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Intralesional Treatment of Plantar Warts

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Abstract

Objectives: This purpose of this review is to assess the safety and effectiveness of intralesional treatments for plantar warts, including immunotherapies and drugs that modulate the immune system or have anti-viral properties. Background: The lack of a therapy that works for everyone makes plantar wart maintenance difficult. Emerging as a viable option, intralesional treatments provide distinct benefits when dealing with many or resistant lesions. In order to cure plantar warts caused by the human papillomavirus, this review delves into the various intralesional medicines and how they work (HPV). Locations of the Data Sets: Research on intralesional therapies for plantar warts up to the year 2023 was scoured via a variety of Medline databases, including PubMed. Research on the effectiveness, side effects, and action mechanisms of various intralesional medicines that met certain inclusion criteria were taken into consideration for this review. To be considered for inclusion in the study, research had to be written and published in English, undergo peer review, and give light on the processes and effectiveness of intralesional therapies for plantar warts. A comprehensive examination of the study's quality, including its ethical clearance, eligibility requirements, controls, and outcome assessment tools, was required for data extraction. Conclusions: There is a wide range of intralesional therapies available for plantar warts, each with its own set of advantages and disadvantages in terms of safety and effectiveness. This study provides an overview of the current state of knowledge about the treatment of plantar warts caused by HPV, including the methods and results of immunotherapies, mycobacterial agents, Candida antigen, and other intralesional agents.

Key words: Topics covered include plantar warts, intralesional injections, mycobacteria, candida, and HPV (HPV).

1. Introduction

Warts are harmless tumours that may be infected with the human papillomavirus (HPV) by close personal contact or occupational exposure. There are several different kinds of these growths, the most common of which being plantar and common warts. Plantar warts, which may be caused by either endophytic or exophytic developments and are often seen in regions of the foot that bear weight, are associated with HPV types 1, 2, and 4. The goals of treatment for these growths include reducing their visual impact, slowing their rate of growth, easing any pain they may cause, and easing any functional restrictions they may impose [1].

Since there isn't a single medication that works for everyone, dealing with warts is no easy feat. The success rates of various therapies, including intralesional immunotherapy, laser interventions, systemic treatments like acitretin, and classic damaging approaches like cryotherapy, vary among different groups. Because of their nondestructive properties, simplicity of administration, and promising outcomes in treating warts, immunotherapies are becoming more popular, whether used topically or systemically [2].

The purpose of this review is to assess the safety and effectiveness of intralesional treatments for plantar warts, including immunotherapies and drugs that modulate the immune system or have anti-viral properties.

2.Materials and Methods

Data Sources: A A systematic literature search was carried out, using Medline databases, to investigate intralesional therapies for plantar warts up to 2023. (including PubMed and Medscape).

Research Prioritization: Strict and open standards were upheld throughout the selection process. Research that fulfilled these criteria were considered for inclusion Described the connection between several intralesional agents and their impact on plantar warts caused by the human papillomavirus; published in peer-reviewed publications; written in English; (HPV).

Data Extraction: Research that did not fulfil the requirements for inclusion was not considered. Taking into account ethical approvals, eligibility requirements, control groups, thorough information, and clearly specified assessment tools, the quality of every research was painstakingly examined. Through the use of a standardised data collecting form, pertinent information pertinent to the review's aims was methodically extracted from all eligible studies.

Wart treatment with intralesional approach

If a patient is dealing with many or resistant warts, intralesional injections may be the best alternative for treatment. Traditional treatments, such as salicylic acid or cryotherapy, are effective, but they might be difficult to implement because to their long duration and need for repeated administrations. Contrarily, intralesional injections not only work as well as conventional therapies, but they also have the remarkable capacity to cause distant warts to regress, meaning that their effects go beyond only the injection site. Offering a compelling option within the range of wart care techniques, this strategy shows promise for patients with stubborn

warts or those looking for a more efficient and maybe more extensive resolution procedure [3].

****Agents that may modulate the immune system inside the lesion:**

Vaccine against measles, mumps, and rubella (MMR):

A potential method for treating cutaneous warts is intralesional immunotherapy with the measles, mumps, and rubella (MMR) vaccination. This approach has several benefits, including the elimination of scars, a decreased likelihood of recurrence, and an exceptionally good safety record. With an average of 2.4 injections and a mean duration of 7.2 weeks to achieve clearance, a 46.5 percent complete clearance rate was demonstrated in an open-label study involving 100 patients. The injections were of 0.3 ml of the MMR vaccine into the largest wart every three weeks for up to three treatments. Despite just injecting the vaccine into the biggest wart, an astounding 82% of individuals with several warts had remote warts cleared up. Adverse effects were mostly modest, albeit some individuals did experience injection site discomfort (53.5%), erythema (8.1%), and post-inflammatory hyperpigmentation (5.6%) [4].

The effectiveness of the MMR vaccination in wart control was further supported by another trial that included 70 individuals with numerous extragenital warts. Half of the patients saw full remission and one-third achieved partial resolution after receiving 0.3 ml of the vaccine into the biggest wart every two weeks for a maximum of five sessions. Remarkably, full eradication was achieved by 75% of patients with remote warts. The vaccination did have some noticeable side effects, such injection site discomfort (100 percent) and minor flu-like symptoms (12.3%), but most of them went away within a day or two with non-steroidal anti-inflammatory medicines, so they were tolerable [5].

The mycobacterium W vaccine (MWV), Bacillus Calmette-Guerin (BCG), and purified protein derivative (PPD) are mycobacterial medicines that have been used as intralesional treatments for warts [3].

The Mycobacterium W vaccine, or MWV,

A delayed hypersensitive reaction is caused by a robust pro-inflammatory response induced by intralesional administration of Mycobacterium indicus pranii, also known as the Mycobacterium W vaccine (MWV). This response involves increased production of IL-2, IL-4, IL-6, and IFN-gamma, as well as the activation of T helper 1 cells, natural killer cells, and cytotoxic T cells. Warts are eliminated both locally and systemically as a result of this reaction. Fever, pain, sterile pustules at injection site, and paresthesia in far-off limbs are some of the side effects that have been recorded [6]. Clearance rates varied between 54.5% and 93.3% in studies conducted by Singh et al. (2014) and Garg and Baveja (2014), whereas adverse effects included headache, myalgias, fever, and local responses [7,8]. Despite the vaccine's effectiveness and a small number of modest, locally felt side effects, Meena et al. (2013) found that 83% of warts were completely gone after treatment. A small number of patients did, however, have painful papules and scars similar to those from the BCG vaccination [9].

(B) Purified protein derivative (PPD): Intralesional immunotherapy with PPD tuberculin antigen successfully controls infection and prevents wart recurrence via a cell-mediated immune response. Sixty percent of the 40 patients in the research by Abd-Elazeim et al. (2014) who used PPD to treat target lesions exhibited full resolution, whereas the control group did not. A small percentage of both the PPD group (15%) and the control group (10%) showed partial responses. One other thing to note is that the recurrence rates were lower in the group that had PPD treatment. Out of the three patients in the control group, only two experienced recurrence [10]. Mild localised adverse effects such as erythema, edoema, low-grade fever, body pains, and eczematous lesions at the injection site were reported in a research conducted by Saoji et al. (2016). The study included 55 patients and had a 76% full clearance rate. These results demonstrate that PPD is a successful and safe therapy for cutaneous warts, with low recurrence rates and modest temporary adverse effects [11].

(C) Bacillus Calmette-Guerine (BCG):

The MwV and BCG vaccines are based on similar processes. A therapeutic response against warts requires a delayed hypersensitivity reaction to the antigen. There is an increase in IL12 levels and a decrease in serum IL4. Over the course of a month, you will be administered one to three doses. A full clearance was seen in two instances with resistant genital condyloma acuminate after injecting 0.4-0.5 cc of BCG. After three or five doses of 0.1 ml BCG, Kumar and Das (2014) observed that stubborn warts were completely cleared, and there was no recurrence at six months. The injection site could become red and painful as a side effect [12].

A cost-effective and promising method for treating cutaneous warts is intralesional immunotherapy using Candida albicans antigen. It has a low recurrence rate and is very safe. In a study conducted by Nofal et al. (2017), 68% of patients reported that their injected warts were completely gone, while a total response rate of 71% in paediatric patients was found. Munoz Garza et al. (2015) also found positive results in their patients. The correlation between the therapy's effectiveness and IFNγ levels is suggestive of a mediating function for treatment response, as patients who had a positive response to treatment had greater levels of IFNγ [13,14]. Additional research by Vlahovic et al. (2015) and Kim et al. (2010) found that 65-82% of patients who had repeated injections of Candida were able to achieve wart clearance, even in those

with impaired immune systems or HIV. Candida antigen injections are a safe and well-tolerated therapy option for many patient groups, despite a few mild side effects such injection site soreness or halo nevi [15,16].

Candida antigen intralesional injections are an easy and convenient way to treat warts. They are known to have long-lasting effects, leave little scarring, and have a low recurrence rate. Nofal et al. (2017) [13] stated that the treatment targets HPV infection by activating cytotoxic and NK cells, which are part of an immune response that includes Th1 cytokines like TNF-α. Notably, Alikhan et al. (2016) demonstrated that the treatment was effective in immunosuppressed patients; a large percentage of patients had full or partial responses, indicating that it might work even in those with impaired immunity. The majority of patients had moderate injection-site discomfort or irritation, and a small number of cases of more noticeable side effects, such as halo nevi and vitiligo, were described, confirming the generally favourable safety profile of Candida antigen treatment [17].

The intralesional antigen was prepared from the gram-positive anaerobic bacteria Propium bacterium parvum (PBP), which was studied by Nasser (2012). The antigen triggers the release of interferon and tumour necrosis factor, which in turn activate the immune system and natural killer cells. Ten participants were given 0.1 ml injections of PBP and ten were given a placebo; a total of twenty patients were participated in the study. Three to five treatments were administered at one-month intervals. In contrast to the placebo group, which exhibited no reaction in 90% of cases and a decrease in size in 10% of cases, the PBP group had a complete response in 90% of patients and a partial response in 10% of patients [18].

**** Intralesional agents with anti-viral activity were demonestrated in Table (1)**

Table (1)An overview of the different intralesional agents used for treating warts [19]:

Intralesional Agents	Treatment Approach	Efficacy and Findings	Adverse Effects
Cidofovir	Anti-viral	Effective for HPV; 98.5% resolution in refractory warts; well-tolerated	Local irritation, pain at injection site
Bleomycin	Anti-mitotic	46–86% complete resolution; pain, erythema, transient induration; severe reactions in rare cases	Hyperpigmentation, pulmonary toxicity (rare)
Pingyangmycin	Anti-tumor antibiotic	87.88% complete response	-------
Vincristine	Vina alkaloid antiblastic	Reduction in lesion size; pain at injection site	-------
Vitamin D	Immune stimulation	80–90% complete resolution; partial response in some cases	-------
5-Aminolevulinic Acid	Adjunct to photodynamic therapy	Good response in half the patients; no adverse reactions	-------
Interferon alpha	Antiproliferative, antiviral	35–39% complete response; mild side effects: pain, headache, flu-like symptoms	-------

Combined digoxin and furosemide (ionic contraviral therapy):

The The cellular ion cotransporters Na+/K+-ATPase and Na-K-Cl are bound by cardiac glycoside digoxin and loop diuretic furosemide, respectively, to decrease K+ inflow. The therapy of HPV-induced illnesses, such cutaneous warts, might benefit from these two drugs [20].

The main use of digoxin is to treat atrial fibrillation and flutter with a quick ventricular response. However, it is no longer recommended for heart failure patients because of the increased risk of death it may cause. It works by lowering heart rate and prolonging the phases of cardiac action potentials by blocking sodium potassium adenosine triphosphatase, an enzyme that increases intracellular calcium. It is important to exercise caution when administering this medication to older adults or those with impaired kidney function because of its narrow therapeutic index and the frequent adverse reactions it causes, including breast enlargement, nausea, loss of appetite, disorientation, and irregular heartbeat (at high doses). It is unclear if it is safe to use it during pregnancy [21].

Loop diuretics like furosemide (Lasix) are essential in treating hypertension, congestive heart failure, and other edematous conditions. Furosemide works by blocking the luminal Na-K-2Cl symporter in the thick ascending limb of the loop of Henle, which significantly reduces sodium chloride without influencing carbonic anhydrase or aldosterone. Its diuretic activity is useful in treating a wide range of medical problems, including severe hypercalcemia and hepatic cirrhosis. There are concerns regarding its ototoxicity [22], particularly with high doses or fast infusion, and long-term use might cause low

potassium levels, hyperglycemia, and even gout. Excessive usage can also lead to substantial hypomagnesemia from impaired magnesium and calcium reabsorption.

As controversial as furosemide is due to its ototoxicity and other possible side effects, it is crucial in treating edematous conditions brought on by heart failure, hepatic cirrhosis, and severe hypercalcemia. Its significant importance in primary healthcare systems is further underscored by its placement on the essential medicines list of the World Health Organization. The fact that it has a wide range of medicinal uses despite possible side effects including low potassium levels and hyperuricemia is evidence of its versatility; it is effective against more than simply hypertension and heart failure. It plays an important role in controlling fluid retention due to its action mechanism, which involves blocking salt and chloride reabsorption in the loop of Henle [23].

Ionic contraviral therapy (ICVT), which combines digoxin and furosemide, has shown encouraging outcomes in the treatment of cutaneous warts. Their combined inhibitory impact on DNA replication was emphasised by Hartley et al., who also indicated that they were effective when applied locally. Research conducted by van der Kolk et al. on healthy individuals afflicted with common warts confirmed the effectiveness and safety of ICVT after topical treatment, revealing a significant diminution in wart size. But there were clear disparities in how common and plantar warts responded; the latter showed more treatment resistance, most likely because callus growth reduced drug permeability [24]. Wart size reduction may occur first, as a result of drug reservoir development in the hyperkeratotic layer, after the therapy's influence on the HPV life cycle reduces HPV load. Like imiquimod's effect in psoriasis therapy, digoxin's recognised effect on the immune response may lead to distant clearance. In their evaluation, Rijsbergen et al. [25] confirmed the feasibility of ICVT as a therapy for cutaneous warts, particularly common warts treated with a combination of digoxin and furosemide.

A multi-purpose medicine, methotrexate is prescribed for a broad range of medical issues, including cancer and inflammatory illnesses. It suppresses inflammation and cell division by preventing DNA synthesis in cells that divide quickly. The most effective and well-tolerated method of administering methotrexate is subcutaneously, while oral administration is also a frequent choice. Psoriasis, lupus, inflammatory bowel disease, and cancer are just a few of the many inflammatory diseases and disorders that may benefit from its medicinal use. Intralesional therapy with it has been investigated for the treatment of viral and plantar warts, but it has not proven as effective as other options in these instances. Adverse effects such as pancytopenia and hepatitis, especially in individuals with renal problems, need thorough pre-treatment assessments of liver and renal function, despite the fact that most side effects are minimal, such as temporary injection discomfort [26]. Table-2

Table (2) Methotrexate, its mechanisms, administration methods, medical applications, intralesional use for warts, and associated side effects [27].

Aspect	
Mechanism of Action	Methotrexate inhibits DNA synthesis in rapidly dividing cells by blocking tetrahydrofolate synthesis, suppressing inflammation, and preventing cell division. Intralesional therapy concentrates drug locally, reducing systemic effects.
Pharmacokinetics	Administered orally (weekly, escalating dose up to 20–30 mg) or subcutaneously, with greater efficacy and tolerability in the latter. Bioavailability varies but SC administration shows higher bioavailability than oral intake.
Medical Uses	Predominantly used in various cancers and numerous inflammatory conditions, including psoriasis, lupus, inflammatory bowel disease, vasculitis, and connective tissue diseases.
Intralesional Use	Investigated for viral warts but showed limited efficacy in trials. Trials on plantar warts showed it to be less effective than alternative treatments like electrocautery, leading to fewer responses.
Side Effects	Mostly minor, transient injection pain; rare but serious side effects include pancytopenia, mucositis, and hepatitis, especially in patients with renal dysfunction. Recommended pre-treatment checks for blood cell counts, liver, and renal function.

3.Recommendations and future prospectives:

Additional research and better clinical techniques show great potential in treating plantar warts with intralesional procedures. Thorough comparison studies comparing the effectiveness and safety profiles of different intralesional treatments should be the focus of future research. To improve treatment results and tackle stubborn cases, researchers are investigating the possibility of synergistic effects that might be revealed by investigating sequential techniques or combination medicines. Longitudinal studies monitoring

recurrence rates and sustained clearance, among other long-term consequences, might provide light on how long intralesional therapies last. In addition, developing a comprehensive knowledge of the immune responses caused by various intralesional medicines might lead to more targeted treatments that are specific to each patient's profile, resulting in better results with fewer side effects.

4.Conclusions

Intralesional The range of choices for treating plantar warts is wide, with a wide range of effectiveness rates and safety profiles. This study provides an overview of the current state of knowledge about the treatment of plantar warts caused by HPV, including the methods and results of immunotherapies, mycobacterial agents, Candida antigen, and other intralesional agents. In order to develop tailored and efficient management plans, it is essential to understand the treatment's safety and effectiveness profiles.

References

[1] 1. D.J. Witchey, N.B. Witchey, M.M. Roth-Kauffman, M.K. Kauffman. Plantar Warts: Epidemiology, Pathophysiology, and Clinical Management. J Am Osteopath Assoc;118:92-105. 2018

[2] 2. A.S. Aldahan, S. Mlacker, V.V. Shah, P. Kamath, M. Alsaidan, S. Samarkandy, et al. Efficacy of intralesional immunotherapy for the treatment of warts: A review of the literature. Dermatol Ther;29:197-207. 2016

[3] 3. T. van der Kolk, M.R. Dillingh, R. Rijneveld, E.S. Klaassen, M.N.C. de Koning, S.T.P. Kouwenhoven, et al. Topical ionic contra-viral therapy comprised of digoxin and furosemide as a potential novel treatment approach for common warts. J Eur Acad Dermatol Venereol;31:2088-90. 2017

[4] 4. Y. Bedoui, X. Guillot, J. Sélambarom, P. Guiraud, C. Giry, M.C. Jaffar-Bandjee, et al. Methotrexate an Old Drug with New Tricks. Int J Mol Sci;20. 2019

[5] 5. M.E. Muse, K.M. Stiff, K.R. Glines, A. Cline, S.R. Feldman. A review of intralesional wart therapy. Dermatol Online J;26. 2020

[6] 6. P. Saini, A. Mittal, L.K. Gupta, A.K. Khare, S. Mehta. Intralesional mumps, measles and rubella vaccine in the treatment of cutaneous warts. Indian J Dermatol Venereol Leprol;82:343-5. 2016

[7] 7. A.S. Surani, R. Un, Y. Marfatia. Efficacy of Intralesional Measles Mumps Rubella Vaccine in the Treatment of Verruca Vulgaris: An Interventional Study. Cureus;15:e34338. 2023

[8] 8. D.M. Thappa, M.J. Chiramel. Evolving role of immunotherapy in the treatment of refractory warts. Indian Dermatol Online J;7:364-70. 2016

[9] 9. S. Singh, K. Chouhan, S. Gupta. Intralesional immunotherapy with killed Mycobacterium indicus pranii vaccine for the treatment of extensive cutaneous warts. Indian J Dermatol Venereol Leprol;80:509-14. 2014

[10] 10. S. Garg, S. Baveja. Intralesional immunotherapy for difficult to treat warts with Mycobacterium w vaccine. J Cutan Aesthet Surg;7:203-8. 2014

[11] 11. J.K. Meena, A.K. Malhotra, D.K. Mathur, D.C. Mathur. Intralesional immunotherapy with Mycobacterium w vaccine in patients with multiple cutaneous warts: uncontrolled open study. JAMA Dermatol;149:237-9. 2013

[12] 12. F.M. Abd-Elazeim, G.F. Mohammed, A. Fathy, R.W. Mohamed. Evaluation of IL-12 serum level in patients with recalcitrant multiple common warts, treated by intralesional tuberculin antigen. J Dermatolog Treat;25:264-7. 2014

[13] 13. V. Saoji, N.R. Lade, R. Gadegone, A. Bhat. Immunotherapy using purified protein derivative in the treatment of warts: An open uncontrolled trial. Indian J Dermatol Venereol Leprol;82:42-6. 2016

[14] 14. P. Kumar, A. Das. Excellent response to intralesional bacillus calmette-guérin vaccine in a recalcitrant periungual wart. J Cutan Aesthet Surg;7:234-5. 2014

[15] 15. A. Nofal, A. Marei, A. Amer, H. Amen. Significance of interferon gamma in the prediction of successful therapy of common warts by intralesional injection of Candida antigen. Int J Dermatol;56:1003-9. 2017

[16] 16. F.Z. Muñoz Garza, E. Roé Crespo, M. Torres Pradilla, P. Aguilera Peirò, S. Baltà Cruz, M.E. Hernández Ruiz, et al. Intralesional Candida Antigen Immunotherapy for the Treatment of Recalcitrant and Multiple Warts in Children. Pediatr Dermatol;32:797-801. 2015

[17] 17. T.C. Vlahovic, S. Spadone, S.P. Dunn, T. Fussell, I. Hersh, T. Green, et al. Candida albicans Immunotherapy for Verrucae Plantaris. J Am Podiatr Med Assoc;105:395-400. 2015

[18] 18. K.H. Kim, T.D. Horn, J. Pharis, J. Kincannon, R. Jones, K. O'Bryan, et al. Phase 1 clinical trial of intralesional injection of Candida antigen for the treatment of warts. Arch Dermatol;146:1431-3. 2010

[19] 19. A. Alikhan, J.R. Griffin, C.C. Newman. Use of Candida antigen injections for the treatment of verruca vulgaris: A two-year mayo clinic experience. J Dermatolog Treat;27:355-8. 2016

[20] 20. N. Nasser. Treatment of common warts with the immune stimulant Propionium bacterium parvum. An Bras Dermatol;87:585-9. 2012

[21] 21. W.C. Lau, C.B. Lau, J.E. Frangos, V.E. Nambudiri. Intralesional cidofovir for the management of refractory cutaneous verrucae: a review of applications and opportunities. Ther Adv Infect Dis;10:20499361231165862. 2023

[22] 22. S.C. Bruggink, M.N. de Koning, J. Gussekloo, P.F. Egberts, J. Ter Schegget, M.C. Feltkamp, et al. Cutaneous wart-associated HPV types: prevalence and relation with patient characteristics. J Clin Virol;55:250-5. 2012

[23] 23. E.H. Yang, S. Shah, J.M. Criley. Digitalis toxicity: a fading but crucial complication to recognize. The American journal of medicine;125:337-43. 2012

[24] 24. T.M. Khan, R. Patel, A.H. Siddiqui. Furosemide. 2018

[25] 25. D. Ding, H. Liu, W. Qi, H. Jiang, Y. Li, X. Wu, et al. Ototoxic effects and mechanisms of loop diuretics. J Otol;11:145-56. 2016

[26] 26. M. Rijsbergen, T. Niemeyer-van der Kolk, G. Hogendoorn, S. Kouwenhoven, C. Lemoine, E.S. Klaassen, et al. A randomized controlled proof-of-concept trial of digoxin and furosemide in adults with cutaneous warts. Br J Dermatol;180:1058-68. 2019

[27] 27. A. Terlou, M. van Seters, A. Kleinjan, C. Heijmans-Antonissen, L.A. Santegoets, I. Beckmann, et al. Imiquimod-induced clearance of HPV is associated with normalization of immune cell counts in usual type vulvar intraepithelial neoplasia. Int J Cancer;127:2831-40. 2010

[28] 28. P. Koźmiński, P.K. Halik, R. Chesori, E. Gniazdowska. Overview of Dual-Acting Drug Methotrexate in Different Neurological Diseases, Autoimmune Pathologies and Cancers. Int J Mol Sci;21. 2020

[29] 29. P. Cipriani, P. Ruscitti, F. Carubbi, V. Liakouli, R. Giacomelli. Methotrexate: an old new drug in autoimmune disease. Expert review of clinical immunology;10:1519-30. 2014