Chapter

Human Papillomavirus Infection: Management and Treatment

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Abstract

Human papillomavirus infections are very common and recurrent. Their presentation varies according to their site of affection. Spontaneous recovery is common in a good number of patients. An ideal wart therapy resolves all or maximum number of warts, is painless, needs only one or a part of a wart treated, needs only minimum number of treatments, leaves no scar, offers lifetime HPV immunity and is easily available for all patients. Various modalities of treatment are available—from some folk and alternative therapies to destructive, antimitotic, virucidal, immunotherapy and combination of therapies. In every modality, the result is significant. Younger individuals with short duration of illness usually have the highest clearance rates for various treatments. Recurrence rate is also high in almost every treatment modality. Immunotherapy has a promising role.

Keywords: human papillomavirus infection, chemical cautery, electrocautery, cryotherapy, laser therapy, immunotherapy

1. Introduction

Human papillomaviruses (HPVs) are a large and diverse group of viruses with 174 completely characterised types, with new HPV types being continuously found [1]. There are five major HPV genera: *Alphapapillomavirus*, *Betapapillomavirus*, Gamma papillomavirus, Mu papillomavirus and Nu papillomavirus. HPVs infect epithelial cells in genital mucosa (*Alphapapillomaviruses* only), oral mucosa or skin (representatives of all five genera). The most common clinical manifestation is verruca, with different morphological forms. The histology shows acanthosis, elongation of dermal papillae, presence of vacuolated cells and koilocytes. Subclinical manifestations are invisible to the human eye. These subclinical lesions are flat and multiple. Their clinical insignificance facilitates their spread, and in women their persistence is possibly related to genital cancer.

2. Diagnosis

2.1 Clinical diagnosis

The clinical picture of cutaneous warts differs by specific location on the body [2]. Most extragenital warts are benign, and usually clinical diagnosis is adequate, but sometimes additional methods are required especially in atypical, subclinical or dysplastic lesions. Genital lesions are more prone to transform to

malignancy, so determining the extent of disease is essential. Examining the wart and scraping off the top layer of the wart to check for signs of dark, pinpoint dots—clotted blood vessels—are common with warts.

2.2 Dermatoscopy

Warts can be visualised exceptionally well by dermoscopy, especially the black dots. Dermoscopy is also very useful in terms of differential diagnosis and follow-up [2].

2.3 Acetowhitening

Genital/mucosal lesions remain undetected for a long time; not only that, all lesions may not be clinically evident at a time. Topical application of 3–5% of acetic acid for 3–5 min and followed by examination with 10X hand lens or colposcope is a reasonable accurate diagnostic tool. Lesions will be represented as tiny white papules. The routine use of this procedure to detect mucosal changes attributed to HPV infection is not recommended because the results do not influence clinical management.

3. Laboratory investigations

3.1 Histology

Acanthosis, epidermal hyperplasia, papillomatosis, compact orthokeratosis, hypergranulosis, tortuous dermal papillary capillaries, and vertical tiers of parakeratotic cells are the typical histological findings of warts. In the granular layer, cells have coarse keratohyalin granules and vacuoles surrounding wrinkled-appearing nuclei. Koilocytes are pathognomonic.

3.2 Immunohistochemistry or immunocytochemistry using type-common and type-specific antibodies

3.2.1 DNA in situ hybridization

In situ hybridization is a direct signal detection assay. It preserves the morphological context with HPV DNA signals. It has low sensitivity; however, in recent years, using improved signal-detecting method, sensitivity increased. It is becoming a valuable screening tool for women of age more than 30 years.

3.3 Polymer-based enzyme-linked immunosorbent assay (ELISA) for immunoglobulin G (IgG) antibody (Ab) against HPV 16 capsid

3.3.1 PCR for HPV DNA

Patients who are diagnosed with condylomata need a Papanicolaou (Pap) test of the cervix in accordance with the guidelines of the American College of Obstetricians and Gynaecologists

Computed tomography (CT) or magnetic resonance imaging (MRI) can be used to determine the extent of spread of cervical carcinoma and extensive anogenital papillomatosis that has spread into the pelvis.

4. Treatment

Warts are usually self-limiting. Large studies have shown complete spontaneous remission in 42% of patients after 2 months; in 53%, after 6 months; and in 65%, after 2 years [2]. The intact immune system plays the most important role for preventing HPV infection. This can be seen in patients with primary immunodeficiency or in immunosuppressed patients.

HPV-induced warts are the most common skin disorder in organ transplant recipients [3]. Children with recalcitrant extragenital wart may suffer from primary immunodeficiency. It has been shown that immunosuppressed patients experience resolution of treatment-refractory warts once their immune status has improved [4]. The known spontaneous remission of HPV-induced warts, which is attributed to cell-bound mechanisms, underscores the role of the immune system, including an increase in Th1 cytokines and infiltration of T cells ($CD4^+$, $CD8^+$) around the diseased tissue [5].

Guidelines for the management of cutaneous warts have been prepared for dermatologists on behalf of the British Association of Dermatologists [6]. The guideline highlighted the ideal aims of treatment of warts as follows: (i) Removal of wart without recurrence. (ii) Treatment should result with no scars. (iii) Immunity that induced by treatment should be lifelong [5]. The general principles observed in the treatment of warts are the following: (1) There is no need to treat all warts. (2) Treatment indications are pain, interference with function, cosmetic embarrassment and risk of malignancy. (3) All the treatments have success rate not very high (average 60 ± 70% clearance in 3 months). (4) An immune response is usually essential for clearance. Immunocompromised individuals may never show wart clearance. (5) Younger individuals with short duration of illness usually have the highest clearance rates for various treatments [5].

There is a high rate of spontaneous remission, especially in children, so 'wait-and-see' approach is feasible in many cases. Regular filing or paring down the hyperkeratotic layer makes the lesion thin and comfortable. Simple measure to limit the spread of lesion should be encouraged. The treatment of warts can be broadly classified into destructive, antimitotic, virucidal, immunotherapy, and some folk and alternative therapies which have recently become popular again.

The goals of wart treatment are to resolve all or a maximum number of warts, make it painless, need only one or a part of a wart treated, only need minimum number of treatments, leave no scar, offer lifetime HPV immunity and be easily available for all patients [7]. The criteria for wart treatment, developed by the American Academy of Dermatology in 1995, [7] include (1) the patient's desire for therapy; (2) symptoms of pain, bleeding, itching or burning; (3) disabling or disfiguring lesions; (4) large numbers or large sizes of lesions; (5) the patient's desire to prevent the spread of warts to unblemished skin of self or others; and (6) an immunocompromised condition [6].

4.1 Destructive therapy

The lesions are damaged or removed by different procedures followed by clinical cure. The destructive therapies include surgical removal by curettage and cautery, chemical cautery, cantharidin, cryotherapy, electrocautery, radiocautery ablation, infrared coagulation, photodynamic therapy, and lasers.

4.1.1 Surgery

Curettage followed by cautery was an early and still widely practiced method of surgical removal of warts. A success rate of 65–85% has been reported in surgical

therapy, but scarring and recurrence rate are high (30%), and the sole of the foot is the site where scarring is particularly problematic. Curettage followed by cautery is most commonly used for filiform warts on the limbs and face [8]. Excision is usually to be avoided as scarring is inevitable, and there is frequent chance of recurrence in the scar.

4.2 Salicylic acid

It is keratolytic, reduces the thickness of warts and may also stimulate an inflammatory response. Over-the-counter preparations are available as 17% salicylic acid combined in a base of flexible collodion or as a 40% salicylic acid plaster patch [9]. It is minimally expensive, convenient and reasonably effective, with negligible pain, but results require weeks to months of treatment. Occasionally, contact dermatitis due to colophony may develop, and to avoid systemic toxicity, it should be applied only in limited area. Treatment result with salicylic acid therapy extremely depends on patient compliance. Before pairing or debridement of the dead, hyperkeratotic tissue, wart(s) should be soaked in warm water for 5 min. The salicylic acid preparation should then be applied to the debrided wart [10].

4.3 Chemical cautery

Strong chemicals can destroy tissue. Trichloroacetic acid (**TCA**) and bichloroacetic acid (**BCA**) are not readily absorbed by tissue; it kills warts by denaturing and destroying the proteins in the cells. Treatment via **chemical cautery** with a solution of 60–90% trichloroacetic acid (TCA) is most effective when treating few small, moist lesions. There is a complete clearance of warts in 70% of patients who received up to 6 treatments of trichloroacetic acid. Thirty percent of patients who were treated with trichloroacetic acid developed ulcerations at the site of its application [11]. Recurrence rate is not clear. Silver nitrate is probably most widely recognised in its historical use to prevent conjunctivitis in newborns [12]. This treatment for warts is currently more widely used in the United Kingdom where non-prescription 95% silver nitrate caustic applicator pencils are available [13]. Chances of excessive burn and pigmentation are there.

4.4 Cantharidin

A terpenoid secreted by blister beetles, which is absorbed by lipids in keratinocytes, activates serine proteases and leads to acantholysis [14, 15]. Depending on the amount, concentration, duration of exposure and occlusion, an intraepidermal blister will form and resolve, within a week [16]. The superficial nature of the injury reduces the risk of scarring. One randomised control trial shows that cantharidin is effective, is safe, yields better cosmesis and requires fewer applications than TCA for the treatment of warts when used sufficiently far from mucosal and intertriginous areas. It was also shown to be well tolerated and that patients being treated with Cantharone were significantly more satisfied than those treated with TCA. This may be attributed to less pain during application and during the entire treatment, better cosmetic results and perhaps fewer visits [17].

4.5 Phenol (carbolic acid)

It is a strong caustic agent that can penetrate deep into tissue, produces chemical burn with escher and is not used routinely for treatment of common wart.

Strong (80%) phenol solution for the treatment of common warts showed that phenol was an effective form of treatment for warts. It must be used by a physician and should not be used in extensive areas [18].

4.6 Retinoic acid

Topical tretinoin, although currently recommended for the treatment of acne, has also been reported to be of benefit in plane warts. A study of 25 children with plane warts treated with 0.05% topical tretinoin cream (applied once daily for 6 weeks) was compared with a control group of 25 untreated children. After 12 weeks, clearance of warts was observed in 84.6% of the treated group as compared with 32% of the control group. It was well tolerated with some redness and peeling in 42.3% of the treated group [19].

4.7 Photodynamic therapy

Photodynamic therapy (PDT) with topical 5-aminolevulinic acid has a good curative effect, especially in recalcitrant facial flat warts [20–22]. It is unclear, but selective photothermolysis of oxyhaemoglobin within the dilated microvasculature of the warts leads to destruction of capillaries followed by improvement of warts, may be the mechanism of action of this curative effect [23]. Many factors affect the efficacy of PDT, including photosensitizer concentration; solvent type; incubation time; type, dose, and time of irradiation of the light; and the area of exposed parts. ALA gel (10%) was applied topically to lesions and incubated for 3 h. The lesions were irradiated by an LED light of 630 ± 10 nm at dose levels of 60–100 mW/cm**.** At the 24-week follow-up, the average effective rate was 88.8%, with no recurrences. No significant side effects were reported [24].

4.8 Cryotherapy

Cryotherapy induces cold thermal injury in the lesion. Cryotherapy may have an effect on wart clearance either by simple necrotic destruction of HPV-infected keratinocytes or possibly by inducing local inflammation conducive to the development of an effective cell-mediated response [25]. Dimethyl ether spray, carbon dioxide snow and liquid nitrogen all produce cold thermal damage to the skin. Different types of devices and techniques are used to induce targeted cold injury to warts. Carbon dioxide slush (−79°C) is now less commonly used.

4.8.1 Mixture of dimethyl ether and propane (DMEP)

It is in aerosol form, easy to handle and stored in normal room temperature, and its preservation time is very high (nearly 3 years), available in market and easy to buy. As the evaporation temperature reaches −57°, therefore, it is likely to be less effective, and efficacy in inducing tissue temperatures adequate for cell necrosis appears low [26]. But one multicentre RCT on comparing effects of DMEP and LN_2 shows that no clinically relevant differences between the efficacy, tolerance and safety of the two cryogenic agents used in primary care were found. The low freezing of DMEP was sufficient for the cryotherapy of benign lesions [27].

4.8.2 Liquid nitrogen therapy

Having a temperature of −196°C, the coldest freeze, is the most commonly used method in medical practice. It is very effective in elimination of a large

variety of very common benign and premalignant skin lesions (verrucas, *Molluscum contagiosum*, seborrheic and actinic keratoses) [25]. Wart clearance may be through necrotic destruction of HPV-infected keratinocytes or by inducing local inflammation that triggers an effective cell-mediated response [25]. Liquid nitrogen can easily be stored and used by simple equipment in clinic-based practice. Available techniques are dipstick, roller, spray gun and Probe. Dipstick is the simplest technique where a cotton swab is dipped in liquid nitrogen and applied on a lesion. It is suitable only for superficial, benign lesions. Cryoroller, whose tip is cylindrical, is dipped in liquid nitrogen and then rolled over the lesional area. It acts better in severe acne and hypertrophic scar. The most popular method is spray technique using cryoprobes [10]. There are variations in freeze times, mode of application and intervals between treatments. Freeze time is the time elapsed from start to end of freeze cycle, i.e., from formation of uniform ice field until lesion is thawed, varying from 5 to 20 s. In short freeze for warts, cryotherapy continued till a 2-mm white halo develops around the lesion; this is enough for plane wart or filiform warts. But long freeze time (maintaining white halo for 5–20 s) is required for plantar warts. The cycle is repeated every 3 weeks on 8–10 occasions. It is better to pare hyperkeratotic lesions before cryosurgery as it acts as insulator. A cure rate of 60–80% can be anticipated [28]. Longer freeze is more effective than traditional (shorter) freeze, and blistering is significantly greater [29]. Plantar warts need comparatively more aggressive therapy. There is no difference between single freeze-thaw cycle and double freeze-thaw cycle in palmer warts but in plantar warts, and double freeze-thaw is more effective [30]. The number of session is important, not the interval between sessions for percentage cure [31]. Two-week intervals between sessions may be an optimal treatment [31].

4.9 Ablation radiofrequency

Localised heating with radiofrequency heat generators and surgical excision with radiofrequency electrosurgical knives have been used with moderate success [32, 33].

Radiofrequency ablation is a common mode of treatment, and it involves the principle of tissue destruction with various waveforms of alternating electric current whose frequencies fall within the range of radiofrequency (500–4000 khz) [34]. The overall cure rate for warts with radiosurgery ranges between 33 and 80% depending on the number of sittings and the type of warts [35, 36].

Electrocautery is a form of electrosurgery that utilises galvanic or direct current for generating heat. Although rarely used nowadays in the developed nations, it is still widely used in the developing countries and is considered more effective for treating thicker lesions with an overall success rate of 56–80% [7].

4.10 Infrared coagulation

It is an instrument that produces noncoherent infrared light with a spectrum of 400–2700 nm. It has been reported as a cheaper, safer and more easily handled alternative to CO_2 laser treatment. Direct application of infrared contact coagulators causes thermal injury to a depth dependent on the duration of exposure [37]. A bulla arises after IRC that may protect the lesion against infection. Cure rate was 66.7% for warts treated with IRC. The instrument allows adjustable tissue necrosis without tissue adhesion and has yielded remissions with a 10.8% recurrence rate [38]. In comparison to electrocoagulation, infrared coagulation produces similar outcomes [37], but it is safer than EC in side effect profile.

4.11 Laser therapy

4.11.1 Carbon dioxide (CO_2) laser

The CO_2 laser was the initial laser modality used to treat warts and has been used since 1980s [39–41]. The CO_2 laser emits infrared light of wavelength 10,600 nm. It is absorbed by tissue water and results nonselective thermal tissue destruction. The CO_2 laser treats warts via two mechanisms. A focused CO_2 laser beam used as a scalpel to excise the wart down to the subcutaneous tissue, followed by the base of the wart, which is vaporised by a defocused beam until a clean surgical field is obtained [42–45]. Cohort studies report that simple and recalcitrant common, palmar, plantar, periungual and subungual warts have been successfully treated with CO_2 laser, with response rates ranging from 50 to 100% [40, 43, 46–53]. Usually, excision by focused mode followed by vaporisation and haemostasis with defocused mode is the common practice. Deeper warts need more passes. Using two to four passes per wart is adequate [46–49]. CO_2 laser treatment may be used for recalcitrant warts but also as a first-line of therapy for warts—mainly in the sole, hands and other parts also [46]. Single verruca lesions usually result better (66.7%) than multiple verruca (62.5%) [46]. It can be used for first-line therapy for periungual and subungual warts. It has been seen that patients with subungual and periungual warts, who have failed previous conventional therapy, respond less than in patients when CO_2 laser therapy was given as first line (47.9% compared to 80.0%) [47]. Subungual warts respond better than periungual warts [47]. Usually one or two sessions are adequate [48]. Patients with one session heal earlier than patients with more than one session [48]. Adverse effects include permanent nail matrix damage and scarring, and nail changes such as distal onycholysis and thickening may occur [47, 48, 51]. CO_2 laser may also be used as excision tool, with a remission rate of 95.5%, but requires specialised unit [49]. Scarring is a possibility [49]. 'En bloc' excision of wart is very much effective [100%] in paediatric age group also with no recurrence, and usually single session is adequate [50]. Many treatment modalities are not feasible in immunosuppressive patients. CO_2 laser can be a safe and comparably effective modality of treatment, even in one intervention [51]. Complete excision of the lesional skin with a portion of deeper tissue and 1-mm non-lesional margin leads to the complete clearance of HPV DNA, which leads to very lower recurrence, though chance of scar formation is there. Dressing with artificial dermis leads to less scar formation [52]. Application of Imiquad after CO_2 laser in recalcitrant wart reduces or stops recurrences [53]. Vapour produced by CO_2 laser with any power density and fluence contains intact papillomavirus DNA. This infected vapour may cause pulmonary infection [54]. Plume produced from laser procedure collected and used as inoculum may produce identical lesions [55]. So, safety precautions during laser surgery may be strictly maintained [55]. It is important to wear surgical masks as it is capable of removing all laser- or electrocoagulation-derived viruses [56], even gas scavenging system to be in use [57]. But a study among CO_2 laser surgeons in all the members of American Society of Laser Medicine shows that the plume does not possess enough infectious material to produce significantly more amount of warts in laser surgeons in comparison to population-based common subjects [58]. But, sitewise, CO_2 laser surgeons have a greater risk of acquiring nasopharyngeal lesions, especially when they treat genital warts with HPV types 6 and 11 [58]. Scar formation is a known side effect of CO_2 lasers, and there are more chances of hypertrophic scar formation if the patient is on cyclosporine for other reasons [59]. In superpulsed CO_2 LASERs, the high irradiances and brief duration make possible very precise removal of target lesion volumes and controlled excision. Here, thermal damage is very less leading to less inflammation and less scarring [60].

4.11.2 Erbium:yttrium/aluminium/garnet (Er:YAG) laser

Non-ablative lasers are largely replacing ablative CO_2 lasers as side effects are less, both for patients and clinicians [61]. Er:YAG laser emits 2940 nm wavelength. It is absorbed 12–18 times more efficiently by water containing superficial cutaneous tissue than CO_2 laser. At 250 microsecond pulse duration and 5 J/cm^2 fluence short pulse, Er:YAG laser ablates 5–20 micrometre of tissue per laser pass, and minimal residual thermal damage that results faster tissue re-epithelialization and less side effects. The disadvantage is intraoperative bleeding [62]. Its mechanism of action in treating warts is through direct ablation of the lesion in the epidermis, layer by layer until normal tissue is visualised. This laser type also has bactericidal effects [61]. Er:YAG laser was tried in all types of common warts—periungual, subungual and plantar warts; complete clearance rate was 68% for plantar warts, 78% for periungual warts and 76% for subungual warts. In patients with extensive involvement, more than one session were needed. Relapse was only in plantar wart patients (17.8%) [62]. Chance of scarring is less in Er:YAG laser [62, 63]. For hard-to-treat palmoplantar warts, a combination of ablative Er:YAG laser and topical 0.5% podophyllotoxin solution yields higher success with complete clearance of 88.6% without any pigmentary changes, wound infection and scarring. Relapse rate is also less [64]. Er:YAG laser procedure can be done without anaesthesia or with topical cream anaesthesia as there is minimal pain, except only in large, very thick plaque in the plantar or palm. The plume contains no viral DNA [65]. Side effects are less with Er:YAG laser, no hyper- or hypopigmentation and no post-operative infection. Healing is very fast, within 7–10 days. Redness persists up to 3 months [66]. In a study of 69 patients with difficult-to-treat warts (periungual or plantar), 72.5% of patients with wart observed complete response (CR) irrespective of the duration of infection with HPV or the age of the patients. Plantar warts were more resistant (13.5% non-responders) than periungual warts (5.9% non-responders), and larger mosaic plantar warts were less sensitive than single warts; 24.0% of patients showed relapse [67]. Wound healing may be assisted/accelerated with LED phototherapy (633 nm). Immediately after Er:YAG ablation, with precise removal of wart tissue, a red LED therapy system is applied (633 nm, 20 min, 96 J/cm^2) to the wound and surrounding area, LED system with same parameters were repeated on the second, sixth and tenth post-operative day. On the sixth post-operative day, the wound has shrunk noticeably and is filled with healthy, granulation tissue, and on day 15, the wound healed completely with minimal scarring; recurrence rate was also less (<6%) [68].

4.11.3 Neodymium:YAG (Nd:YAG) laser

Principal emission of Nd:YAG is at 1064 nm, in the infrared range [Nd:YAG produces heat]. Heat therapy depends on the principle that diseased tissue which is being treated is more sensitive to the effects of the elevated temperature than normal tissue and this is less able to recover after heat exposure [69]. Side effects such as coagulation, blister or crusts are less after hyperthermia. Response is excellent (77%), though in 23% of the method failed, and there is no recurrence in 9 months follow-up. Nd:YAG can be used in all types and site warts including periungual, hand and plantar warts [70]. HPV DNA becomes completely absent in hyperthermia-treated wart lesions, in comparison to cryotherapy where 96% wart lesions are positive for HPV DNA by in situ hybridization [71]. The light of the solid state Nd:YAG laser can easily be guided by fibres to tissue and perform good coagulation and homeostatic function, in laryngeal, as well as genital, easily and more precisely. Its continuous suction endures a minimal load of potential infectious laser plume [72]. For therapeutic treatment, Nd:YAG laser can be utilised

for genital tract lesion and cervical conization for early neoplasms like dysplasia, carcinoma in situ and microinvasive carcinoma [73, 74]; these are caused by HPV infections. Invasive lasers like CO_2 are normally considerably more painful and require longer recovery time, and also side effects like scarring are high. A long pulsed Nd:YAG laser emits 1064 nm wavelength light, in infrared spectrum, in longer wavelength with lower haemoglobin, and melanin absorption coefficients allows deeper delivery of higher energy in hyperkeratotic and thicker epidermis that are assisted with warts [75]. Several studies have evaluated the use of the Nd:YAG laser in the treatment of simple and recalcitrant common, palmoplantar, periungual and subungual warts, with efficacies ranging from 46 to 100% [61, 76–78]. Laser protocol varied among different studies: spot size between 3 and 7 mm, pulse duration of 1–20 ms, fluence of 100–200 J/cm^2, cooling methods, number of pulses between 1 and 8, treatment interval from 2 weeks to 12 months and mean number of treatments between 1.49 and 4.65. In a study of Han et al. [76], 348 patients of all types of simple and recalcitrant common, palmoplantar and periungual warts are treated with Nd:YAG laser (spot size, 5 mm; pulse duration, 20 ms; 200 J/cm^2; no cooling; 1–2 pulses). After a mean of 1.49 treatments, wart clearance rate was 96% though there were differences in clearance rates after initial treatment depending on location (72.6% for common warts vs. 44.1% for palmoplantar warts) [76]. For determination of effectiveness and safety of a novel 100 microsecond pulsed 1064 nm Nd:YAG laser in treatment of Verruca vulgaris, low energy (200 mjouls) Nd:YAG, in monthly intervals for 3 months was given to 25 patients with lesion on hands-nineteen patients had complete clearance; with minimal discomfort [61]. At least partial response (50% reduction) in verruca size was noticed in all lesions [61]. Aggressive treatment of hand warts may cause tissue damage. To avoid the tissue damage, a novel modification was tried [77]. Fifty one recalcitrant verrucas were treated with ND:YAG laser; all warts were administered in at least three pulses. The circle of pulses given in that way that the three circles overlapped each other only on the site of verruca- so that highest level of energy reached only to the wart. The adjacent tissue can avoid unintended tissue damage [77]. All lesions subsided, 88.35% lesions in one laser session, remaining patients were required two laser sessions- those lesions were periungual and palmar. There was no recurrence in 12 months follow-up, no major side effects, no nail dystrophy or severe post-treatment scarring. Hyperpigmentation was present in 5.48% patients [77].

4.11.4 Pulsed dye laser

Among non-ablative modalities, pulsed dye laser (PDL) can be used for a selective, non-bloody destruction of extragenital and genital warts [79]. It emits a wavelength of 585, which is absorbed by haemoglobin and oxyhaemoglobin [79, 80]. Mechanism of action is unclear, but may be a result of intense heating of dermal vessels that leads to damage of viral DNA-containing keratinocytes. The theory is based on the presence of dilated and congested vessels at the base of most verruca and the mechanism of selective photothermolysis that results in the targetting of haemoglobin by the PDL [80]. The heat and immunological process and the removal of the blood supply to the wart may be the reason for the effectiveness of PDL in verruca therapy, but it is not above controversy [81]. This selective damage to blood vessels, sparing unnecessary damage to healthy adjacent cellular structure, avoids the scarring [82]. The local dermal vascular destruction of the warts stimulates cell-mediated immune response that is important for eradication of viral warts [83]. So, PDL for wart therapy, even in facial wart, is attractive [84] for its efficient and cosmetic resolution [84, 85]. The PDL is usually painless or minimally painful like snapped by a rubber band [86], though some patients complain of severe

intraoperative pain [87, 88], so local anaesthesia may be required. Purpura may develop due to sudden burst of wart vasculature—that develops within minutes in the treated areas—which takes 10–14 days to subside spontaneously [88]. Even perianal warts in child patients are also treatable with PDL without any complications and with 100% clearance [89]. Verruca plana lesions on face in Asian (type IV-V skin) clear completely with PDL without producing significant pigmentary and textural complications [90]. Safety is one of the major advantages of this technique [91]. But the absence of any proven superiority over the standard treatments in terms of efficacy, coupled with high costs, means that PDL should only be used as second-line therapy in patients with cosmetic needs [91].

Laser protocols are different in all studies, and variation of results may be for that reason. Different protocols include spot size of 5–10 mm, fluence of 5 j/m^2–15 j/m^2, pulse duration of 38 ns–1.5 ms, consecutive 2–3 pulses with overlap of 1–2 mm, 1–12 sessions, interval of 2–4 weeks and cooling methods [90–98]. In immunocompetent children, the overall response rate is 75%, and the remaining 25% had partial clearance, with an average number of treatment for complete clearance to be 3.1—face and perineum are areas most likely to be cleared in one treatment (50 and 20%, respectively) [99, 100]. It is also a more effective therapy especially against those that have not been eradicated by other treatments [101]. Though less, adverse effects are also not very much uncommon, about 8.2% of patients had adverse effects like wound formation (3.8%), residual scarring (2.9%), infection (1.0%) and collapse (0.5%); 63% of patients had excessive pain [97]. But opinion about pain and patient compliance are different in other study [102]. Here only 6.34% of patients classified the method as too painful and withdrew after the first one or two treatments They have concluded that FPDL is safe and effective for the removal or reduction of verrucae vulgares, and requires less patient compliance compared with other treatment options. PDL followed by intralesional Bleomycin gives very good result with complete clearance, even in immunosuppressive patients, though the overall treatment session was high (1.8 vs. 3) [98], but should be aware of common side effects seen such as painful haemorrhagic blistering and superficial ulceration [103].

4.11.5 Potassium titanyl phosphate (KTP) laser

The KTP laser has been utilised in the treatment of recalcitrant cutaneous warts, and when treated to complete clearance, no recurrence occurred [104].

5. Virucidal therapy

5.1 Glutaraldehyde

Glutaraldehyde is a tissue fixative that polymerises keratin. Its effectiveness lies in desiccation of surface virions and resultant reduction of antigenic load [105]. However the mechanism of action of glutaraldehyde against warts has not been clarified precisely. Glutaraldehyde therapy (GA) for warts was first introduced in 1971 [106]. Therapeutic responses with glutaraldehyde in periungual, palmar and plantar warts were 80, 60 and 68.5%, respectively [107]. When GA is buffered by suitable alkalinating agents to a pH of 7.5–8.5, the solution becomes antimicrobially active [108]. The concentration of glutaraldehyde is another consideration for use. Though 2 w/v% is the minimum for antimicrobial activity [108], undiluted high concentration of 25% solution appeared to work faster on warts of all kinds [107]. The benefits of using glutaraldehyde as first-line treatment for warts, especially resistant ones, are the same as those of cryotherapy [107].

5.2 Formaldehyde

Formalin (formaldehyde) is a virucidal agent and has strong disinfectant properties and exerts its effects by causing damage to the upper layers of epidermal cells that contain the virus, thus destroying viruses [28, 109]. Formalin application was effective in 83.3% of patients, but complete disappearance of warts was seen in 11.1% [110]. The most common side effects of formalin include redness, irritation and dryness of skin [111].

5.3 Acyclovir, valacyclovir and other antiretroviral drugs

Oral antivirals are not a regular treatment modality, but isolated case report about improvement in wart lesion after oral treatment with acyclovir [112], valacyclovir are there. Plantar wart is cleared completely with 1 gm valacyclovir for 60 days [113]. Improvements of wart with intravenous cidofovir in one HIV seropositive patient with complete clearance are available [114]. Nearly total clearance of multiple viral wart with didanosine, stavudine and efavirenz triple antiretroviral therapy in a 34-year-old male homosexual patient was seen, accompanied by a significant improvement in immune status [115]. The observations are not powerful enough to assume causality (instead of a simple casual or placebo effect).

6. Antimitotic therapy

6.1 Bleomycin

Bleomycin is a chemotherapeutic agent which has an antitumor, antibacterial and antiviral activity which may be related to its ability to bind with deoxyribonucleic acid (DNA), causing bleomycin strand scission and elimination of pyrimidine and purine bases [116]. It selectively affects squamous cell and reticuloendothelial tissue [117]. Bleomycin is not thought to bind directly to HPV [10]. Bleomycin causes acute tissue necrosis that may stimulate an immune response, as evidenced by the fact that it is less effective as a wart treatment in immunosuppressed renal transplant patients [118–121].

Adverse effects include injection pain and burning, erythema, swelling and pain within 24–72 h after injection before a black thrombotic eschar forms. Local complications after periungual injections are nail loss [122] or dystrophy [123]. Reynaud's phenomenon in treated fingers, local pigmentation [124] or urticaria [122], even flagellate hyperpigmentation [125] are reported after.

In a systemic review [126], comparing intralesional bleomycin with placebo, the studies have given conflicting results. Intralesional bleomycin was compared with saline or sesame oil; duration was 6 weeks to 3 months. The RCTs in the review favour I/L Bleomycin, and only one study opined placebo to be more effective. The result of wart clearance was between 18 and 94%, but the study showed clearance rate to be 94%, which was not significantly different from the result (73%) achieved by placebo injections of saline. Concentration of 0.5% bleomycin is more effective than concentration of 0.25% or 1% bleomycin. Pain was experienced by most patients, irrespective of doses. In a study of comparison between intralesional Bleomycin and cryotherapy, 0.1% concentration of bleomycin was used [127]. Greater efficacy in clearing warts was shown with intralesional bleomycin than in cryotherapy. The clearance rates of warts for intralesional bleomycin therapy found were 97%, and in 94.9% of patients, all warts treated with bleomycin were cleared. There was significantly less number of treatment sessions, with a mean of 1.38 in case of bleomycin treatment than the cryotherapy where the mean is 3.08.

6.2 Podophyllotoxin

Podophyllotoxin is a topical antimitotic that is purified from the plant families Coniferae and Berberidaceae (e.g. species of *Juniperus* and *Podophyllum*) or can be synthesised chemically. It is the active agent of podophyllin resin and is available as a 0.5% solution. Podophyllotoxin binds to microtubules and causes mitotic arrest in the metaphase of cell division [128]. Treatment should be limited to no more than 10 cm^2 of wart tissue, and no more than 0.5 mL/day of solution should be given. This is a patient-applied therapy. Podophyllin is a non-standardised unstable plant extract, derived from may apple (*Podophyllum peltatum Linné*), and contains the active agent podophyllotoxin. American *Podophyllum* contains one fourth the amount of podophyllotoxin than Indian *Podophyllum* does. The potency of podophyllin varies considerably between batches. The exact mechanism of action is unknown. Since it tends to work better on mucosal surfaces, it is used primarily to treat genital warts. Little information is available regarding treatment of non-genital warts with this medication. A single topical application of podophyllin cures less than one third of patients with genital warts [129, 130].

It results in necrosis when applied to anogenital warts. Only a trained medical professional can apply it, and it cannot be dispensed to a patient. CDC guidelines for anogenital warts, recommended regimens for External Anogenital Warts (i.e. penis, groin, scrotum, vulva, perineum, external anus and perianus), includes patient-applied therapy with podofilox (podophyllotoxin) 0.5% solution or gel—using a cotton swab or finger. This podofilox solution (using a cotton swab) or gel (using a finger) should be applied to anogenital warts twice daily for 3 consecutive days, followed by 4 days of drug interval. If necessary, it can be repeated, for up to four cycles. The total treated area should not exceed 10 cm^2, and up to 0.5 ml podofilox should be used per day [131]. If possible initial application should be demonstrated by one healthcare provider for demonstration of proper application and technique and to identify the appropriate warts for treatment. Mild to moderate pain or local irritation might develop after treatment [131].

Podophyllotoxin, the active ingredients of podophyllin, is contraindicated in pregnancy. Though human data not available during application in lactating mother, it is considered as potential toxic. Podophylline, a raw form, is also contraindicated in pregnancy and breastfeeding mother, due to the potential severe myelotoxicity and neurotoxicity in the mother, though no human data available. The American college of Obstetricians and Gynecologists and other sources contraindicated the use of podophyllum agents include the use of podophyllotoxin (podofilox) during pregnancy and in the vagina or cervix at any time [132]. In a randomised comparative study, 60 women with genital warts were treated with either weekly application of 20% podophyllin solution or self-treatment with 0.5% podophyllotoxin cream twice daily for 3 days in weekly intervals. Patients were treated for a maximum of four treatment cycles, and final assessment was carried out after 3 months. Podophyllotoxin cream had a significantly better clearance than podophyllin solution, a primary clearance of was 82% vs 59%. These final clearance decreased to 71% and 48% at the 3-month follow-up, respectively. Total wart clearance was 94% with podophyllotoxin and 74% with podophyllin solution. Podophyllin cream came to as easy to apply and effects significantly better than podophyllin solution. Local side effects were mild to moderate with erythema, and erosion appeared to be higher in the podophyllotoxin group but not so serious to discontinue treatment [133].

7. Immunotherapy

This treatment uses the patient's own immune system to fight the warts. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in general. Because of the cumbersome nature of the conventional procedures and a high risk of recurrence, immunotherapy is becoming more and more popular, especially in the treatment of refractory cutaneous and genital warts. These include various topical, intralesional and systemic agents. There are no well-defined criteria or consensus on when immunotherapy should be tried in a patient with warts. Current indications [134] include the following (**Table 1**).

1. Recalcitrant warts

2. Recurrent warts

3. Extensive warts

4. Difficult-to-treat areas—periungual and palmoplantar sites

7.1 Imiquimod

Imiquimod is a non-nucleoside heterocyclic amine which acts as an immune response modifier that may stimulate cytokines, including interferon-α, interleukin-1, interleukin-6, tumour necrosis factor-α, granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor [135]. In a quantitative systemic review of published randomised control trials, six RCTs were evaluated, and all six studies were conducted in the sitting of home administration

Agents	Indication, dosage and administration
Topical agents	
Imiquimod	For genital and cutaneous warts, 5% cream, 3 times a week, for 16 week
Sinecatechins	For cutaneous warts, 10% ointment 3 times a day for maximum 16 weeks
BCG	For cutaneous and genital warts, applied topically on the warts in normal saline or salicylic acid, washed after 2 hours, weekly treatment for 6 to 12 weeks
Intralesional (IL) agents	
Mw vaccine	For cutaneous warts, 0.1 ml intradermal into 3-5 warts or all warts, followed by 0.1 ml intralesional, 2-4 weekly, maximum 10 sittings
BCG vaccine	For cutaneous and genital warts, 0.1-0.5 ml intralesional injection in largest wart, in 2 weeks interval in 5 sittings.
PPD	For genital warts, 0.1 ml weekly intradermal injection in the forearm for 12 weeks
MMR vaccine	For cutaneous warts, 0.3-0.5 ml into single largest wart fortnightly for up to 5 sittings
Candidial extract	For cutaneous warts, 0.1-0.3 ml injected into the largest wart at first sitting, then 3 weekly intralesional injections
Trichophyton antigen	For cutaneous and genital warts, 0.3 ml injected into largest wart every 3 weeks, maximum of 5 sittings
Tuberculin	For cutaneous warts, 2.5 units into few warts every 2 weekly
Vitamin D3	For cutaneous warts, 0.2 ml of 7.5 mg/ml, Vitamin D intralesional, 2 sittings 4 week apart
Interferon alpha 2B	For genital warts, 1-2 million units 3 days/week (Monday-Wednesday-Friday) for 3 weeks
Systemic	
Zinc	For cutaneous warts, 10mg/kg/day (2.5 mg/kg/day elemental zinc) for 2 months
Cimetidine	For cutaneous warts, 20-40 mg/kg/day for 3-4 months
Levamisole	For cutaneous warts, 2.5-5 mg/kg/day, 2-3 consecutive days every 2 weeks for 4-5 months.
Echinacea	For cutaneous warts, 600 mg single oral dose (single study)
Propolis	For cutaneous warts, 500 mg single oral dose (single study)
HPV vaccines	For cutaneous warts, 0.5 ml intramuscularly, at 0, 2 and 6 months (2 dose or 3 dose regimen) may be followed

Courtesy of Prof Devinder M Thappa and Minu J Chiramel [134].

Table 1.
Various agents used in immunotherapy of warts.

after initial professional examination and advice wart locations are genital, both in males and females. Five of the studies are on immunocompetent patients and one study on HIV-positive patients; 90% of the study population are male. Imiquimod was used as 5% cream in 4 trials and 2% cream in one trial, with complete clearance achieved in 51% in imiquimod group but only 6% patients in placebo group. The number needed to treat (NNT) was 2.2 (95% confidence interval 2.0–2.6). At least 50% reduction in wart area occurred in 72% of patients treated with Imiquimod 5% cream and 20% in placebo treated group. The number needed to treat was 1.9 (1.7–2.2). Warts were completely cured and did not recur in 37% (31% to 43%) of patients treated with imiquimod 5%, and 4% (2% to 6%) of patients treated with placebo. The NNT was 3.0 (2.5 to 3.8). Fewer patients were cured with 1% imiquimod in two trials, and for this concentration the NNT was 9.5 (5.9 to 25). Imiquimod 5% cream was significantly more effective than imiquimod 1% cream for complete wart clearance [136]. Common adverse events were localised itching, erythema, burning and erosion or excoriation, there was rarely any withdrawal from study due to these adverse effects. In HIV infected patients with warts, at least 50% reduction of wart area was seen in 38%, and in placebo it was 14%. Adverse events were similar to non-HIV group [137]. It is found to be effective and safe in children and there are reports of safe use in pregnancy [138, 139]. Disadvantages of using imiquimod 5% cream were the high cost and the length of average treatment (9.5 weeks).

7.2 *Mycobacterium w*

Mycobacterium indicus pranii or *Mycobacterium w* is rapid growing nontubercular mycobacteria, which has been found to induce a strong pro-inflammatory response while injected intralesionally. There is a prominent delayed hypersensitivity response, leading to clearance of warts both at the site of injection and distally [140]. The response varied by 54–93% in cutaneous warts and 89% in genital warts [140–143]. It is administered in two ways—either with an intradermal sensitising dose or without it. In the first method, a sensitising dose of 0.1 ml is administered intradermally in the deltoid region followed by 2–4 weekly intralesional injections in few warts (maximum 0.1 ml in each sitting) for up to 10 sittings. In the latter, the sensitization dose is missed, and direct intralesional injections are started [140, 141]. Mycobacterium *w* vaccine came as equally efficacious in treatment of refractory extragenital warts in comparison with cryotherapy and Imiquimod, 5%,. Mw vaccine has an added advantage of clearance of distant warts and reduction of viral load [144, 145]. The reported side effects include pain, nodularity, ulceration, scarring at the site of injection, flu-like symptoms, fever and lymphadenopathy [143]. Paraesthesia on the limb distal to the site of injection has also been reported [146].

7.3 *Bacillus* Calmette-Guérin vaccine

The delayed hypersensitivity response against the antigen is the key to clinical response against warts, same as that of the Mw vaccine. It increases the serum levels of IL-12 and decreases the level of IL-4 [147]. One to three doses are administered 1 month apart. In cutaneous warts (common, plantar, and plane warts), there was a resolution rate of 39.7% [148]. Topically applied BCG paste (weekly for 6 weeks) has also been found to be effective in children with common warts and plane warts with 65% resolution [149], and usually there are no side effects. However, another report in India showed a high incidence of flu-like symptoms precluding further doses in 57% of patients, making one question its safety in tuberculosis endemic countries like India [150].

7.4 MMR vaccine, *Candida, Trichophyton and tuberculin* antigens

Various types of vaccines and antigens were tried for wart management. Measles, mumps and rubella (MMR) viral vaccine accelerates the clearance of virus and viral infected cells by stimulation of cell-mediated and humoral immunity [151]. In this double-blind RCT, MMR vaccine was tried for three injections in 2-week interval with normal saline as control; 75% of patients had complete clearance, and another 16.6% had more than 50% clearance. There were no side effects, and in 6-month follow-up, there was no relapse [151]. In another study of MMR vaccine, 81.4% of patients had complete clearance; another 10% had partial clearance, in comparison to 27.5% and 15% with saline control [152]. A preliminary, open-label (PPD: purified protein derivative) study to investigate the effectiveness of the tuberculin antigen in the treatment of recalcitrant warts, taking advantage of the vaccination schedule in their country was designed. Three consecutive intralesional tuberculin (5TU PPD RT23-tween 80 solution) injections with 3-week intervals into each target wart, depending on the tuberculin reactivity, were performed. Injections of 0.3, 0.2 and 0.1 mL of antigen were administered to patients with indurations of 5–9, 10–15 and > 15 mm, respectively. Five patients (29.4%) demonstrated complete clearance, five (29.4%) had partial and five (29.4%) minimal response. Some patients showed complete clearance of untreated facial warts also. Patients with initial PPD test site in duration less than 10 mm had no or minimal response [153]. Mumps and *Candida* antigen injection in paediatric age group with recalcitrant warts had 47% complete resolution, and 13% had partial resolution. Injections were given in three weekly intervals, and an average of 3.87 injections was given. Patients with initial high response to skin antigen test shows excellent result [154]. Injection with mumps, *Candida* or *Trichophyton* antigen, alone or in combination, is given in 3-week interval, up to 10 injections. In patients who have completed the study, 50% had complete clearance, and the other 50% had 75–90% clearance. Local erythema and oedema were the only side effects, in 30% of patients. Patients who had complete clearance had clearance also in their distant verruca lesions [155]. *Candida albicans* intralesional immunotherapy in single also came as safe, well tolerated and suitable for multiple warts of hand and fingers, plantar warts and recalcitrant warts, even in non-injected warts [156]. In a randomised, single blinded, placebo-controlled large study of mumps, *Candida* and *Trichophyton* antigen, with or without interferon α 2b, 41% of patients with antigen alone, 57% antigen and interferon and 9% in only interferon had complete clearance in comparison to 19% only in the normal saline group [157]. The combination of mumps, *Candida* and *Trichophyton* also came to be effective as 74% of patients responded to test antigen had complete clearance with significant number also showing resolution of untreated distant warts [158]. Response of other studies with *Candida* antigen varied as 72% [159], 74% [160], 85% [161], 56% [162] and 87% [163], indicating antigen therapy in wart is a good hope for target and distant wart lesions with minimum side effects.

7.5 Interferons

Interferon has been shown to be active against HPV both in vitro and in vivo, to protect murine cells against infection with bovine papillomaviruses and to eliminate extrachromosomal viral DNA from infected cells [164, 165]. In a systematic meta-analysis, the rate of complete response in locally used interferon was 44.4% in comparison to placebo, 16.1%. The complete response rate of systemically used interferon as compared to placebo for treating genital warts had no perceivable discrepancy, for systemically used interferon 27.4% and placebo 26.4%. Both groups

had near same recurrence rate (interferon 21.1% vs. placebo 34.2%, $p > 0.05$). In subgroup analysis, it was noticed that relapse was less in intralesional interferon in comparison to placebo group, but relapse rate were the same in between systemic and placebo groups. Adverse events were mostly mild and transient and could be tolerated [166].

7.6 Zinc

Dietary zinc has profound effects on the human immune system and deficiency leads to reduced immune capacity [167, 168]. It can be given as topical preparation, oral medication or intralesional. Topical preparation as 10% zinc sulphate lotion yields complete clearance in 80% in plane wart [169]; plane warts were seen in 85.7% [170]. Complete clearance noticed in 61% patients after 1 month therapy and 87% after 2 months of therapy with oral zinc sulphate 10 mg/kg/day in a placebo-controlled trial [171]. But it was not the same in other studies, 50% complete clearance with the same dose after 2 months in another open level clinical study [172]. Intralesional 2% zinc sulphate too has been found to induce clearance of warts [173].

7.7 H2 receptor blockers

H2 blockers, such as cimetidine and ranitidine, have been tried in treatment of warts. They block the type 2 histamine receptors on suppressor T cells and augment cell-mediated immunity [174]. It increases the levels of IFNγ and IL-2 and decreases the levels of IL-18 [175]. It has been used in a dose of 20–40 mg/kg/day for 3–4 months with response rate ranging from 30 to 87% [176, 177]. There is no significant difference between cimetidine and placebo [178], and some author proposed a placebo effect for cimetidine [179].

7.8 Levamisole

Levamisole, an antihelminthic agent, is found to have immunomodulatory effects, making it effective in various dermatological disorders including viral warts at a dose of 2.5–5 mg/kg/day for 3 consecutive days every 2 weeks for 4–5 months [180–182]. The response to levamisole was approximately 60%. Side effects are rash, nausea, abdominal cramps, taste alteration, alopecia, arthralgia and a flu-like syndrome and rarely cause myopathy, leukocytoclastic vasculitis, lichenoid eruptions and leukoencephalopathy [183, 184].

7.9 HPV vaccines

Since 2006, two vaccines against Human papillomavirus (HPV) have been licenced in more than 100 countries [185]. Both vaccines target HPV types 16 and 18, which account for about 70% of all cervical cancer cases, and the quadrivalent vaccine also targets HPV types 6 and 11, associated with 90% of genital warts (GWs) [186]. In Denmark, the quadrivalent HPV vaccine was introduced into the children's vaccination programme in January 2009 for 12-year-old girls. In 2014 the European Medicines Agency and the World Health Organisation Strategic Advisory Group of Experts recommended a two-dose schedule for 9–13-year-old girls. However, three-dose schedule offers better protection against genital warts than a two-dose schedule in a nationwide study. But, if the dosing interval extends (about six months), the two dose schedule came as effective as three. The quadrivalent HPV vaccine that comprises the L1 protein of HPV types 6, 11, 16 and 18 has been in use on a large scale

in countries like Denmark with a decline in the prevalence of genital warts [187]. Similar decline in genital warts has been noticed in the UK and Australia [188, 189].

7.10 Autoimplantation therapy

Autowart inoculation by means of homologous autoimplantation helping to induce specific cell-mediated immunity has been proposed as a treatment option for recalcitrant, extensive and genital wart [190]. About 83 patients with all types of wart lesions were included in a study. At 16 weeks of therapy, 69.5% of patients recovered completely, and more than 75% improvement occurred in another 8.5% patients. No significant complication was documented. There was no recurrence within study period [191]. Another study also had noticed 73.3% total clearance of warts, with a majority of them (91%) within 2 months [190]. Inoculation site infection and post-inflammatory hyperpigmentation and hypopigmentation are the side effects.

7.11 Contact sensitizers

Contact sensitizers are a mode of inducing a type IV hypersensitivity reaction, thus making them a form of topical immunotherapy [28]. Diphencyprone (DCP) is the preferred compound. DCP 2% solution is applied after every 10–14 days, on the medial side of upper arm—till there is appearance of local erythema and vesiculation—and this may be repeated up to three times. Warts were then first pared followed by application with stepwise concentration of DCP: 0.01, 0.05, 0.10, 0.25, 0.50, 1.0, 1.5, 2.0, 3.0, 4.0 and 6.0%. Treatments are applied every 1–4 weeks. Resistant palmoplantar warts treated with DCP over 8 years [192] exhibited 88% clearance rate. However, a large percentage of patients developed adverse effects (56%), including painful blistering at the site of sensitization and near warts, pompholyx-like or generalised eczematous eruption, influenza-like symptoms, vesiculation elsewhere due to passive transfer of DCP and inguinal lymphadenopathy. They concluded that patients with recalcitrant palmar, plantar, periungual and digital warts are good candidates for DCP therapy [193].

8. Others

There are various other agents being tried infrequently in the management of warts.

Historic folk remedies have included many variants.

Duct tape occlusion therapy involves placing a piece of duct tape over the wart. The mechanism of action of this technique still remains unknown [194].

Components of garlic (*Allium sativum*) have been shown to have antiviral activity and to inhibit cellular proliferation of virally infected cells, resulting clearance of wart with less recurrence [195].

Application of paste made of baking powder and castor oil is age old technique for warts.

Herbal preparations such as Echinacea and propolis are reported to boost the immunity when administered orally [196], act as immunomodulators and improve warts.

Sinecatechins are derived from green tea extract (*Camellia sinensis*) and are marketed as a 10% ointment, containing around eight catechins. A clearance rate of 46–52% has been noticed in various studies [197].

Glycyrrhizic acid, obtained from the root of *Glycyrrhiza glabra*, has antiviral, anti-inflammatory and antiulcerative properties. When used with an

immunostimulant [198], it was shown to have a slightly better efficacy than podophyllin (87%). The glycyrrhizic acid is a safe and effective treatment for the management of anogenital warts during pregnancy [199].

Intralesional injection of 0.2 ml of 15 mg/kg vitamin D3 led to complete resolution [200] in 19 (82.60%) out of 23 patients with palmoplantar warts and 14 (77.77%) of 18 patients with verruca vulgaris.

9. Conclusion

Numerous varieties of approaches for wart management are there. It is difficult to choose the best wart treatment. It should be determined by type of wart, whether old or new; site; immune status of the patient; pregnancy; the effects and side effects of the wart management procedure; its compliance with patient; and above all the availability of the planned modality of treatment. A rational consideration of all factors can provide an appreciable benefit.

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