



LITERATURE REVIEW

Treatment of Warts in Pediatrics: A Review

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Abstract

Cutaneous warts, or verruca vulgaris, are a viral skin condition caused by the Human Papilloma Virus (HPV) that are very common in children. Many physicians struggle with treatment of warts, due to the resistant nature of the lesions. There are a variety of treatment modalities that are offered. The goal of this paper is to review the different treatments that are beneficial and safe to use for warts in the pediatric population. We will break down the adverse effects, benefits, and efficacy of each of the options.

Introduction

Verruca Vulgaris, also known as common warts, are caused by non-malignant strains of HPV, including: 1, 2, 3, 4, and 57 [1]. They are typically benign lesions that rarely have malignant transformation [2]. On the skin they appear as rough, painless papules that can be gray or flesh colored, and are found on different areas of the body [3]. Other subtypes of HPV that are associated with cervical cancer are not the same strains that cause verruca vulgaris. Warts are commonly seen in the pediatric population and therefore such cases are encountered by family physicians.

Transmission of verruca vulgaris is via direct skin contact, especially in areas of the body that have breaks in the epithelium [2]. Data on the prevalence of warts amongst the pediatric population greatly varies. A National Health survey reported that 0.89% of the population have warts [3]. A school study in Egypt of 1045 students that aged from 6 to 12-years-old found that 10.3% of that population had common warts [4].

There are many different treatment options that have been used over the years to treat pediatric warts. The treatment strategies can be organized into three

groups: physical or chemical destruction, immune modulating agents, and antiproliferation agents. The goal of this review is to examine and assess each of the different treatment options.

Treatments

Destructive methods

Salicylic acid: Salicylic acid is a topical chemical agent that destroys the epithelial layer infected by the wart. It is considered a type of destructive treatment. A systematic review reported a cure of 75% with salicylic acid compared to 48% cure rate placebo after reviewing data from six different studies [5]. It is still considered the only treatment that is approved by the Food and Drug Administration (FDA) [6]. Therefore, salicylic acid is considered a first line treatment. A Cochrane systematic review assessed six studies comparing placebo versus salicylic acid treatment, showing a significant improvement in reduction of warts with the administration of salicylic acid recording a 95% Confidence Interval 1.20 to 2.03 [7]. There were no significantly harmful side effects reported except minor skin irritation [7]. Another study found that it was beneficial to file the wart down alongside the treatment with salicylic acid [8]. Salicylic acid may be a favorable option for children due to the lack of significant side effects. However, reported duration of treatment with salicylic acid is approximately 3 to 6 months until clearance of warts, making this option a relatively lengthy treatment course [6].

Cryotherapy: Cryotherapy is another type of destructive wart treatment. This technique includes “freezing” a wart with liquid nitrogen for 20-30 seconds with treatments repeated every 3 to 4 weeks until resolution [6]. A systematic analysis examined 3 trials that showed

no significant difference between receiving cryotherapy for warts for 2, 3, or 4 weeks [7]. It has been reported that increased time in freezing cycles may overall benefit children as it would decrease the total amount of office visits [8]. However, increased freezing time may cause greater discomfort to the patient, which may be especially distressing in a child. One large trial analyzed by the Cochrane review revealed no significant increase in cure rate for 3 weeks of treatment versus 3 months of treatment for adults or children with warts on the hands or feet.

A Cochrane review found that more aggressive treatments increase incidence of adverse effects including skin blistering and pain [7]. However, the amount of time qualifying an aggressive treatment varies among physicians due to differences in practices. Another side effect with cryotherapy is hypopigmentation after healing of the lesion has occurred. Ultimately, this treatment is beneficial due to ease of accessibility, though recommendations for the aggression of treatment should be up to the discretion of the physician and pain tolerance of the child.

Surgery: Three types of surgical interventions for removal of warts include excisional, electrosurgery, and curettage. For immediate results, surgery is a favorable option. However, there may be associated difficulties in treatment that are accentuated in the pediatric population, such as pain or fear of needles upon injection of lidocaine to locally anesthetize the area. According to a systematic review, there is scarring, pain and a high recurrence rate of warts after surgery, making it a less common treatment for warts [7].

Cantharidin: Cantharidin is also known as “beetle juice” as it is derived from secretions of blister beetles of the family Meloidae. This substance causes destruction of epithelial cells by generating a blister formation around the affected area [9]. The concentration dose used for the skin is 0.07% to 1%. Cantharidin liquid is applied to warts and remains covered for 24 hours [6]. This process can be repeated for 1-3 weeks until the wart resolves [9]. There have been no randomized control trials to test the efficacy of cantharidin on non-genital warts [7]. Adverse effects may include hyperpigmentation, erythema, scarring, pain, and itching [6].

One similar type of solution that was tested with less severe side effects includes a combination of cantharidin 1%, podophyllin 2%, and salicylic acid 30%. This topical solution is termed CPSI. A retrospective study examined the CPSI treatment in a population of 83 adults and 52 children. They estimated the recurrence rate of 10.6% for treated warts in children [10]. The most common adverse effects were burning sensation, blistering, and pain, but no other serious effects were noted [10]. If available, both CPSI and Cantharidin are favorable treatment options in the pediatric population due to ease of application and limited adverse effects.

Duct tape: Duct tape is an all-purpose adhesive with a variety of household uses. It serves as a convenient and cheap alternative that patients are able to attempt at home [11]. The wart is covered by the duct tape for 6 days then gently scraped. This cycle is repeated until the wart resolves [6]. One study analyzed the efficacy of wart treatment amongst 121 primary school children at 0, 2, 4, and 6 weeks. In a six-week study there was no difference between the placebo group and the duct tape group. The difficulties of the duct tape treatment method tend to be the tape’s lack of adhesiveness and erythematous reactions at the tape site in some children [11].

Photodynamic therapy (PDT): Photodynamic therapy uses a wavelength of light that exogenously targets the tissue by stimulating photosensitive agents, such as 5-aminolevulinic acid to create oxidative stress on the cells, causing destruction [9]. A Cochrane review analyzed two random control trials that used PDT [7]. The first study examined PDT vs. cryotherapy and found clearance rates up to 73% and 20%, respectively [7]. The second study analyzed active 5-ALA-PDT vs. PDT-placebo in 45 adults. The results yielded clearance rates of 56% with active treatment and 42% with placebo, which was statistically significant [7]. Adverse reactions include local erythema, burning, and pain [6].

A separate study of 72 pediatric and adult subjects compared the use of 5-ALA PDT in conjunction with superficial shaving vs. cryotherapy treatment on plantar warts [12]. In the first group, the patients’ warts were shaved with a razor prior to photosensitizer application and PDT. Superficial shaving with PDT was found to require less treatment and have higher cure rates than cryotherapy for recalcitrant plantar warts, which was statistically significant [12]. Patients reported less pain with the superficial shaving PDT than cryotherapy. Although adverse effects of burning and erythema may be unwanted in the pediatric population, this presents as a timely alternative for children with plantar warts.

CO₂ lasers: CO₂ lasers function by emitting an infrared wavelength to thermally destroy tissue in a focused or defocused beam [9]. A JAMA review examined cohort studies that reported success rates varying between 50%-100% for common, palmar, plantar, periungual, and subungual warts [13]. In most cases 1 or 2 treatment sessions were needed to achieve remission [13]. Side effects included scarring, hypopigmentation, postoperative pain, and prolonged wound healing, which was accentuated in immune compromised patients [13]. Due to the adverse effects, CO₂ lasers present as a painful and extensive treatment option for children with significant recovery time.

Er:YAG lasers: Er:YAG lasers are 10 times more selective for water than CO₂ lasers, therefore minimizing the thermal damage causing the severe side effects associated with CO₂ lasers. The goal of the Er:YAG laser

is to ablate the infected epidermis until normal tissue is revealed [13]. A JAMA review article examined 4 prospective studies that investigated the efficacy of Er:YAG lasers in treatment of warts. One study reported a 72% response rate after 1 treatment but a relapse rate of 24% in plantar warts [13]. Another study of 58 patients with plantar warts treated at higher fluence and followed by LED found all lesions to have healed with only a 6% recurrence rate [13]. Adverse effects included discomfort, while infection or pigment changes were not noted [13]. The benefit of greater tissue selectivity to decrease severe side effects may make Er:YAG lasers a preferred destructive option in the pediatric population.

Pulsed dye lasers: Pulsed Dyed Lasers (PDL) emit a pulse dyed wavelength of 585 to 595 nm. PDL targets destruction of capillaries, which cuts off the blood supply to the affected tissue [13]. Additionally, heat emitted from the laser helps destroy HPV itself [13]. A systematic review of PDL-treated warts showed remission rates ranging from 40%-100% [13]. One study measured the amount of treatments, ranging from 1.3 to 6.3 with an interval from 1 to 8 weeks [13]. Two large studies were analyzed by a JAMA review, with the first study reporting a 49.5% clearance for simple and recalcitrant flat, periungual, plantar, and common warts [13]. Three recent random control trails that compared PDL to conventional therapy were also reviewed and concluded that PDL was not more effective [13]. Adverse effects included petechiae, purpura, and crusting [6]. As there is currently no standardized protocol for PDL, its use in pediatrics is not firmly established.

Thermotherapy: Thermotherapy can be applied in numerous ways, including hot water pads, ultrasound, and lasers. Hyperthermia is hypothesized to increase the apoptosis in infected apoptotic keratinocytes [14]. Previous studies have shown clearance rates at 40 °C to 45 °C [14]. One randomized study compared the efficacy of cryotherapy and thermotherapy in 52 students, using an electrode that came into direct contact with the wart. Clearance rates were 79.2% in the thermotherapy group and the 58.3% in the cryotherapy group, however this was not statistically significant [14]. Adverse effects included burning sensation, blister formation, and subsequent hyperpigmentation [14]. There are limited studies on the efficacy of thermotherapy. A cost-effective and convenient thermotherapy modality for pediatrics may be placing a 45 °C to 48 C cloth to affected areas [9].

Formaldehyde: Formaldehyde is a viricidal agent that is applied as a topical 0.7% gel or 3% to 10% solution onto the wart [6]. In a recent controlled study of 57 patients, formaldehyde was used to treat verruca plantaris. The overall cure rate was 65.4% in the treatment group however it was not statistically significant [15]. This agent is an allergen and may cause contact dermatitis [6]. It should be used with caution in patients with atopic dermatitis or a history of skin sensitivities.

Retinoids: Both topical and oral retinoids can be employed to treat warts via inhibition of HPV replication. Acitretin is a systemic retinoid that can be used [16]. While its use for warts was only studied in adults, acitretin is prescribed in the adolescent population to treat acne. Recommendations in children have not been specifically studied [16].

Tretinoin is topical retinoid that has been used for wart treatment [17]. A case-controlled study examined 50 pediatric patients and found 86% clearance of warts when compared to placebo, which was statistically significant. Only one patient reported erythema and skin irritation [17]. Topical retinoids provide an easy and safe option for the pediatric population.

Trichloroacetic acid: Common warts may occur in the oral cavity and can be managed with trichloroacetic Acid (TCA), which breaks down infected tissue through chemical destruction. TCA is most commonly used in gynecological wart management. Recently, a prospective cohort study analyzed the use of TCA for oral mucosal lesions [18]. Out of the 20 patients analyzed 30% were children and 70% were adults, and 80% of lesions resolved over 15 days to 4 months [18]. Adverse effects associated with TCA are irritation, peeling, and pain [19].

Immunotherapy

Contact allergens: The two types of contact allergen therapy used for treatment of refractory warts are diphenylcyclopropenone (DPCP) and Squaric Acid Dibutylester (SADBE). These agents induce a type IV hypersensitivity reaction, so treatments require initial sensitization [8]. Treatment should be used with caution in patients that have allergic contact dermatitis [7].

In the pediatric population, DPCP 1% is applied to the wart and kept covered for 8 hours repeatedly for 1 to 4 weeks [6]. A retrospective study analyzed 27 patients with a mean age of 10.7 to determine efficacy of DPCP with periungual warts. The study found an 85% success rate and significant resolution in patients that underwent less than 6 months of treatment [20]. Of note, DPCP is more stable in solution and less expensive than SADBE [8].

A pediatric review examined SADBE in treating warts by analyzing two different case series. The first case series included 29 pediatric patients and found a resolution rate of 69%. The second case series included 188 mostly pediatric patients and reported a resolution rate of 84% [8]. Possible adverse reactions of such agents are urticaria and skin eruptions, but show success in resolution of warts [20].

Cimetidine: Both oral cimetidine and ranitidine are Histamine-2 blockers on suppressor T cells and increase lymphocytic proliferation and the inflammatory response to phagocytose virally infected tissue [21]. There are varying reports of efficacy for treatment of warts with

cimetidine ranging from 30% to 80% [21]. The adverse effects of cimetidine, include, nausea, vomiting, dizziness, and headaches [21]. In a recent study, cimetidine was examined in 8 pediatric heart transplant patients. The results revealed 6 out of 7 children with verruca vulgaris had complete resolution in six months without any serious side effects, except one child who developed gynecomastia [22]. A 2007 systematic review found no significance in the efficacy of H2 antagonists and determined that large scale studies need to be developed to analyze H2 antagonist effect on wart treatment [23].

Imiquimod: Topical 5% imiquimod increases anti-tumor and anti-viral effects by increasing specific cytokines that modulate the immune response [21]. A Cochrane review analyzed two random control trials that found 10% to 12.8% clearance of common warts [7]. Another study analyzed imiquimod in combination with duct tape vs. duct tape and petroleum and found 40% of patients had complete resolution with active treatment vs. 0% clearance with duct tape and petroleum [24]. Adverse effects include burning sensation, pain, erythema, and vitiligo-like depigmentation [21]. Imiquimod may be an effective treatment in the compliant pediatric population.

Interferon: Interferons (IFN) are small natural proteins that increase antiviral and antiproliferative effects of infected cells. Intralesional IFN-alpha is used for treatment of warts. A systematic review of intralesional IFN-alpha application did not show any significant results in wart clearance compared to placebo [7]. There are reports of high dose IFN-alpha causing flu-like symptoms, and local pain from injection in high and low doses. Other reported adverse effects include elevations in white blood cell, hematocrit, and aminotransferase levels [7].

Intralesional antigen: Three types of intralesional antigens used for wart treatment are candida, mumps, and trichophyton. These are injected into the wart to help provoke an intracellular immune response [21]. A blinded, randomized control trial found no difference in wart clearance in patients treated with candida, mumps, or trichophyton [25]. However, when compared with patients injected with IFN-alpha or saline, there was a greater response in patients injected with antigen [25]. Adverse effects included fever, myalgias, and edema and erythema at the injection site [25]. Further studies need to be completed to establish efficacy in the pediatric population.

Bacillus Calmette-Guerin (BCG) vaccine: The use of intradermal BCG vaccine elicits a delayed Type IV hypersensitivity response, which attracts T cells to attack HPV in infected cells [25]. One study analyzed the efficacy of the BCG vaccine in 40 adults with recurrent warts and reported 73.56% clearance of lesions. Adverse effects included pain and erythema from injection, itching, and flu-like symptoms [26].

BCG can also be applied in a topical form. One study analyzing the topical treatment of BCG in 80 children discovered 65% complete resolution in children with common warts [27]. No side effects were reported and it was determined to be safe and effective for children [27]. Topical BCG may be a preferred option over intralesional BCG.

Zinc oxide: Zinc allows for regulation of the immune response by increasing phagocytosis and interaction between viral components and host cells [28]. One study examined the efficacy of topical 15% zinc oxide in 16 adult patients with common warts and found reduction in volume by 62.5% in the zinc group and 5% in the placebo, but the findings were not statistically significant. There were no side effects reported [28]. Another study of 12 pediatric subjects used nitric zinc complex solution to treat periungual warts, palmar warts, and plantar warts and found 83.9% clearance. Some patients experienced mild burning sensation and pain [29]. This presents as an easily accessible and safe option for the pediatric population.

Anti-Mitotic agents

Intralesional bleomycin: Bleomycin is a chemotherapeutic agent used to treat localized warts with minimal systemic absorption [30]. The efficacy of bleomycin has been widely disputed due to few randomized control trials. A Cochrane review of seven trials reported different efficacies. Four of the trials reported the treatment as ineffective while others reported efficacies of 18%, 42%, and 45% [7]. The injection itself can be painful and other side effects include erythema, edema, ulceration, hematic crust formation, and eschars [30]. This treatment option has not been heavily studied in children and is not recommended due to excessive pain with injection.

5-Fluorouracil: 5-Fluorouracil (5-FU) inhibits DNA and RNA synthesis, which decreases the number of replicating virally-infected cells in warts. In an open-label pediatric study, the clearance rate of topical 5% 5-FU in treatment of common warts was reported at 87% after 6 months [31]. Side effects included erythema, hyperpigmentation, and erosion [31]. This provides an effective treatment option for the pediatric population, with lack of reported pain. However, in some rare cases topical 5-FU has shown systemic absorption, leading to inflammatory colitis and Steven Johnson's syndrome [31].

In a Cochrane review, seven randomized control studies of 5-FU were analyzed. Three trials that analyzed topical 5-FU compared to placebo reported cure rates of 50%. A more recent study reported statistically insignificant cure rates [7]. Adverse effects in the studies included onycholysis in patients with periungual warts, blistering and local skin irritation [7].

Other methods

Wait and see method: There are many reports of

warts that clear spontaneously over time. In a prospective cohort study this hypothesis was tested in 1,134 primary school children ages 4-12 years of age [32]. Complete resolution was found in 52% within 11 to 18 months for patients with common and plantar warts [33]. While this method avoids adverse effects, it requires an extended amount of time until complete regression.

Conclusion

Salicylic acid is the only approved treatment by the FDA and is therefore the standardized first line treatment for warts [7]. For pediatric patients, topical alternatives are generally better tolerated and there for favored over injected treatments due to decreased pain. The efficacy and safety of many treatments discussed have not been thoroughly established and require larger randomized trials to determine statistically significant results.

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