Dermatology Practical & Conceptual

Comparative Analysis of Intralesional Immunotherapy and Conventional Treatments for Non-Genital Warts: A Systematic Review and Network Meta-Analysis

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Key Message: Network meta-analysis reveals intralesional immunotherapy, particularly needling and furosemide with digoxin, surpasses conventional treatments for non-genital warts, highlighting a need for broader accessibility and further comparative studies.

Key words: intralesional immunotherapy, cryotherapy, HPV, network meta-analysis, non-genital warts

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ABSTRACT

Introduction: Warts, benign skin growths caused by various human papillomavirus strains, are categorized as genital and non-genital. Non-genital warts often lack noticeable symptoms but can lead to psychological distress due to factors like embarrassment. Traditional treatments, including physical and chemical methods, show limitations, prompting the exploration of novel approaches like intralesional immunotherapy. The clinical challenge lies in selecting the most effective modality.

Objective: In our study, we used the network meta-analysis (NMA) as a statistical tool to explore the most effective intralesional immunotherapy interventions.

Methods: Comprehensive searches of Web of Science, PubMed, Cochrane, and Scopus databases were conducted until December 2023. Eligible studies were analyzed for outcomes presented as risk ratios (RRs) with 95% confidence intervals (CI). Treatments were ranked using the P-score in an NMA performed with R software.

Results: We included 68 RCTs in our study. For complete response, needling showed a significant difference compared to *Candida albicans* antigen (RR= 0.13, 95% CI [0.02; 0.99]) and Mw (RR= 0.12, 95% CI [0.02; 0.94]). In overall response, both bleomycin and furosemide with digoxin were significant compared to autoimplantation (RR= 0.46, 95% CI [0.24; 0.88]) and (RR= 0.40, 95% CI [0.18; 0.91]) respectively. Similarly, both were significant compared to cryotherapy (RR= 0.45, 95% CI [0.27; 0.76]) and (RR= 0.40, 95% CI [0.19; 0.82]) respectively.

Conclusion: This NMA indicates needling, furosemide with digoxin, and PBP antigen stimulants as effective for non-genital warts, surpassing traditional treatments in complete and overall response. Direct comparisons in future research are warranted to confirm their superiority.

Introduction

Warts are defined as non-cancerous skin growth related to viral infection, mostly associated with various strains of human papillomavirus (HPV) [1,2]. The virus infects the outer layer of the skin as it enters the body from an area where the skin is damaged [3]. Warts are divided into genital and non-genital warts. The non-genital type of warts may be present on different body parts, such as verruca vulgaris, the most common type of wart. There are many other different types, such as plantar warts, flat warts, filiform warts [4], periungual warts [5], and mosaic warts [6]. Typically, these warts do not exhibit noticeable symptoms, although some types, like plantar or subungual warts, may cause tenderness, especially when fissured [7,8]. Although warts cannot cause mortality directly without developing into a cancerous type, which is higher in genital warts [9], non-genital warts can put a heavy burden on the patients, as these warts can significantly impact an individual's psychological well-being, leading to a diminished quality of life. This influence is manifested through embarrassment, fear of negative judgment from others, and frustration stemming from the persistent recurrence of the warts [1,10,11]. The psychological toll encompasses emotional aspects such as shame, anxiety about social perception, and the ongoing emotional strain associated with the continual reappearance of the warts [10,12].

Multiple treatment approaches exist for warts, including physical methods like cryotherapy, electrosurgery, ablative laser procedures, or surgical removal. Chemical options involve salicylic acid or trichloroacetic acid, while anti-proliferative agents like podophyllin, 5-fluorouracil, or bleomycin [13,14] are also utilized. Regrettably, none of the treatments have demonstrated complete effectiveness as a cure with a 100% cure rate [14,15]. Additionally, these available methods may induce pain, lead to scarring, and are linked to elevated rates of wart recurrence [16]. Due to the previous side effects and the problems with physical, surgical, or chemical methods, new methods are required to treat the warts with a higher success rate. Intralesional immunotherapy constitutes a therapeutic modality employed recently in wart treatment. This procedure entails the direct injection of immunomodulatory agents into the wart or adjacent tissue, intending to elicit a heightened immune response against the HPV causative agent [17,18]. The overarching objective is the augmentation of the local immune milieu, thereby facilitating the eradication of wart lesions.

Objective

Choosing among the various modalities poses a clinical challenge when there is a lack of clear evidence favoring one method over another. To fill this knowledge gap, we conduct our study using NMA. This statistical approach facilitates the comparison of multiple treatments, which would fit this type of study that contains multiple interventions [19].

Methods

Our network meta-analysis was performed according to the PRISMA statement and the guidelines of the Cochrane Handbook for systematic reviews [20-22].

Searching Databases and Keywords

We searched four main databases with the following terms: ((Intralesional OR Injection* OR Inject*) AND (immunotherap* OR "purified protein derivative" OR "PPD-B" OR "PPD B" OR "PPD-L" OR "PPD L" OR "Purified Protein Derivative" OR PPD OR "PPD-S" OR "PPD-CG" OR "PPD CG" OR "PPD-F" OR "PPD F" OR Trichophyton OR

Trychophyton OR Endodermophyton OR BCG OR "Bacillus Calmette Guerin" OR "Calmette's Vaccine" OR Calmette OR "Calmette Guerin Bacillus" OR "Measles Mumps Rubella" OR "Measles-Mumps-Rubella" OR "Measles, Mumps, Rubella" OR MMR OR "Mumps-Measles-Rubella" OR "Mumps Measles Rubella " OR "Mumps-Measles-Rubella" OR "Triviraten Berna" OR Priorix OR Trimovax OR Pluserix OR Virivac OR Monilia* OR "Cyberlindnera jadinii" OR Candida OR "Lindnera jadinii" OR "Hansenula jadinii" OR "Pichia jadinii" OR "Saccharomyces jadinii" OR "Torula utilis" OR Mycobacteri* OR "vitamin D" OR Calciferol OR autoinoculate OR autoimplant OR "Corynebacterium parvum" OR INF OR interferon OR INF-g OR "Propionibacterium parvum" OR "Propionibacterium acne" OR Vaccin*) AND (Wart OR Verruca OR Verrucas OR "human papilloma virus" OR papillomavirus OR HPV)). The search was done until December 2023. We also did a manual search for the references of the included studies.

Eligibility Criteria and Study Selection

We included studies that met the following criteria: (1) Population: All patients with non-genital warts, either single or multiple. (2) Intervention and comparator arms: Intralesional immunotherapy compared with any other treatment modality including: needling, furosemide and digoxin, polyvalent bacterial protein antigen (PBP Ag) stimulant, purified protein derivative vaccine (PPD) and cryotherapy, bleomycin, Bacille Calmette-Guérin vaccine (BCG), PPD and isotretinoin, ozone gas, multiple PPD, PPD and *Candida albicans* antigen with MMR, *C. albicans* antigen, *C. albicans* antigen and cryotherapy, mycobacterium with vaccine (Mw), measles, mumps, and rubella vaccine (MMR), PPD, isotretinoin, photodynamic therapy (PDT), vitamin D3, 5-FU, mumps, Candida or Trichophyton (MCT) antigen and interferon (IFN) α-2b, MMR subcutaneous (SC), autoimplantation, *C. albicans* antigen and isotretinoin, zinc sulfate, MMR intradermal (ID), cryotherapy, DPCP, MCT antigen, IFN α-2b and PDL, formic acid 85%, IFN α-2b, PDL, and placebo. (3) Outcomes: Complete response, no or minimal response, overall response, and partial response. (4) Study design: Randomized clinical trials (RCTs) only.

Data Extraction

We extracted the data related to the following:

1. Summary and baseline characteristics of the included studies; including study arms, site, trial registration, age, male, follow-up duration, type of warts, warts duration, number of sessions, adverse events, recurrence rate, inclusion criteria, primary endpoints, and conclusion.
2. Outcomes of Complete response, no or minimal response, overall response, and partial response.
3. Quality assessment domains.

Quality Assessment

We employed the Cochrane risk of bias tool (version 1) to evaluate the quality of the interventional studies included in our analysis. This tool is detailed in chapter 8.5 of the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.

Statistical Analysis

We performed a frequentist network meta-analysis employing random-effects models. Binary data were extracted as risk ratio [RR] and their corresponding 95% confidence interval [CI]. All statistical analyses were conducted using R programming through net-meta statistical packages. Heterogeneity was evaluated across clinical, methodological, and statistical domains. The assessment of statistical heterogeneity involved the use of I2 statistics.

Definitions of the Outcomes

Overall response: The proportion of patients who have a partial or complete response to therapy in getting rid of warts.

Complete response: The proportion of patients with thorough eradication and absence of not only the targeted central wart that was subjected to injection but also any supplementary lesions situated in close proximity to the treated area.

Partial response: This was achieved by calculating the proportion of patients who showed treatment response (more than 25% but less than complete response).

No or minimal response: This was achieved by calculating the proportion of patients who showed either no improvement in the warts or minimal treatment response (less than 25%).

Results

After conducting our literature search on various search databases, we found 3,614 records. We found a total of 1,357 duplicates with the use of the endnote system. We excluded and removed these duplicates and excluded 2,109 articles based on title and abstract screening. With a final full-text screening for 148 papers, we finally included 68 studies (Figure 1).

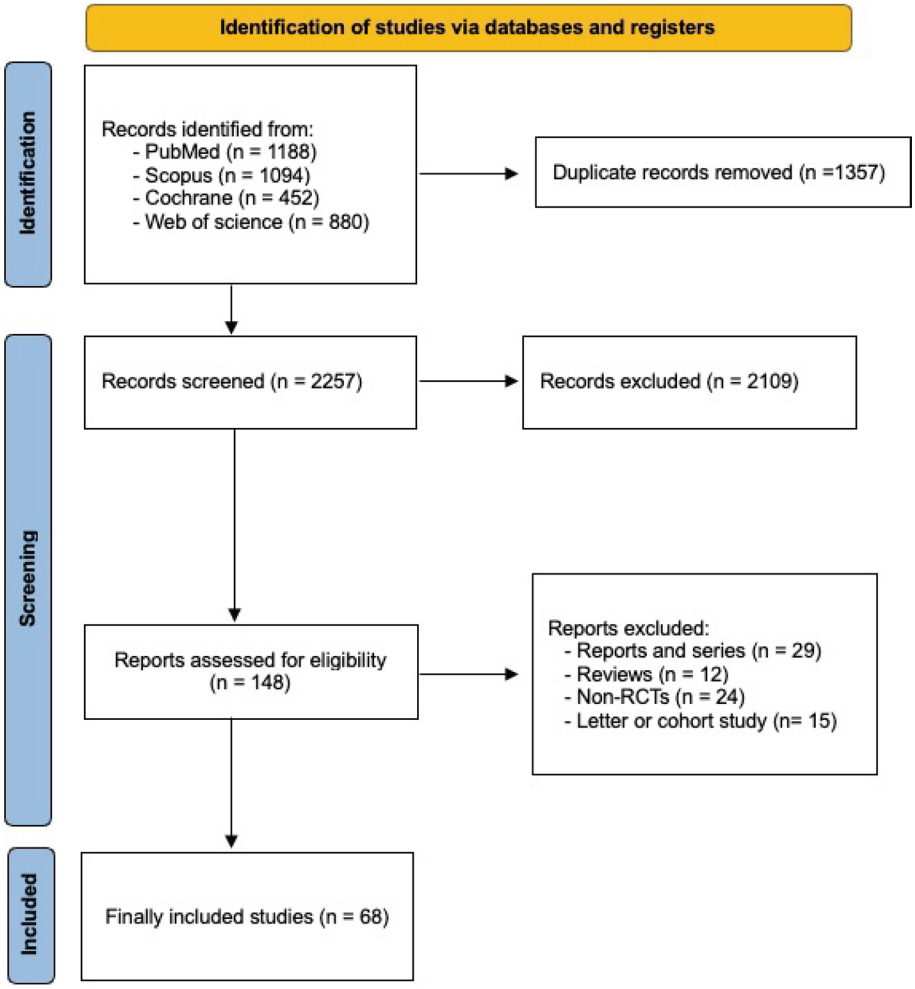

Figure 1. PRISMA flow chart.

Study Characteristics and Quality

A total of 68 studies, including 4,996 patients, were included in our study. The included studies were from Egypt, India, the United States, Thailand, Pakistan, Malaysia, Libya, Saudi Arabia, Iran, Korea, Brazil, and the Philippines. The mean age ranged from 20 years to 40 years. The majority of follow-up periods were 3 and 6 months. The plantar warts were the most common type in the included population. A low percentage of the warts showed recurrence (Supplementary Table 1). Using the ROB tool for the included RCTs, almost all the included studies were of moderate quality. Full details are displayed in (Figure 2).

Main Outcomes

Complete Response

The top 5 interventions demonstrating the most significant effectiveness in achieving a complete response in wart treatment, based on P-scores, are as follows: Needling followed by furosemide and digoxin followed by PBP antigen stimulants followed by bleomycin, and finally BCG. On the other hand, the 3 interventions with the lowest effect on achieving the complete response according to P-scores are IFN α-2b, placebo, and PDL (Figure 3).

Almost all of the highest interventions in results showed significance compared with IFN α-2b, placebo, and PDL. Needling was significant compared to *C. albicans* antigen as the results were (RR= 0.13, with 95% CI [0.02; 0.99]). Needling was also effective compared to Mw as the results were (RR= 0.12, with 95% CI [0.02; 0.94]). PPD and cryotherapy were significant compared to MMR as the results were (RR= 0.52, with 95% CI [0.28; 0.95]). BCG was substantial compared to MMR as the results were (RR= 0.68, with 95% CI [0.47; 0.98]) (Figure 3).

Overall Response

The top five interventions demonstrating the most significant effectiveness in achieving an overall response in wart treatment, based on P-scores from our results, are as follows: PBP antigen stimulants followed by furosemide and digoxin followed by bleomycin followed by PPD and

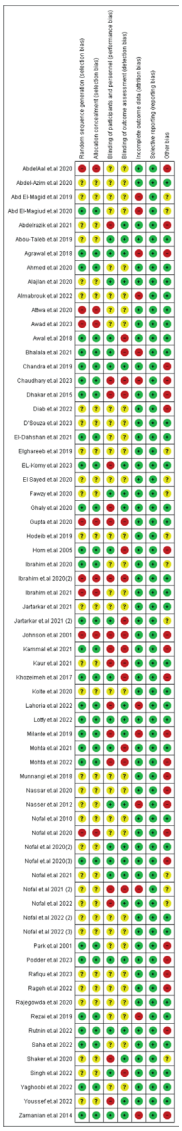

Figure 2. Risk of bias summary graph of the included randomized control trials.

isotretinoin and finally 5-FU. On the other hand, the lowest three interventions in achieving the complete response according to P-scores are KOH 5%, placebo, and MMR ID (Figure 4).

Both bleomycin intervention and the mix of furosemide and digoxin were significant when compared with autoimplantation as the results were (RR= 0.46, with 95% CI [0.24; 0.88]), and (RR= 0.40, with 95%CI [0.18; 0.91]) respectively. Additionally, both bleomycin intervention and the mix of furosemide and digoxin were significant when compared with cryotherapy as the results were (RR= 0.45, with 95% CI [0.27; 0.76]), and (RR= 0.40, with 95% CI [0.19; 0.82]) respectively. PPD and Isotretinoin and 5-FU were significant when compared with cryotherapy as the results were (RR= 0.54, with 95% CI [0.29; 0.99]), and (RR= 0.62, with 95% CI [0.40; 0.95]) respectively (Figure 4).

No or Minimal Response

Based on P-scores from our results, the top five interventions demonstrating the lowest response in wart treatment are as follows: Placebo followed by IFN α-2b followed by KOH 5% followed by MMR ID followed by zinc sulfate. Furosemide and digoxin mix was significant when compared with placebo, IFN α-2b, KOH 5%, MMR ID, and zinc sulfate as the results were (RR= 0.03, with 95% CI [0.00; 0.35]), (RR= 0.04, with 95% CI [0.00; 0.53]) (RR= 0.03, with 95% CI [0.00; 0.69]), (RR= 0.04, with 95% CI [0.00; 0.72]), and (RR= 0.05, with 95% CI [0.40; 0.70]). PPD and isotretinoin mix was significant when compared placebo, and IFN α-2b (RR= 0.08, with 95%CI [0.01; 0.54]), and (RR= 0.09, with 95%CI [0.01; 0.88]). *C. albicans* antigen was significant when compared to placebo, and IFN α-2b (RR= 0.16, with 95% CI [0.09; 0.28]), and (RR= 0.17, with CI [0.04; 95%, 0.71]) respectively (Figure 5).

Partial Response

Based on P-scores from our results, the top 5 interventions demonstrating partial response in wart treatment are 5-FU, bleomycin, PDT, DPCP, and formic acid 85%. On the other hand, the lowest 3 interventions in achieving the partial response according to P-scores are needling, furosemide and digoxin, and MMR ID. MMR ID was significantly lower in partial response when compared with 5-FU, bleomycin, and PDT (RR= 0.01, with 95% CI [0.00; 0.32]), (RR= 0.02, with 95% CI [0.00; 0.54]), and (RR= 0.06, with 95% CI [0.01; 0.48]) (Figure 6).

Discussion

To the best of our knowledge, our NMA included all the available treatment interventions for non-genital warts. We set our comparison based mainly on efficacy outcomes for treating warts at the place of injection and the distantly related warts. Our results revealed that the most efficacious interventions yielding complete response encompassed needling, the combination of furosemide and digoxin, and PBP antigen stimulants. Conversely, IFN α-2b, PDL, and formic acid 85% exhibited a lower complete response rate. The combination of furosemide with digoxin, PBP antigen stimulants, and bleomycin were among the top interventions yielding overall responses. Nevertheless, KOH 5%, MMR ID, and cryotherapy exhibited comparatively lower efficacy in achieving overall response. Regarding the outcome of no or minimal response, interventions with the lowest efficacy included IFN α-2b, KOH 5%, and MMR ID. Meanwhile, the least interventions in this outcome were the mix of furosemide and digoxin, PBP antigen stimulants, and the combination of PPD and isotretinoin. The partial response outcome mirrored the trends observed

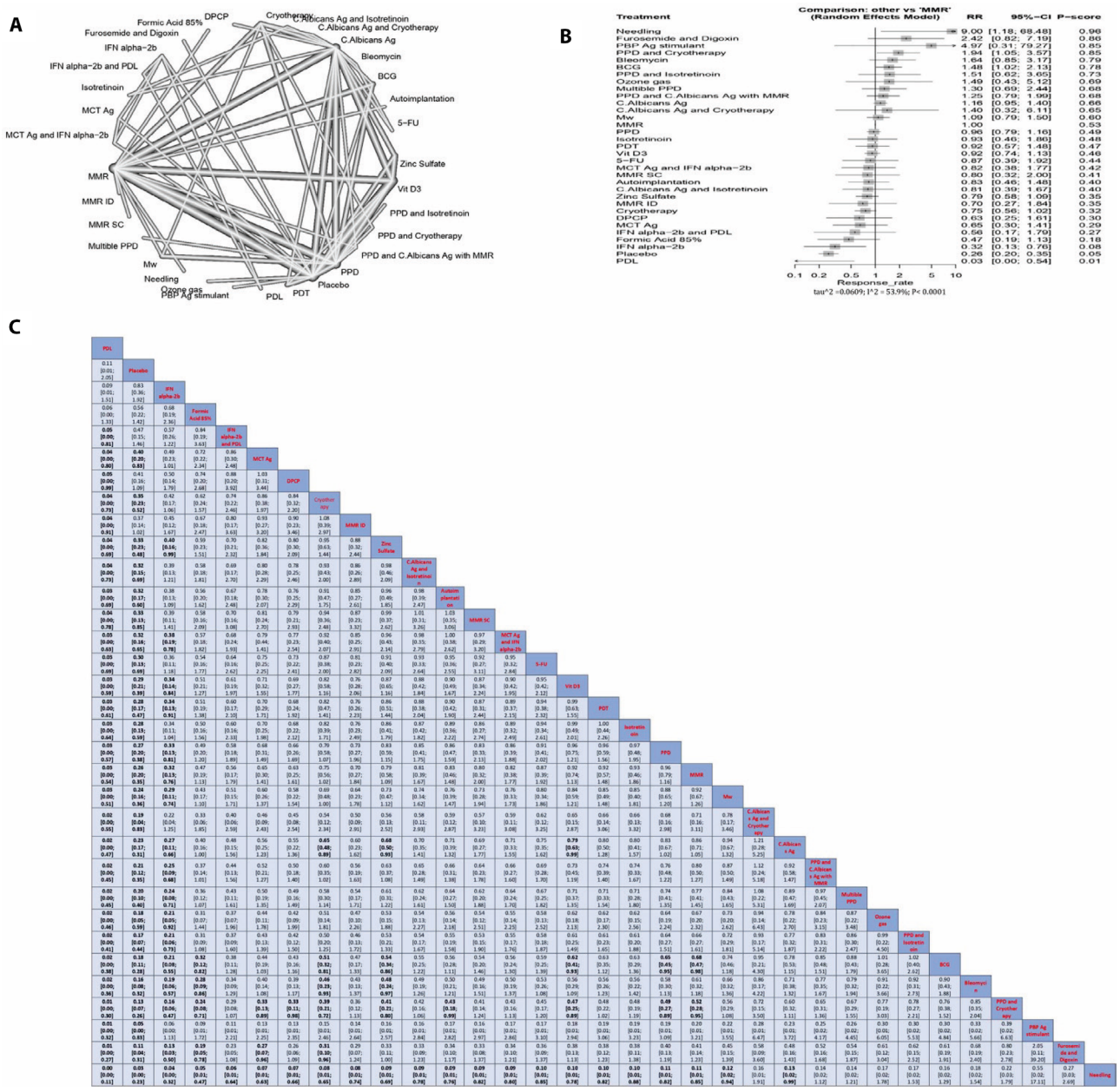

Figure 3. Complete response: (A) Network graph showing direct evidence between the evaluated interventions. (B) A forest plot comparing all interventions. (C) The league table represents the network meta-analysis estimates for all interventions' comparisons.

in the no response category, with needling, the mix of furosemide and digoxin, and MMR ID demonstrating the highest efficacy and lowest partial response. At the same time, 5-FU, bleomycin, and PDT exhibited the most increased occurrence of partial response in the participants.

Recently, there has been a notable increase in the prominence and utilization of intralesional immunotherapy methods due to their promising results compared to traditional methods for treating warts [23,24]. Our results suggest that cryotherapy is not a superior intervention in the treatment of non-genital warts despite the widespread utilization of cryotherapy. According to our findings, it demonstrates lower effectiveness and inferiority compared to intralesional immunotherapy [24]. Our finding aligns with a previous meta-analysis that investigated the efficacy of cryotherapy for plantar warts [25]. Although intralesional immunotherapy would result in better results than traditional methods, adverse events may present as localized immunologic or irritant reactions or systemic and constitutional symptoms, including fever and flu-like manifestations. While pain at the injection site was a prevalent observation in most studies, it was seldom of extended duration [13,26]. Traditional treatments designed with a destructive mechanism for warts may similarly exhibit efficacy in addressing prominent lesions [27].

It is crucial to acknowledge that the availability and feasibility of these treatments in clinical practice may vary

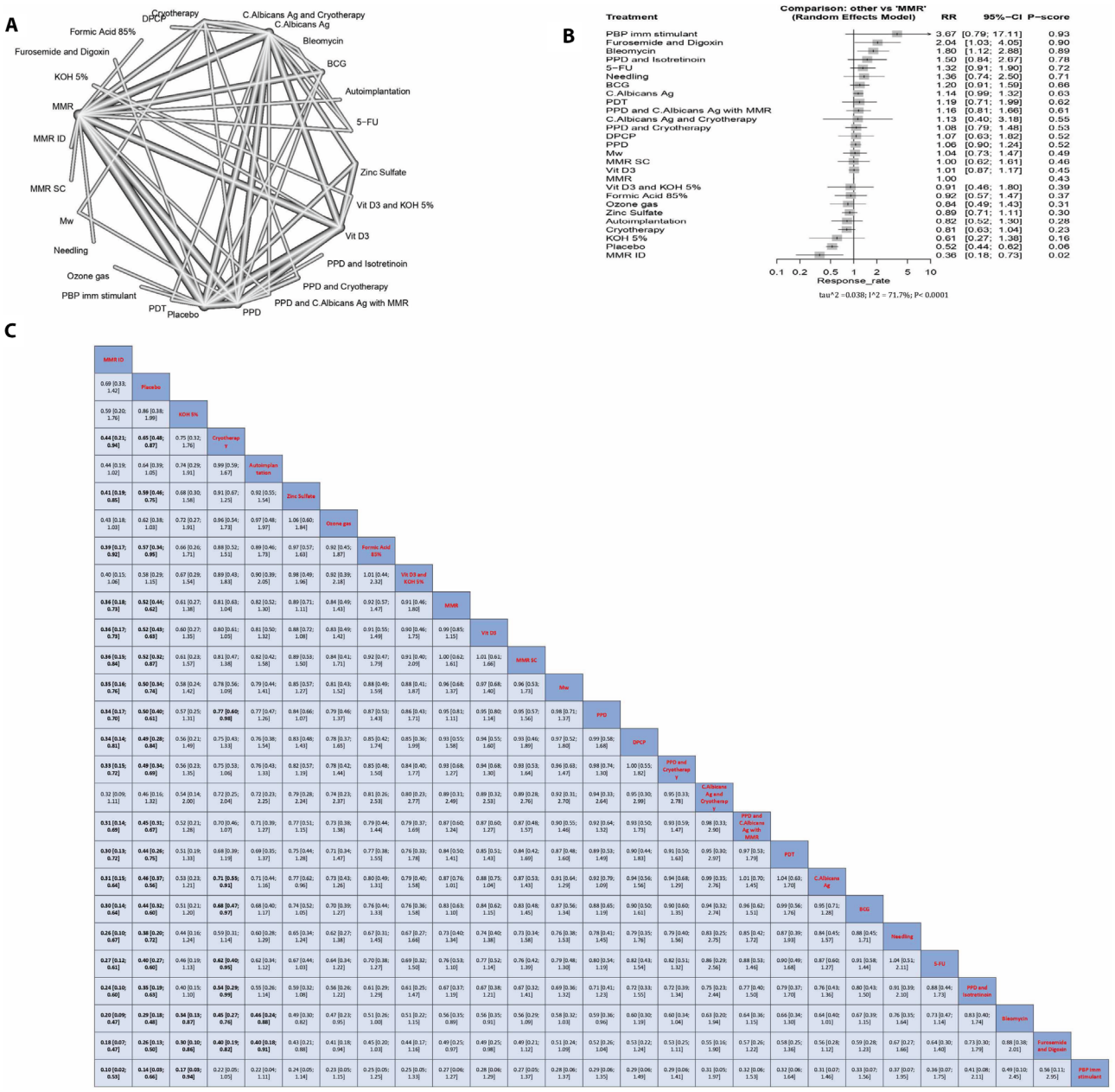

Figure 4. Overall response: (A) Network graph showing direct evidence between the evaluated interventions. (B) A forest plot comparing all interventions. (C) The league table represents the network meta-analysis estimates for all interventions' comparisons.

significantly. For instance, treatments that showed high efficacy in our study might not be universally accessible due to factors such as cost, infrastructure requirements, and regional disparities. Similarly, treatments that demonstrated lower complete response rates, might be more readily available in certain regions or healthcare settings. Therefore, while our study provides valuable insights into the comparative efficacy of various treatments, the real-world implementation of these findings will require further research and strategic planning to overcome these practical challenges. This includes exploring cost-effective alternatives, strengthening healthcare infrastructure, and advocating for equitable healthcare policies

Our study has several strengths as we included all the interventions of intralesional immunotherapy that are used and available. We have high numbers of RCTs with high number of population. We also compared all the available interventions, assessing the most effective treatments through NMA. Our main limitation was the heterogeneity of the included studies regarding the final outcome and inclusion criteria and severity of warts. Nevertheless, Our study is limited by the lack of head-to-head studies between treatments and the sparse literature available for certain types of treatments. This may affect the generalizability of our findings. Also, the number of warts can significantly impact treatment decisions and outcomes. While our study did not specifically

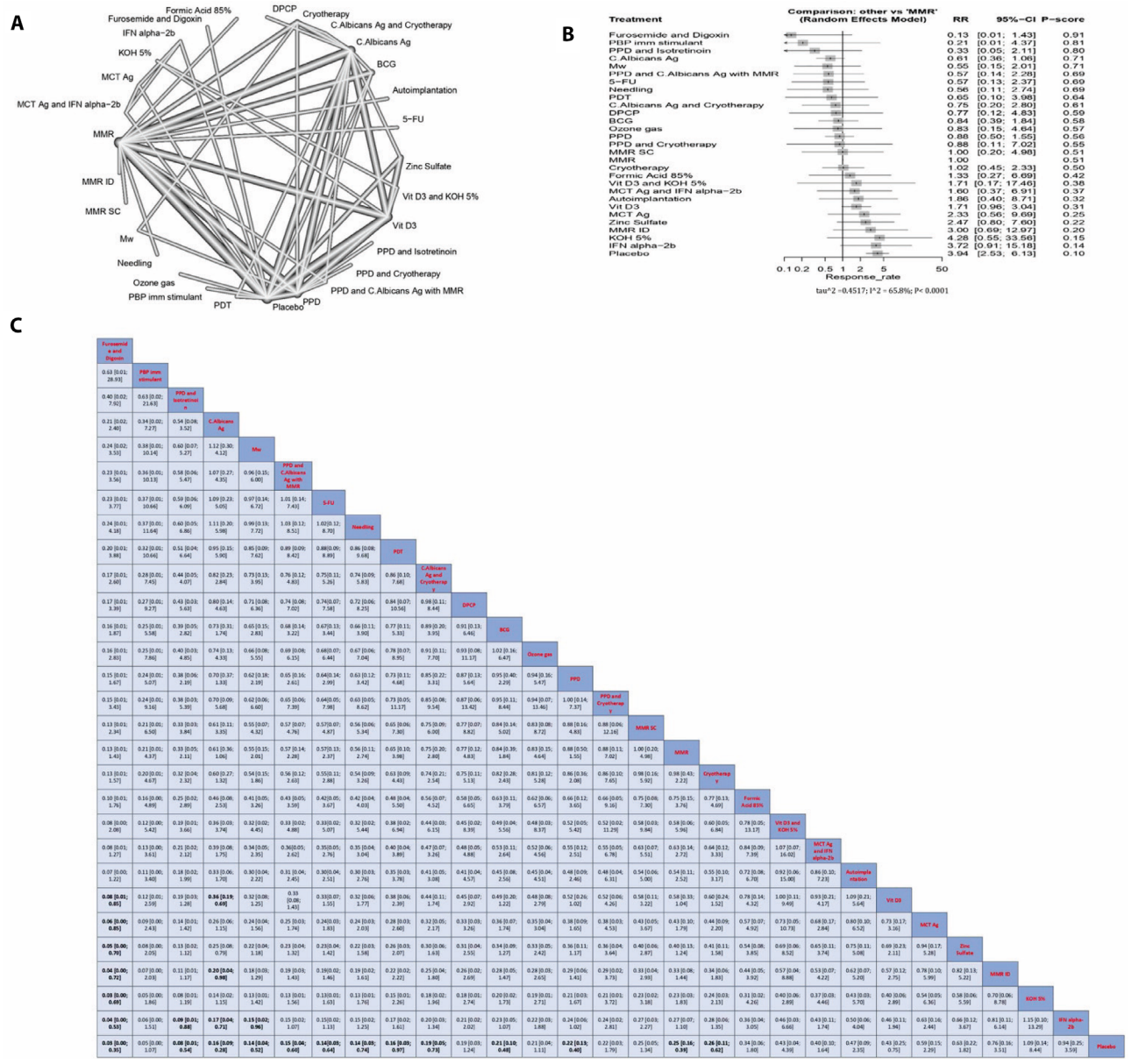

Figure 5. No or minimal response: (A) Network graph showing direct evidence between the evaluated interventions. (B) A forest plot comparing all interventions. (C) The league table represents the network meta-analysis estimates for all interventions' comparisons.

stratify patients based on single or multiple warts due to limitations in the included studies, we recognize that the treatment approach for warts can vary significantly depending on whether the patient presents with single or multiple lesions. We encourage future research to consider stratifying analyses based on wart count to provide more tailored clinical guidance. Moreover, we need more head-to-head studies between the most effective treatments.

Conclusion

Our comprehensive NMA evaluated different treatment modalities for non-genital warts, focusing on efficacy outcomes. Needling, the combination of furosemide and digoxin, and PBP antigen stimulants proved the highest efficacy in complete response. Conversely, IFN α-2b, PDL, and formic acid had the lowest complete response rates. Top choices for overall responses included furosemide with digoxin, PBP antigen stimulants, and bleomycin. For no or minimal response, the mix of furosemide and digoxin, PBP antigen stimulants, and PPD with isotretinoin were the least groups achieving minimal response, which indicates high effectivity. Needling, furosemide with digoxin, and MMR ID were highly effective in partial responses. Meanwhile, 5-FU, bleomycin, and PDT showed the highest partial response rates. Overall, we can conclude that both furosemide with digoxin and PBP antigen stimulants showed the best results. However, direct comparison studies are required to prove the superiority.

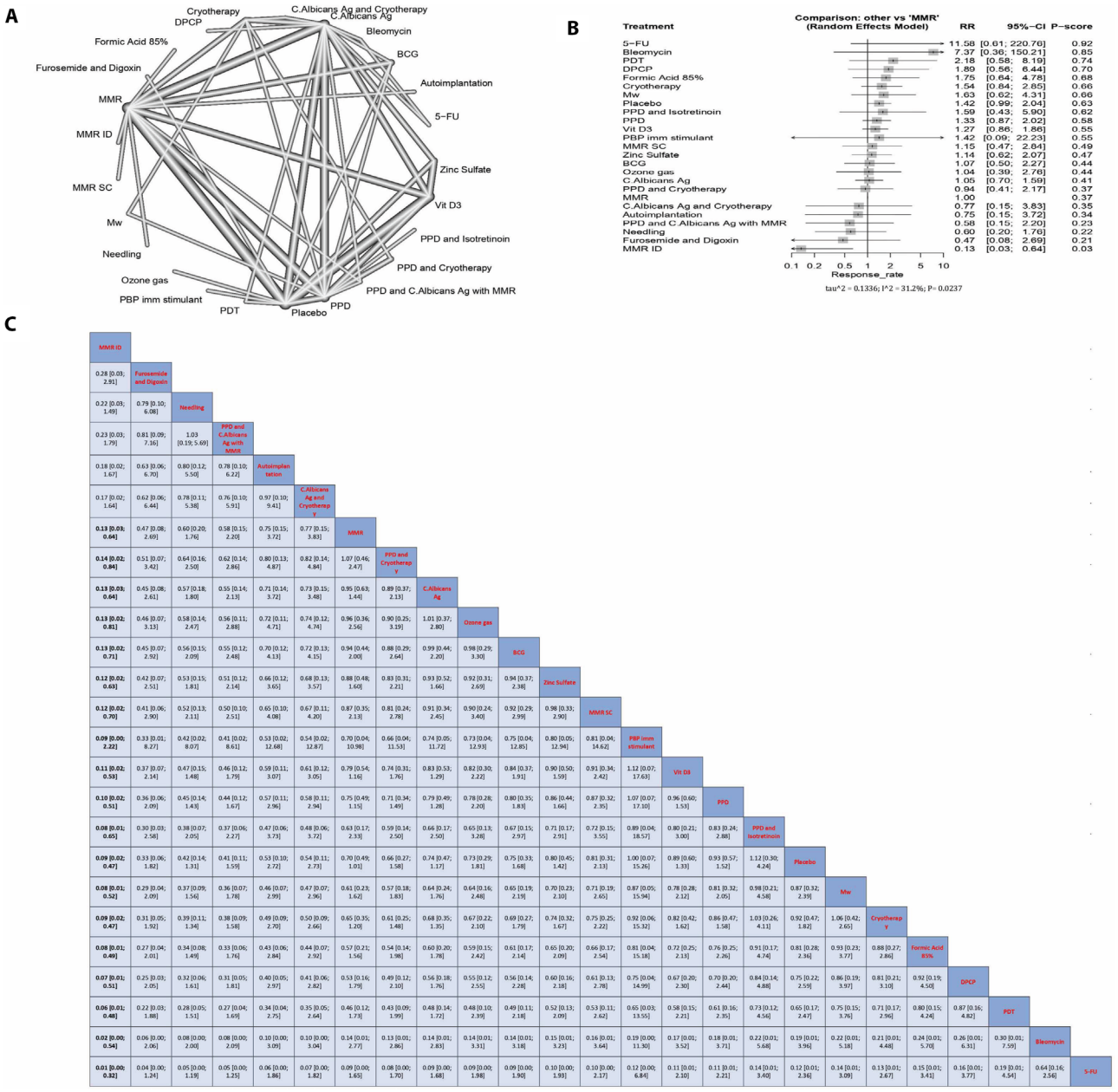

Figure 6. Partial response: (A) Network graph showing direct evidence between the evaluated interventions. (B) A forest plot comparing all interventions. (C) The league table represents the network meta-analysis estimates for all interventions' comparisons.

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