0.01-0.5% especially in plane verrucae. A very thin daily application may be increased to two or three times daily if necessary. Sun protection should not be forgotten if exposed areas are being treated [3].

5-Fluorouracil (5-FU): It is an antimetabolite which inhibits DNA and RNA synthesis and is a successful agent in treatment of verrucae. 1-5% cream formulations and 1, 2, 5% solutions are available. It most frequently causes local irritation. Since it is teratogenic, it is contraindicated in pregnancy and it is right to use it in females of fertile age alongside appropriate birth control methods [3]. In a study conducted in our country by İşçimen et al, intralesional 5-FU has resulted in 58% complete remission and 29% partial remission. In another group of patients to whom 5-FU was applied mixed with lidocaine, 61% complete remission and 22% partial remission were

achieved. Both groups' results were found to be superior to placebo; and there was no statistically significant difference between the two groups [26].

In a study of 40 patients, a mixture of 5-FU, lidocaine and epinephrine was injected intralesionally and compared to placebo. The patients were given a total of 4 weekly injections and followed for 6 months. Cure rates of patients receiving the mixture were reported as 64.7% [27].

Randomized controlled clinical trials using 5-FU and salicylic acid mixture were analyzed. In 8 randomized controlled clinical trials where a total of 625 patients were recruited, complete remission rate was 63.4%. In 4 randomized controlled clinical trials of 101 patients with plantar verrucae, complete remission was reported as 23.1%. When all the studies were compared, the mixture of 5-FU and salicylic acid demonstrated a cure rate of 63.4%, whereas a cure rate of only 23.1% was achieved with only 5-FU [28].

Podophylotoxin (Podophylox): It is an antimetabolite. Since it may be systemically absorbed, it is contraindicated in pregnant patients. 0.5% solution or 0.15% cream formulation is available in some countries. It is not yet available in our country. It is usually preferred on mucosal areas and applied 3 days a week and stopped the other 4 days of the week. 4-6 weeks of therapy is necessary. 30-50% of patients report pain, erythema, erosions and edema. Due to these side effects, it should be applied to small areas (4-10 cm2) and the daily dose should not exceed 0.5 ml [3].

In a study where 144 patients with plantar verrucae were retrospectively analyzed, the combination of podophylotoxin /cantharidine /salicylic acid resulted in 95.8% total remission after 6 weeks of use [29].

Formaldehyde: It is a strong disinfectant. When used on verrucae, it leads to damage in the upper layer of cells. 0.75% gel, 3, 10 and 20% solution and 10% spray formulations are available. 200 children with plantar verrucae have been treated for 6-8 weeks with 3% concentration and 80% remission has been reported [3].

Gluteraldehyde: 10 and 20% solution and 10% gel formulations are available [3] 57 patients with simple plantar verrucae have been treated with either a combination of monochloroacetic acid and 10% formaldehyde or formaldehyde alone and no significant difference between the modalities has been observed. A mean 61.4% cure rate has been noted [30].

In a study, 20% gluteraldehyde solution was applied daily and a cure rate of 72% in 3 months was reported. Brown skin discoloration and cutaneous necrosis are its most important side effects. When combined with salicylic acid it may lead to contact sensitization and this treatment method is reported to be 70% successful [3].

Imiquimod: It was first used on genital verrucae but nowadays it is used widely for non-genital verrucae too [3]. It mainly stimulates interferon alpha and besides TNF alpha, IL 1-6 and 8 and modifies the topical immune response [31]. It induces migration of *Langerhans* cells to lymph nodes and this stimulates T cells specific to the virus. Since tumor suppressor markers have been demonstrated to increase after treatment with imiquimod, it is thought to protect from neoplasia. Combination with salicylic acid has been reported to be more effective in plantar verrucae. Necessitation of long term treatment is a disadvantage. Its major side effects are erythema, erosions, pruritus, sensitivity and burning sensations and flu-like symptoms. Recurrence is reported to be 10-20% [3].

15 patients with periungual and subungual verrucae were treated with 5% imiquimod and followed for 16 weeks. 80% showed total remission. According to this study, imiquimod may be successfully used for patients with periungual verrucae [31].

Sidofovir: Sidofovir is a potent nucleoside analogue that is a competitive inhibitor of DNA polymerase. Topical, intralesional and intravenous use of sidofovir have been reported in the treatment of verrucae. It is approved for the treatment of CMV retinitis in AIDS patients [32]. Since irritation has been reported with twice-a-day application, it is advised to be used once daily. No systemic side effects have been reported with local application and it is recommended to be used at a concentration of 3%. Intravenous applications are known to be nephrotoxic. It may also cause neutropenia [3].

In 7 pediatric patients with resistant verrucae, applications of sidofovir at a concentration of 1% resulted in complete remission in 4. Since sidofovir is a costly treatment, it should be reserved for patients with recalcitrant patients [32].

Cantharidine: Cantharidine has been used in dermatology for the treatment of molluscum contagiosum and verrucae since the 1950s. It causes local blisters. Scar formation is not seen. There is no pain during application but it may occur afterwards. The application of cantharidine causes neutral serine proteases to be released. This results in the separation of tonofilaments of the desmosomal plaques in the epidermis. Due to degeneration of the desmosomal plaques, an intraepidermal blister is formed. Since the blister is intraepidermal, there is no scar formation [33]. The application is repeated every 1-3 weeks. Caution is advised not to apply it to normal skin areas. Rarely lymphangitis has been reported [3].

Durmazlar et al have applied 0.7% cantharidine to 15 patients with facial verrucae with intervals of 3 weeks. Complete remission was noted in all patients at the end of 16 weeks [33].

Cantharidine may be used safely and effectively in the treatment of resistant verrucae.

Interferons (INF): Interferons are endogenous cytokines with antiviral, anti-tumoral and immune modulator effects and are of three major types. INF–α is produced by leukocytes, INF-β is produced by fibroblasts, and INF-γ is produced by T lymphocytes and natural killer cells [34]. In the treatment of verrucae, 0.1 ml of (1 million IU) INF–α2b is applied 3 times per week for 3 weeks intralesionally. To avoid systemic side effects, a maximum of 5 lesions should be treated per session [42].

Success rate of intralesional injections are 19-62% whereas for topical applications, it is reported to be 33-90%. [14] Disadvantages are that interferons are costly and require multiple injections [3]. They are advised to be used on resistant lesions [34].

Others: Intralesional injection of candida injection acts by activating the immune system locally. In a retrospective study conducted on pediatric patients, the intralesional injection of candida injection has resulted in complete remission in 87% [35]. In a placebo-controlled study where intralesional candida, mumps and trichophyton antigens were used, all were found to be effective against verrucae. In this study the patients were divided into 4 groups. The first group was injected with only INF-α2b, the second with antigen + INF-α2b, the third with only antigen, the fourth with only saline. Complete remission was achieved with antigen + INF-α2b in 57%, 41% in the group receiving only antigen, 9% in the group receiving only INF-α2b and 19% in the group receiving saline [36].

As a result, the intralesional injection of candida or mumps antigen is shown to be safe and effective in the treatment of verrucae. This treatment is recommended to be used especially for resistant verrucae as a second-line treatment [9, 37, 38, 39]

Silver nitrate is reported to be an effective alternative treatment for the treatment of verrucae, though it may cause scar formation [3]. In a placebo-controlled study of 60 patients with palmoplantar verrucae, silver nitrate solution was applied every other day. At the end of 3 weeks, complete remission was achieved in 63.3% of the patients. [40] In a study conducted by *Yazar* and *Başaran*, silver nitrate was compared with placebo. And 43% complete remission was reported with silver nitrate [41].

It is known that zinc is a regulator of the immune system. Oral zinc sulfate is reported to lead to high cure rates in resistant verrucae [42]. Topical zinc may induce immunity. It may induce T lymphocytes to facilitate antigen recognition and trigger inflammation.

In a study where 20% topical zinc oxide was compared to salicylic acid (15%) and lactic acid (%15) mixture, half of the patients receiving topical zinc oxide showed complete remission [43].

Topical formic acid is a carboxylic acid and is used for the treatment of pediculosis capitis at a concentration of 8%. In a placebo-controlled study of 100 patients, 85% formic acid was used for a maximum of 12 applications and 92% complete remission was reported. Secondary infection, pain, erythema and burning sensation were reported [44].

In a study the use of hypnosis was reported to be more effective than topical salicylic acid and placebo. When similar studies are taken into consideration, this method may be considered as an alternative in the treatment of verrucae [3].

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