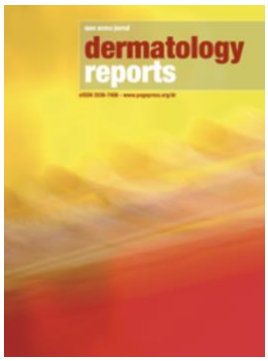

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The efficacy of cryotherapy compared to the other modalities for the management of palmoplantar warts: a systematic review and network meta-analysis

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Abstract

There are several treatment modalities for Palmoplantar Warts (PPW) introduced, but none have been proven to be significantly effective in all patients. The study aims to assess the efficacy and safety of cryotherapy compared to other modalities for PPW.

Searches were conducted in Medline, Embase, Scopus, and CENTRAL databases, along with additional reference and citation tracking from included studies.

Randomized Controlled Trials (RCTs) comparing various treatments for PPW were included.

Two independent pairs extracted the data from the included studies. Outcomes assessed included cure rates, pain scores, recurrence rates, and adverse events. Network meta-analysis using Netmeta in R software was utilized, with treatments ranked by p-scores.

A total of 27 RCTs that enrolled 2,539 participants were deemed eligible. As per p-scores, needling yielded the highest odd for the cure rate (p=1.00), followed by intralesional injection of the Measles, Mumps, and Rubella (MMR) vaccine (p=0.90). For the pain score, 76% topical monochloroacetic acid (p=0.13) showed the lowest mean pain score, while cryotherapy yielded the highest score (p=0.90). Furthermore, cryotherapy showed the highest odds for recurrence rate (p=0.75), followed by intralesional injection of Candida antigen (p=0.61). 0.05% intralesional bleomycin (p=0.93) was the highest agent for adverse events rate, followed by cryotherapy (p=0.61).

Needling was the most effective in achieving a cure rate. Cryotherapy has the highest odds for pain score and recurrence rate, while 0.05% intralesional bleomycin has the highest adverse events profile.

Introduction

Warts are benign lesions caused by Human Papillomavirus (HPV) infecting the epidermal cells.[1] The estimated annual incidence of warts is 14%.[2] The HPV types most frequently detected on the plantar form of warts are 1, 2, 4, 10, 27, and 57.[3] The clinical manifestations of HPV infection include common warts, genital warts, flat warts, deep palmoplantar warts, and plantar cysts.[4]

Several treatment modalities, such as cryotherapy, bleomycin, salicylic acid, intralesional immunotherapy, and/or laser, have been introduced, but none have been proven to be significantly effective in all patients.[5] Treatment modality should be chosen with consideration of various factors such as patient comorbidities, age, site of warts, size, number, cost of therapy and side effects associated with the treatment.[6] Cryotherapy is considered by most healthcare providers as the treatment of choice in common wart management. It involves the application of liquid nitrogen-induced cold to the infected tissue, leading to ice crystal formation within cells, vascular thrombosis, and osmotic difference induced by cooling followed by rapid thawing.[5] According to a previous systemic review, cryotherapy appears to induce lower cure rates than other treatments. Analysis revealed that plantar wart cure rates were significantly lower with cryotherapy compared to other treatment modalities, with evidence of the superiority of antivirals and chemotherapy over cryotherapy in the treatment of plantar warts.[7] Another systematic review, including a total of 43 articles, was conducted, which reported that intralesional agents have equal or superior efficacy when compared to first-line salicylic acid or cryotherapy. One advantage reported of intralesional injections is the rate of complete resolution of distant warts.[8]

Currently, there are few systematic reviews discussing the efficacy of cryotherapy in Palmoplantar Warts (PPW), and thus, scarce evidence-based data regarding this scope. The

aim of this systematic review is to assess the efficacy and safety of cryotherapy compared to the other modalities for the management of palmoplantar warts.

Materials and Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the extension statement for network meta-analysis. This systematic review and network meta-analysis protocol were registered at PROSPERO (CRD42023403203).[9]

Study selection

The studies of interest were Randomized Controlled Trials (RCTs) published in English only. The patient population of interest was individuals of any age with a chief complaint of palmoplantar warts of different sizes and durations. The interventions included in the review were any treatment modality for PPW, while the control was cryotherapy. Studies including participants with other common/genital warts, non-English, or non-RCT study design were excluded. The outcomes of interest were cure/response rate, pain score, recurrence rate, and adverse events.

Data sources

From database inception to March 1st, 2023, we searched Medline, Embase, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL). The references and citations of the included trials were also searched for relevant studies. The complete search strategy is shown in the Supplementary Materials. Two independent pairs, in duplicate, screened titles, abstracts, read the full texts, and extracted the data from the included studies. A third reviewer subsequently validated the data extraction and resolved any discrepancies.

Data extraction and risk of bias

The data extraction was performed using an Excel sheet, and the following data was extracted from each eligible trial: name of the first author, the year of publication, study arms, number of warts, number of participants in each arm, age, gender, number of treatment sessions, follow up period, and the desired outcomes reported by each trial. We used the modified Cochrane Collaboration assessment tool to assess the risk of bias of the eligible studies and classified studies into the following categories: high risk of bias, some concerns, or low risk of bias.[10]

Network meta-analysis

For each study, binary (events and sample size) and continuous (mean and standard deviation) data were extracted for the intervention and control group. These binary and continuous data were used to calculate effect sizes presented as Odds Ratio (OR) and mean difference, respectively. The efficacy of different treatment modalities was explored using frequentist network meta-analysis and the Netmeta statistical package in R. Prior to running network meta-analysis, the assumptions of transitivity were explored among the included trials. Within-designs and between-designs inconsistency were quantified using I^2 and Cochran's Q statistic and the full design-by-treatment interaction random-effects model. The random-effects model was used for all statistical analyses. Further consistency checks included evaluating differences between effect estimates based on direct and indirect evidence. Using a diameter package, a direct evidence plot was used to visualise the proportion of direct and indirect evidence for each comparison. All treatments were ranked using the *netrank* function, yielding p-scores. The ranking of treatments was further corroborated by visualising a forest plot using morphine as a reference group. We adopted 95% as a significance level.

Results

Study selection and network structure

The search resulted in a total of 871 articles. After the removal of duplicates, 694 remained for titles and abstracts screening, and 90 articles remained for full-text assessment. Of those, 63 were excluded for reasons listed in the PRISMA flow diagram**.** Eventually, a total of 28 articles met the inclusion and exclusion criteria of this review.[11-37]

Characteristics of the studies

A total of 2,539 participants were included in this review. Of them, 1,112 (43.80%) received cryotherapy. The remaining 1427 (56.20%) participants received other treatment modalities. In terms of gender, 1,247 (49.11%) of the included participants were male, 1,081 (42.57%) were female, and 211 (8.32%) were not reported/missing from the original trials. The median age of the participants in the included trials was 27.07 (8.06-38.34). The median number of warts was 3.40 (1.00-16.40), and the follow-up period ranged from 4 weeks to 13 weeks after treatment (Supplementary Table 1).

Risk of bias assessment

Of the 27 included RCTs, 9 had an overall low risk of bias, 11 had some concerns, and 7 had an overall high risk of bias. Supplementary Figures 1 and 2 show the details of the risk of bias in the included trials.

Cure and response rate

The network plot for the cure rate of different treatment modalities for PPW was reported in all 27 included studies.[11-37] As per p-scores, needling yielded the highest odd for the cure rate (p=1.00) followed by intralesional injection of Measles, Mumps, Rubella (MMR) vaccine (p=0.90), 5% imiquimod with 15% salicylic acid solution (p=0.89), radiofrequency ablation

(p=0.88), 1% cantharidin, 5% podo-phyllotoxin, and 30% salicylic acid (p=0.83), 40% trichloroacetic acid (p=0.73), intralesional cryotherapy (p=0.686), 1064-nm long-pulsed Nd:YAG laser (p=0.685), 50% topical salicylic acid + cryotherapy (p=0.64), and thermotherapy (p=0.62) (Supplementary Table 2). Compared to cryotherapy alone, many agents showed a significant improvement in terms of cure Supplementary Figure 3. There was significant within-design inconsistency (Q=22.64, p<0.0001) and between-design inconsistency (Q=24.46, p<0.0001). The forest plot that presents the pooled effect size from both direct and indirect evidence for cure rate is presented in Supplementary Figure 4.

Pain score

A total of 4 studies reported the pain score among patients undergoing treatment for PPW (Supplementary Figure 5).[19,23,32,37] As per p-scores, 76% topical Monochloroacetic Acid (MCA) (p=0.13) showed the lowest mean for pain score followed by intralesional cryotherapy (p=0.19), 1% cantharidin+ 5% podo-phyllotoxin + 30% salicylic acid (p=0.36), cryotherapy + 40% topical salicylic acid (p=0.53), 1064-nm long-pulsed Nd:YAG laser (p=0.85), and cryotherapy alone which has the highest pain score (p=0.90) (Supplementary Table 3). Compared to cryotherapy alone, 76% topical monochloroacetic acid (RR=-2.00, 95% CI: -2.16 to -1.84), intralesional cryotherapy (RR=-1.89, 95% CI: -2.48 to -1.30), and cryotherapy +40% topical salicylic acid (RR=-1.00, 95% CI: -1.16 to -0.84) showed significant reduction in pain score (Supplementary Figure 6). Additionally, within-design inconsistency (Q=0.00, p= not applicable) and between-design inconsistency (Q=0.00 p=1.00) were not significant. The Forest that presents the pooled effect size from both direct and indirect evidence for pain score is presented in Supplementary Figure 7.

Recurrence rate

Four out of 27 RCTs reported a recurrence rate of warts after treatment **(**Supplementary Figure 8).[17,20,25,35] As per p-score, cryotherapy alone yielded the highest odds for recurrence rate (p=0.75) followed by intralesional injection of Candida antigen (p=0.61), intralesional cryotherapy (p=0.60), ablative CO_2 laser (p=0.54), 40% trichloroacetic acid (p=0.40), cryotherapy + intralesional injection of Candida antigen (p=0.32), 0.07% topical cantharidin + cryotherapy (p=0.24) (Supplementary Table 4). As compared to cryotherapy alone, only 0.07% topical cantharidin + cryotherapy yielded a statistically significant odds ratio (OR=0.41, 95% CI: 0.24 to 0.68), while the risk of recurrence for other agents was not significantly different (Supplementary Figure 9). Furthermore, within-design inconsistency (Q=0.00, p= not applicable) and between-design inconsistency (Q=0.45 p=0.5) were not significant. The forest plot that presents the pooled effect size from both direct and indirect evidence for the recurrence rate is presented in Supplementary Figure 10.

Risk for adverse effects

The network plot showing the adverse effect of treatment modalities for PPW was reported in 5 studies testing 6 treatments (Supplementary Figure 11).[11,13,18,21,26]

As per p-score, 0.05% intralesional bleomycin yielded the highest odds for adverse events after treatment (p=0.93), followed by cryotherapy alone (p=0.61), 40% trichloroacetic acid (p=0.53), 50% topical salicylic acid (p=0.47), needling (p=0.23), and 40% topical salicylic acid (p=0.20) (Supplementary Table 5). Compared with cryotherapy alone, only 40% topical salicylic acid yielded a statistically significant Odds Ratio (OR=0.47, 95% CI: 0.38 to 0.60), while the risk of adverse events for other agents was not significantly different (Supplementary Figure 12). Within-design inconsistency (Q=0.00, p=0) and between-design inconsistency (Q=0.00 p=0) were not applicable. The most reported cutaneous adverse events were

application-site pain (68.81%), erythema (47.22%), edema (38.05%), hemorrhagic bulla (33.78%), ulceration (31.67%), and bulla (30.66%) (Supplementary Table 6).

Discussion

Various treatment modalities have been adopted for the treatment of different types of PPW, but the gold standard or the optimal method is yet to be determined. Nevertheless, cryotherapy has been introduced as a choice of management with high efficacy as well as minimized adverse effects. For instance, cryotherapy using liquid nitrogen is a widely implemented dermatologic therapy for the management of PPW.[38] Cryotherapy can directly destroy the viral-affected keratinocytes[39] and trigger the immunologic reaction, causing secondary induced cell damage.[40] However, sometimes, the cell damage is not sufficient to destroy the dormant virus in adjacent cells.[5] As a result, treatments sometimes are deemed ineffective, leading to more adverse events such as pain, scarring, relapsing, and recurrent warts.[41] Infection with warts causes pain and limitation of some activities according to the site affected, leading the patient to seek medical care, and for other reasons such as cosmetic, and prevention of infections to other areas of the body or other people.[11,42]

The aim of this systematic review and Network Meta-Analysis (NMA) of 27 RCTs is to deliver a comprehensive comparison between the most used treatment agents for the management of PPW. Our NMA demonstrated that needling yielded the highest effectiveness in terms of developing a cure, followed by intralesional injection of MMR vaccine, 5% imiquimod with 15% salicylic acid solution, radiofrequency ablation, 1% cantharidin, 5% podo-phyllotoxin + 30% salicylic acid, 40% trichloroacetic acid, respectively. A prospective non-randomized study of 82 patients with single or multiple plantar/palmar/palmoplantar warts who were treated with a standardized needling procedure. Showed complete resolution in 58 (70.7%) with a single treatment session, and partial response in 5 (6.1%) patients.[43] This is compatible

with results from a retrospective review of 45 patients, which demonstrated complete resolution of verrucae in thirty-one (69%) cases, reduction in size, and pain in three patients, whilst 11 showed no improvement following needling treatment.[44] On the other hand, a recent systematic review and meta-analysis showed that the cure rate of planter warts was significantly lower in the cryotherapy group compared to the physical treatment, keratolytic, antiviral, chemotherapy, and retinoid group.[7] Moreover, a network metanalysis comparing intralesional immunotherapeutic modalities to cryotherapy, placebo, or imiquimod showed that PPD and MMR were the most effective in achieving complete primary and distant recovery of warts (along with autoinoculation for distant recovery) and reducing the recurrence rate at the same site compared with cryotherapy and other immunotherapeutic modalities.[45] Similarly, previous systematic reviews conducted on the range of treatments for plantar warts considered the combination of cryotherapy together with salicylic acid as one of the treatments of choice[46] but it has appeared to produce lower cure rates (45.61%) than alternative treatments, such as laser (79.36%), a combination of cantharidin 1%, podophyllotoxin 5%, and salicylic acid 30% (CPS formulation) (97.82%), or topical antivirals (72.45%), intralesional bleomycin (83.37%), intralesional immunotherapy (68.14%).[5] These findings provide insight into the low efficacy of cryotherapy as a management modality for PPW.

In this review, the studies that reported on needling and MMR injection had a small sample size, while the studies that showed the best ranking with the largest sample size were the studies that reported on bleomycin and topical salicylic acid. This may indirectly give an insight into the fact that patients may prefer bleomycin and topical treatments to needling methods. The clinical guideline for the diagnosis and treatment of cutaneous warts published in 2022 recommended the use of local injections of bleomycin, long-pulsed 1064 nm Nd:YAG laser combined with topical moisturizing cream treatment or optimized CO_2 laser (level of evidence of 1b), local hyperthermia and cryotherapy (level of evidence of 2b) for the treatment of plantar

warts.[47] In short, this review supports the assumption that 0.1% intralesional bleomycin and 50% topical salicylic acid are clinically the best agents in terms of having a cure.

Considering the pain score, MCA (p=0.13) was found to have a lower pain score, while paradoxically, cryotherapy has the highest mean for pain score, recurrence, and adverse event rate. This finding is supported by the results of a previous RCT done by Bruggink *et al.* where it was found that a lower proportion of patients reported pain during MCA application compared with cryotherapy for both common and plantar wart groups, and the most serious side effects reported were blistering and superficial wounds for all four treatment arms.[19] Additionally, a review article of topical treatments for cutaneous warts involving 85 randomized controlled trials concluded that adverse effects, such as pain, blistering, and scarring, were more common with cryotherapy, which is consistent with the finding of our network meta-analysis, where erythema, edema, and ulceration were the most commonly.[38]

Strengths and limitations

To the best of our knowledge, this is the first NMA to compare the efficacy and safety of most available forms of treatment modality for palmoplantar warts; since there are many treatments available, it is crucial to compare effectiveness and safety. When direct head-to-head data from clinical trials are not available, it is necessary to utilize quantitative analysis to perform indirect comparisons through a network meta-analysis. Nevertheless, we acknowledge that our review has some limitations. First, due to the lack of data from most of the included RCTs, we did not compare the assessed arms in terms of patient satisfaction with treatment. In addition, some comparisons in our NMA relied on a few studies with small sample sizes and should be further investigated; also, different routes of administration, such as systemic treatment, were excluded from this study.

Conclusions

This network meta-analysis showed that needling is the most effective in treating palmoplantar warts, followed by intralesional injection of MMR vaccine, 5% imiquimod with 15% salicylic acid solution, and radiofrequency ablation, respectively. With respect to the safety profile, cryotherapy has the highest adverse event profiles and recurrence rate, whereas Monochloroacetic acid has the least adverse event profile. These findings can help physicians select the appropriate treatment agents for palmoplantar warts and will help structure evidence-based guidelines for the treatment of PPW.

References

1. Hashmi F, Bristow I. Treating plantar warts: utilizing natural immunity to induce wart regression. Dermatol Nurs. 2014;13:42-6.
2. Witchey D, Witchey N, Roth-Kauffman M, Kauffman M. Plantar warts: epidemiology, pathophysiology, and clinical management. J Am Osteopath Assoc. 2018;118:92-105.
3. Viennet C, Gheit T, Muret P, et al. Assessment of the efficacy of a new formulation for plantar wart mummification: new experimental design and human papillomavirus identification. Clin Exp Dermatol. 2013;38:85-8.
4. Al Aboud AM, Nigam PK. Wart. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431047/
5. García-Oreja S, Alvaro-Afonso FJ, García-Alvarez Y, et al. Topical treatment for plantar warts: a systematic review. Dermatol Ther. 2021;34:e14621.
6. Bruggink SC, Gussekloo J, de Koning MN, et al. HPV type in plantar warts influences natural course and treatment response: secondary analysis of a randomised controlled trial. J Clin Virol 2013;57:227-32.
7. García-Oreja S, Álvaro-Afonso FJ, Tardáguila-García A, et al. Efficacy of cryotherapy for plantar warts: a systematic review and meta-analysis. Dermatol Ther. 2022;35:e15480.
8. Muse ME, Stiff KM, Glines KR, et al. A review of intralesional wart therapy. Dermatol Online J. 2020;26:13030/qt3md9z8gj.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62:e1-34.
10. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

11. Cockayne S, Curran M, Denby G, et al. EVerT: cryotherapy versus salicylic acid for the treatment of verrucae - A randomised controlled trial. Health Technol Assess. 2011;15:1-170.
12. Abdel-Latif AA, El-Sherbiny AF, Omar AH. Silver duct tape occlusion in treatment of plantar warts in adults: is it effective? Dermatol Ther. 2020;33:1-6.
13. Karrabi M, Kheirkhah M, Shahrestanaki E, et al. Comparison of 40% trichloroacetic acid and cryotherapy for the treatment of plantar warts: a single-blind, randomized clinical trial. Dermatol Ther. 2020;33:e13559.
14. Abd El-Magiud EM, Abd El-Samea GM, Gaber HD. Intralesional injection of measles, mumps, and rubella vaccine versus cryotherapy in treatment of warts: a randomized controlled trial. Dermatologic Therapy. 2020;33:e13257.
15. Amar A, Nida S, Malik S. Efficacy of topical adapalene in treatment of plantar warts. Pakistan Armed Forces Medical Journal. 2020;70:240-4.
16. Kaur Arora A, Dogra A, Kumar Gupta S. Efficacy of cryotherapy versus radiofrequency ablation in the treatment of plantar warts. Iranian Journal of Dermatology. 2014;17:85-90.
17. Boroujeni NH, Handjani F. Cryotherapy versus CO_2 laser in the treatment of plantar warts: a randomized controlled trial. Dermatology practical & conceptual. 2018;8:168.
18. Bruggink SC, Gussekloo J, Berger MY, et al. Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: randomized controlled trial. Cmaj. 2010;182:1624-30.
19. Bruggink SC, Gussekloo J, Egberts PF, et al. Monochloroacetic acid application is an effective alternative to cryotherapy for common and plantar warts in primary care: a randomized controlled trial. Journal of Investigative Dermatology. 2015;135:1261-7.
20. Cengiz FP, Emiroglu N, Su O, Onsun N. Effectiveness and safety profile of 40% trichloroacetic acid and cryotherapy for plantar warts. The Journal of Dermatology. 2016;43:1059-61.

21. Cunningham DJ, Brimage JT, Naraghi RN, Bower VM. Needling versus liquid nitrogen cryotherapy for the treatment of pedal warts: a randomized controlled pilot study. Journal of the American Podiatric Medical Association. 2014;104:394-401.
22. Hafeez L, Jabbar A, Tahir R, et al. Efficacy of intralesional bleomycin versus cryotherapy in the treatment of palmoplantar warts. Journal of Pakistan Association of Dermatologists. 2021;31:661-7.
23. Liu JJ, Li HT, Ren YY, et al. Long-pulsed neodymium-doped yttrium-aluminum-garnet laser versus cryotherapy for the treatment of cutaneous warts: a randomized controlled trial. Journal of the American Academy of Dermatology. 2022;87:1328-35.
24. Maj A, Siddique MA, Hussain LC. Efficacy of topical 1% adapalene versus cryotherapy in treatment of plantar warts. Pakistan Journal of Medical & Health Sciences. 2022;16:3743.
25. Meymandi SS, Vaseli MB, Aflatoonian M, Abroud F. Efficacy of cryotherapy combined with topical cantharidin application versus cryotherapy and placebo in the treatment of verruca vulgaris: A randomized, controlled clinical trial. Journal of Pakistan Association of Dermatologists. 2017;27:42-7.
26. Adalatkhah H, Khalilollahi H, Amini N, Sadeghi-Bazargani H. Compared therapeutic efficacy between intralesional bleomycin and cryotherapy for common warts: a randomized clinical trial. Dermatology Online Journal. 2007;13.
27. Ahmad HM, Abdel-Azim ES, Abdel-Aziz RT. Clinical, histopathologic, and viral load study after treatment of plantar warts with 10% formaldehyde soaks versus liquid nitrogen cryotherapy. Journal of the Egyptian Women's Dermatologic Society. 2018;15:165-71.
28. Anwar A, Tahir K, Shahid M, Aman S. Comparison of efficacy of ablative CO2 laser vs. liquid nitrogen cryotherapy in the treatment of palmoplantar warts. Journal of Pakistan Association of Dermatologists. 2021;31:366-72.

29. Gibson JR, Harvey SG, Barth J, et al. A comparison of acyclovir cream versus placebo cream versus liquid nitrogen in the treatment of viral plantar warts. Dermatology. 1984;168:178-81.
30. Ali M, Siddiqui MA, Hussain M. Comparative study between treatment with cryotherapy alone versus cryotherapy plus salicylic acid dressing for planter warts. Pakistan Journal of Medical & Health Sciences. 2022;16:3871.
31. Muhammad J, Akhtar N, Ahmad MK, Anwar MI. Comparison of efficacy between intralesional bleomycin and cryotherapy in plantar warts. Journal of Pakistan Association of Dermatologists. 2019;29:35-9.
32. Kaçar N, Taşlı L, Korkmaz S, et al. Cantharidin–podophylotoxin–salicylic acid versus cryotherapy in the treatment of plantar warts: a randomized prospective study. Journal of the European Academy of Dermatology and Venereology. 2012;26:889-93.
33. Siddiqui S, Aman S. Comparison of efficacy of cryotherapy versus Ionic Contraviral Therapy (ICVT) in the treatment of viral warts. Journal of Pakistan Association of Dermatologists. 2022;32:15-21.
34. Stefanaki C, Lagogiani I, Kouris A, et al. Cryotherapy versus imiquimod 5% cream combined with a keratolytic lotion in cutaneous warts in children: a randomized study. Journal of Dermatological Treatment. 2016;27:80-2.
35. Attwa E, Elawady R, Salah E. 'Cryo-immuno-therapy'is superior to intralesional Candida antigen monotherapy in the treatment of multiple common warts. Journal of Dermatological Treatment. 2021;32:1018-25.
36. Izadi Firouzabadi L, Khamesipour A, Ghandi N, et al. Comparison of clinical efficacy and safety of thermotherapy versus cryotherapy in treatment of skin warts: a randomized controlled trial. Dermatologic Therapy. 2018;31:e12564.

37. Albalat W, Attwa E, Ebrahim HM. Intralesional cryotherapy versus cryotherapy spray for the treatment of recalcitrant plantar warts: a prospective, randomized study. J Dermatolog Treat. 2020;26:1-7.
38. Kwok CS, Gibbs S, Bennett C, et al. Topical treatments for cutaneous warts. Cochrane Database of Systematic Reviews. 2012;2012:CD001781.
39. Keefe M, Dick DC. Cryotherapy of hand warts--a questionnaire survey of 'consumers'. Clin Exp Dermatol. 1990;15:260-3.
40. Dawber R. Cold kills! Clin Exp Dermatol. 1988;13:137-50.
41. Aldana-Caballero A, Marcos-Tejedor F, Mayordomo R. Diagnostic techniques in HPV infections and the need to implement them in plantar lesions: a systematic review. Exp Rev Mol Diagn. 2021;21:1341-8.
42. Gibbs S, Harvey I. Topical treatments for cutaneous warts (review). Cochrane Database Syst Rev. 2006;2006:CD001781.
43. Kumari P, Yadav D, Vijay A, et al. Falknor's needling method as a potential immunotherapy in palmo-plantar warts. Indian Journal of Dermatology, Venereology and Leprology. 2019;85:129.
44. Longhurst B, Bristow I. The treatment of verrucae pedis using Falknor’s needling method: a review of 46 cases. Journal of Clinical Medicine. 2013;2:13-21.
45. Salman S, Ahmed MS, Ibrahim AM, et al. Intralesional immunotherapy for the treatment of warts: A network meta-analysis. Journal of the American Academy of Dermatology. 2019;80:922-30.
46. Hekmatjah J, Farshchian M, Grant-Kels JM, Mehregan D. The status of treatment for plantar warts in 2021: no definitive advancements in decades for a common dermatology disease. Clin Dermatol. 2021;39:688-94.

47. Zhu P, Qi RQ, Yang Y, et al. Clinical guideline for the diagnosis and treatment of cutaneous warts (2022). Journal of Evidence-Based Medicine. 2022;15:284-301.

Online supplementary material.

Supplementary Figure 1. Risk of bias graph.

Supplementary Figure 2. Risk of bias summary.

Supplementary Figure 3. Cure forest plot pooled.

Supplementary Figure 4. Forest plot net split for cure rate.

Supplementary Figure 5. Network graph for pain score.

Supplementary Figure 6. Pain Forest plot pooled.

Supplementary Figure 7. Forest plot net split for pain score.

Supplementary Figure 8. Network graph for recurrence rate.

Supplementary Figure 9. Recurrence rate forest plot pooled.

Supplementary Figure 10. Forest plot net split for recurrence rate.

Supplementary Figure 11. Network graph for complication rate.

Supplementary Figure 12. Complications Forest plot pooled.

Supplementary Table 1. Characteristics of the included studies.

Supplementary Table 2. Ranking for cure rate.

Supplementary Table 3. Ranking for pain score.

Supplementary Table 4. Ranking for recurrence rate.

Supplementary Table 5. Ranking for complication rate.

Supplementary Table 6. Details of treatment-related adverse events.