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Topically applied treatments for external genital warts in non-immunocompromised patients: A systematic review and network meta-analysis

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What's already known about this topic?

Conventional topical treatments for external genital warts can be used in an efficacious and safe manner. However, the lack of head-to-head comparative analysis of various therapies renders the choice of a treatment a clinical challenge.

What does this study add?

Podophyllotoxin 0.5% solution was significantly superior to imiquimod 5% cream for lesion clearance, although it was associated with a higher overall rate of adverse events. Sinecatechins was inferior to imiquimod 5% cream in wart clearance. For recurrence, all modalities did not significantly differ from each other. Some unconventional agents were potentially better than conventional therapies regarding their efficacy or safety, although additional studies are required to confirm these results.

Summary

Background: Selecting a topical treatment from among the numerous topical agents for external genital warts remains challenging without clear evidence.

Objectives: To comparatively evaluate the efficacy and safety of topical agents for external genital warts via a network meta-analysis

Methods: We included all randomised, controlled trials that evaluated any topically applied treatment for external genital warts. Using the R package netmeta, network meta-analyses were performed with a frequentist approach.

Results: We identified 41 relevant studies comprising 6,371 patients. Among conventional agents, podophyllotoxin 0.5% solution (odds ratio, 1.94; 95% confidence interval, 1.02–3.71) was significantly more efficacious compared with imiquimod 5% cream for lesion clearance; however, it was associated with higher overall adverse event rate. Sinecatechins 15% ointment (odds ratio, 0.21; 95% confidence interval, 0.12–0.34) was significantly less efficacious compared with imiquimod 5% cream. Idoxuridine, polyhexamethylene biguanide, cidofovir and SB206 showed comparable therapeutic efficacies to conventional therapies. None of the treatments were significantly different from each other with respect to recurrence, patients with severe adverse events, or patients who withdrew because of treatment-related adverse events.

Conclusions: Conventional modalities were efficacious and well tolerated, although each of them had their advantages and disadvantages. Additional efficacy and safety studies are warranted for unconventional agents.

Introduction

The detrimental impact of genital warts on the quality of life and psychosocial well-being has widely been recognised.[1–5] In addition, the socioeconomic burden of genital warts is significant, because they are among the most common sexually transmitted infections.[6]

Several treatment modalities are currently available for external genital warts. Although physical destruction leads to high clearance rates,[7,8] the outcomes vary depending on the proficiency of the clinician. Moreover, physical destruction is associated with extreme pain and high recurrence rates[9] and modalities, such as electrosurgery and laser surgery, may cause human papilloma virus (HPV) transmission, if HPV particles are present in the smoke plume.[10] Topically applied therapies can be easily performed by physicians or patients themselves. Topically applied therapies have typically longer treatment duration compared with that of physical methods;[11] however, because they are primarily field directed, they offer advantages when treating multiple lesions, which have a substantial risk of latent HPV presence in the clinically normal epithelium beyond the warts.[12]

Topically applied therapeutic agents for external genital warts include imiquimod, podophyllotoxin, sinecatechins, trichloroacetic acid (TCA) and podophyllin and unconventional or newly emerging modalities, such as cidofovir gel, idoxuridine, polyhexamethylene biguanide, sodium nitrite with citric acid and SB206 12%. The lack of head-to-head comparative analysis of various therapies renders choice of treatment a clinical challenge. Therefore, we performed a network meta-analysis (NMA) that provided direct, indirect and mixed evidence[13] to simultaneously compare multiple treatments regarding their efficacy and safety.

Materials and methods

We performed this study following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study protocol was registered on PROSPERO (CRD42019131710).

Literature search strategy

An electronic search of five databases (Medline via PubMed, EMBASE, Cochrane Central, Web of science and Scopus) was performed in April 2019 according to the search strategy described in Supplementary Table 1. We used no filters for language or publication period. Reference lists of selected articles were also examined. Two independent reviewers screened the retrieved reports

for eligibility through title, abstract and full-text review. Discrepancies were adjudicated through a third reviewer.

Study eligibility criteria

We included all randomised controlled trials (RCTs) that evaluated the safety and efficacy of any topically applied agents for treating external genital warts in non-immunocompromised patients. No restrictions were made regarding patient sex or race. We excluded studies with intra-individual designs, physically destructive therapies, systemic therapies, patients with genital warts on intravaginal, intra-anal or intraurethral areas and studies lacking outcomes defined in our inclusion criteria.

Data extraction and outcomes

Two independent reviewers extracted data that were checked by a third reviewer. Discrepancies in this process were resolved through expert discussions. The extracted data included first author's last name; publication year; country of origin; inclusion criteria; exclusion criteria; sample-size determination; baseline demographic data; number of participants randomised; final number of participants assessable; treatment schedules, frequencies and durations; complete clearance; recurrence; adverse events; patients with severe adverse events (SAEs); or patients who were lost to follow-up because of treatment-related side effects. SAE was defined as an adverse event, measured as the most severe grade in the scale of each study, regardless of the kinds of adverse events. Complete clearance was defined as complete lesion clearance at 8 ± 4 weeks after treatment. Recurrence was defined as presence of any wart at 12 ± 4 weeks after complete clearance. Adverse events included local skin reactions and any treatment-related side effects. SAE data related to the treatment and the exact causes of patient withdrawals were also collected. Intention-to-treat analysis was performed whenever possible, except for recurrence, for which a per-protocol analysis was used.

Risk of bias assessment

We used the Cochrane Collaboration's tool for assessing risk of bias in randomised trials,[14] which comprised six specific domains — random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting and other

sources of bias. Two authors independently assessed the risk of bias of the included studies. Discrepancies were settled through discussions.

Statistical analysis

The NMA was performed by the R package netmeta, using a frequentist approach. We employed a random effects model assuming there can be inherent heterogeneity between trials in this study. We presented all outcomes as odds ratios (ORs) with 95% confidence intervals (CIs). P-score based on frequentist point estimates and standard errors was used to rank different topical treatments.[15] A higher score meant better treatment. Heterogeneity between studies was assessed using Cochran Q statistics and the I^2 measure from the netmeta statistical package. The I^2 Values of 25–49% are considered low, 50–74% are considered moderate, and 75% or more are considered high levels of heterogeneity. Decomp.design function was used to assess the global inconsistency in each model. *P* value of < 0.05 is suggestive of significant inconsistency. Net split function was used to evaluate the consistency between direct and indirect evidence. We also employed net heat plot, a graphical tool for locating inconsistency in NMA. The stronger the intensity of the colour, the greater the inconsistency between specific direct evidence in the whole network. Publication bias was assessed using comparison-adjusted funnel plots. Subgroup analyses or pairwise meta-analyses were also performed if applicable to further explore the data. *P* value < 0.05 indicated a significant difference.

Results

Literature search and study characteristics

We initially retrieved 1,438 records from electronic database searches. After removing duplicates and excluded studies, 41 RCTs (6,371 patients) met eligibility criteria (Fig. 1).[16–56] Figure 2 shows the network plots, depicting direct evidence between treatments. A total of 25 treatments were used in 41 RCTs: imiquimod 1% cream (n = 2), imiquimod 2% cream (n = 2), imiquimod 2.5% cream (n = 2), imiquimod 3.75% cream (n = 2), imiquimod 5% cream (n = 9), podophyllotoxin 0.15% cream (n = 3), podophyllotoxin 0.25% solution (n = 1), podophyllotoxin 0.3% cream (n = 2), podophyllotoxin 0.5% cream (n = 6), podophyllotoxin 0.5% solution (n = 12), podophyllotoxin 0.5% solution or cream (n = 1), podophyllin 0.5% solution (n = 2), podophyllin 2.0% solution (n = 1), podophyllin 20–25% solution (n = 8), sinecatechins 10% ointment (n = 3), sinecatechins 15%

ointment (n = 3), TCA (n = 2), TCA with podophyllin 25% (n = 1), sodium nitrite with citric acid cream (n = 1), SB206 12% gel (n = 1), polyhexamethylene biguanide cream (n = 1), interferon alpha cream (n = 2), idoxuridine 0.25% cream (n = 2), idoxuridine 0.5% cream (n = 1) and cidofovir gel (n = 1). Because imiquimod 5% cream is a standard, topically applied therapy for external genital warts in South Korea, this was used as the main comparator, along with the placebo to analyse treatment outcomes. The baseline characteristics of patients, detailed treatment schedules, frequencies and durations are described in Supplementary Table 2. Risk of bias in the included studies is shown in Supplementary Table 3. Only eight studies showed low or unclear risk of bias for all domains,[17,25,26,29,30,42,43,53] thereby rendering a high risk of bias across trials for each outcome. Results from all comparisons, regarding each outcome, are shown in Supplementary Figures - 1 (complete clearance), -2 (recurrence), -3 (adverse events) and - 4 (patients with SAEs or patients who withdrew because of treatment-related adverse events).

Complete clearance

For complete clearance, 41 RCTs were included in NMA.[16–56] All treatments were significantly more efficacious than the placebo (Fig. 3 a). Compared with imiquimod 5% cream, only interferon alpha cream (OR, 6.22; 95% CI, 1.77–21.78) and podophyllotoxin 0.5% solution (OR, 1.94; 95% CI, 1.02–3.71) were significantly more efficacious. Imiquimod 5% cream had significantly better therapeutic efficacy compared with imiquimod 1% (OR, 0.21; 95% CI, 0.14–0.34), 2.5% (OR, 0.25; 95% CI, 0.13–0.49) and 3.75% (OR, 0.36; 95% CI, 0.18–0.70) cream; sinecatechins 10% (OR, 0.18; 95% CI, 0.11–0.30) and 15% (OR, 0.21; 95% CI, 0.12–0.34) ointment; and sodium nitrite with citric acid cream (OR, 0.27; 95% CI, 0.11–0.69) (Fig. 3 b). Each treatment's P-score showed that idoxuridine 0.5%, interferon alpha, idoxuridine 0.25%, imiquimod 2% and polyhexamethylene biguanide creams were the most efficacious for complete clearance (Table 1). We conducted a subgroup analysis excluding the studies performed before the introduction of imiquimod.[19,22,23,26,28,29,30–32,35,37,44,46,48,53–55] The difference between the efficacy of imiquimod 5% cream and podophyllotoxin 0.5% solution was insignificant, whereas sinecatechins ointments remained inferior to imiquimod 5% cream in this analysis.

When we conducted another subgroup analysis excluding the studies on unconventional modalities,[29,30,36,38,42,52] podophyllotoxin 0.5% solution continued to show better efficacy than imiquimod 5% cream. Sinecatechins remained inferior to imiquimod 5% cream in this anylsis.

The ranks among conventaionl options by P-score analysis was identical with the previous ranks shown in Table 1.

Recurrence

A total of 18 RCTs were included in NMA for recurrence;[17,18,21,23,24,26–28,31,34–36,43,44,50,53,54,56] showed that none of the topical agents were significantly different from the placebo or imiquimod 5% cream (Fig. 3 c, d) and also from each other in entire comparisons (Supplementary Fig. 2). The P-score analysis revealed that imiquimod 1% cream, placebo, sinecatechins 15% ointment, imiquimod 5% cream and sinecatechins 10% ointment were the most efficacious for lowering recurrence (Table 1).

Adverse events

A total of 19 RCTs were included in NMA for adverse event analysis,[16–22,24,26,31,32,37,38,45,46,52,53,55,56] which showed that, except for imiquimod 1% and 2% cream, interferon alpha cream, SB206 12% gel and sodium nitrite with citric acid cream, all treatment options were associated with significantly higher overall adverse event rates compared to placebo (Fig. 3 e). Podophyllin 0.5% (OR, 4.71; 95% CI, 1.38–16.11) and 2.0% solution (OR, 5.31; 95% CI, 1.56–18.06); podophyllotoxin 0.15% (OR, 4.21; 95% CI, 1.35–13.11) and 0.5% cream (OR, 2.32; 95% CI, 1.22–4.42); and podophyllotoxin 0.5% solution (OR, 2.46; 95% CI, 1.20–5.06) were related to significantly higher overall adverse event rate compared with imiquimod 5% cream. Only imiquimod 1% cream (OR, 0.41; 95% CI, 0.23–0.73) and placebo (OR, 0.25; 95% CI, 0.16–0.40) showed significantly lower overall rate of adverse events than imiquimod 5% cream (Fig. 3 f). The P-score indicated that, in addition to the placebo, treatments with imiquimod 1% cream, sodium nitrite with citric acid cream, imiquimod 2.5% cream and imiquimod 3.75% cream showed favourable outcomes regarding adverse events (Table 1). When we conducted a subgroup analysis excluding the studies performed before the introduction of imiquimod,[19,22,26,31,32,37,46,53,55] the difference in overall adverse event rate between imiquimod 5% cream and podophyllotoxin 0.5% cream became insignificant. When we conducted another subgroup analysis only including studies on imiquimod 5% cream and podophyllotoxin 0.5%, [16,18–22,24,31,32,37,46,53,55,56] podophyllotoxin 0.5% was still related to significantly higher overall adverse event rate compared with imiquimod 5% cream. In pairwise meta-analyses, podophyllotoxin 0.5% (OR, 7.47; 95% CI, 5.69–9.79; I^2 = 27%)

and imiquimod 5% (OR, 4.74; 95% CI, 3.81–5.91; $I^2 = 0\%$) were associated with higher overall adverse event rates compared with placebo.

Patients with SAEs or patients who withdrew because of treatment-related adverse events

The analysis of 17 studies[19,23,31–33,35–38,42–44,50,52,53,55,56] showed that imiquimod 5% cream (OR, 8.68; 95% CI, 1.01–74.43), podophyllin 2.0% solution (OR, 38.43; 95% CI, 1.28–1156.07), podophyllotoxin 0.5% cream (OR, 5.98; 95% CI, 1.07–33.54), polyhexamethylene biguanide cream (OR, 55.87; 95% CI, 3.33–937.61) and sinecatechins 10% (OR, 8.03; 95% CI, 3.97–16.24) and 15% cream (OR, 8.54; 95% CI, 4.23–17.25) were associated with significantly higher numbers of patients with SAEs or patients who were lost to follow-up because of treatment-related side effects compared to the placebo (Fig. 3 g). Except for the placebo, none of the treatments was significantly different from the imiquimod 5% cream (Fig. 3 h). Moreover, none of the treatments, other than the placebo, were significantly different from each other in entire comparisons (Supplementary Fig. 4). Placebo, podophyllotoxin 0.15% cream, cidofovir gel, SB206 12% gel and podophyllotoxin 0.3% cream were the top-ranked treatments (Table 1). SAEs or adverse events that led to patient withdrawal are described in Table 2. All treatment-related SAEs were limited to local reactions.

Heterogeneity and consistency analysis

Only NMA for adverse events showed moderate heterogeneity between studies. NMA analyses of the remaining three outcomes showed high homogeneity (Supplementary Table 4). The results of decomp.design function supported the global consistency for all NMAs (Supplementary Table 5), indicating the reliability of the results. Only NMA for recurrence showed local inconsistency in net heat plot and net split function analysis (Supplementary Fig. 5, 6).

Publication bias assessment

Comparison-adjusted funnel plots (Fig. 4 a, b, c and d) were symmetrical, implying no evidence of publication bias.

Discussion

Though several systematic reviews on topical agents for genital warts have been performed, [57–59] they were examined using conventional meta-analysis. In contrast, we have used NMA to evaluate

the evidence for topical agents' efficacy for treating genital warts. Unlike traditional meta-analysis, where two interventions are compared using pooled head-to-head data, NMA allows not only for comparisons between more than two interventions, but also for comparisons between interventions that have not been contrasted directly in RCTs.[13] These advantages enable clinicians to take informed treatment decisions that are based on evidence from NMA, particularly in the absence of clinical trials directly comparing candidate treatments. In this study, we systematically reviewed all topically applied treatment options for external genital warts that were studied in at least one RCT and met our eligibility criteria.

All topical agents included in this study were statistically superior to the placebo in terms of complete clearance of lesions which is consistent with results from previous conventional meta-analyses.[57–59] In their meta-analysis, Yan et al. reported that both imiquimod 5% and podophyllotoxin 0.5% were significantly better than the placebo for complete lesion clearance.[59] However, they were unable to conclude superiority, inferiority or equivalence of imiquimod and podophyllotoxin due to the absence of a direct comparison. A subsequent RCT demonstrated the equivalence of imiquimod 5% cream and podophyllotoxin 0.5% solution.[33] In the present study, although NMA included all direct and indirect comparisons, we found podophyllotoxin 0.5% solution was significantly better than imiquimod 5% cream in terms of complete clearance. In this study, we also included non-conventional or newly emerging modalities reported in at least one RCT. Among these agents, idoxuridine, polyhexamethylene biguanide, cidofovir and SB206 12% were found to be promising in lesion clearance. However, the limited number of clinical trials on these agents and the high or unclear overall risk of bias in those studies[29,30,36,42,52] restricted their utility.

We found only two studies by the same author who employed topically applied interferon alpha for external genital warts and found high efficacy which could be attributed to a regimen of three times daily application.[46,48] The reproducibility of these results could not be confirmed, because interferon alpha is poorly absorbed in the normal skin, unless warts are located on the mucosal epithelium.[60]

Sinecatechins' therapeutic efficacy was significantly lower than other conventional, self-applied topical treatments, such as imiquimod 5% or podophyllotoxin. Considering the placebos in studies on sinecatechins[27,43,50] were more efficacious than those in other studies, our results should be confirmed via clinical trials in the future.

The current study revealed the similarity in recurrence among all treatment modalities in entire comparisons. Modalities such as sinecatechins or imiquimod requiring longer treatment periods to remove warts tend to be better options regarding recurrence according to the P-score analysis. This could be attributed to their mechanism of action which includes provoking a host immune response.[20,27]

Imiquimod, an immune response modifier,[21] and sodium nitrite with citric acid, a nitric oxide-releasing agent that also can activate immune response in the skin,[38] offered the best options in terms of safety. On the other hand, cytodestructive agents, such as podophyllin or podophyllotoxin,[9] were related to significantly higher overall rate of adverse events compared with imiquimod.

Creams with lower than 5% concentration of imiquimod have been examined in several RCTs.[17,21,24,39,45,47] The authors surmised that creams with lower imiquimod concentrations would reduce treatment period by increasing the application frequency as well as reducing the incidence of treatment-related adverse events. However, in our analysis, imiquimod 2.5% or 3.75% showed significantly lower efficacy than imiquimod 5% in clearing genital warts, while the overall rates of treatment-related adverse events were not significantly different. Only imiquimod 1% was associated with significantly lower incidence of adverse events than imiquimod 5% but showed lower efficacy in lesion clearance. While imiquimod 2% was significantly better at lesion clearance than imiquimod 5%, the patients applied the cream twice daily in one of the two studies on imiquimod 2%.[45] As a result, the P-score analysis showed inferiority over the imiquimod 5% in terms of safety.

SAEs or patients who withdrew because of treatment-related adverse events were quantitatively and qualitatively analysed in this study. Because the two variables used in this analysis were the number of patients with SAEs or patients who withdrew because of treatment-related adverse events and the size of the safety population, our results were influenced by both the treatment period and each agent's safety characteristics. With longer treatment durations, the likelihood of a patient experiencing an SAE or withdrawal from the trial increased. There was a tendency for topical agents with relatively longer treatment period to be ranked at the bottom of our analysis. All specific treatment-related SAEs were limited to local reactions and death or permanent damage related to treatment was not reported in any RCTs included in this study.

P-score measures the mean certainty that a treatment is better than another treatment, based only on the point estimates and standard errors of the frequentist NMA estimates.[61] Therefore, P-scores

of unconventional therapies should be interpreted with caution because of the large uncertainties with effect estimates. There can also be large uncertainties in the P-score analyses from NMAs regarding recurrence and patients with SAEs or patients who withdrew because of treatment-related adverse events considering the large uncertainties with effect estimates in general in those NMAs. Clinicians should be aware that P-scores has no major advantage compared with CIs when choosing a treatment over another.[61]

This study is not without limitations. First, the heterogeneity of each study's baseline characteristics, such as male to female ratio, warts number, size, site and duration were not considered in the analysis. Second, the results can be influenced by variation in choice of study design, although global consistency was supported by statistical tests for all outcomes. Third, the number of RCTs included was relatively small considering the number of treatment modalities, such that some comparisons in NMA relied on only one study. In addition, only eight treatment modalities could be evaluated in terms of all four outcomes — complete clearance, recurrence, adverse events and patients with SAEs or patients who withdrew because of treatment-related adverse events. Lastly, one or more domains of risk of bias assessment of included studies were unclear or high, which decreased this study's overall evidence level.

In conclusion, all topically applied treatment options included in this analysis were efficacious and well tolerated, although they each had advantages and disadvantages affecting the four outcomes assessed. Cytodestructive agents, such as podophyllin and podophyllotoxin, were highly efficacious in rapidly clearing lesions, but they were more likely to have safety concerns. In clearing genital warts, sinecatechins was significantly less efficacious than podophyllotoxin 0.5% or imiquimod 5%. Immune-modifying or enhancing agents, such as imiquimod and sinecatechins, took longer to achieve resolution; therefore compliance with treatment was another factor to be considered when choosing these therapeutic agents. Unconventional therapies were found to be at least comparable to conventional therapies for eradicating external genital warts.

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Concept and design, data acquisition, data analysis/interpretation, drafting manuscript, critical revision of manuscript and final approval: JM Jung, CJ Jung, WJ Lee, CH Won, MW Lee, JH Choi and SE Chang
Statistical analysis: JM Jung and CJ Jung
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Figure legends

Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of literature search and study selection.

Figure 2. Network plots demonstrating direct evidence between the assessed topical treatments in terms of complete clearance (a), recurrence (b), adverse events (c), patients with severe adverse events, or patients who withdrew because of treatment-related adverse events (d). A line between any two treatments means there is at least one trial comparing them. The line thickness is proportional to the number patients who participated in the trials between two treatments. The shading indicates a three-arm study.

Figure 3. Forest plots of network meta-analysis for complete clearance (a) others *vs.* 'Placebo, (b) other *vs.* Imiquimod 5% cream', for recurrence (c) other *vs.* 'Placebo, (d) others *vs.* Imiquimod 5% cream', for adverse events (e) others *vs.* 'Placebo, (f) others *vs.* Imiquimod 5% cream', for patients with severe adverse events or patients who withdrew because of treatment-related adverse events (g) others *vs.* 'Placebo, (h) others *vs.* Imiquimod 5% cream'.

Figure 4. Comparison-adjusted funnel plot of trials included in network meta-analysis for complete clearance (a), recurrence (b), adverse events (c) and patients with severe adverse events or patients who withdrew because of treatment-related adverse events (d).

Supplementary Figure 1. Results from all comparisons regarding complete clearance.
Supplementary Figure 2. Results from all comparisons regarding recurrence.
Supplementary Figure 3. Results from all comparisons regarding adverse events.
Supplementary Figure 4. Results from all comparisons regarding patients with severe adverse events or patients who withdrew because of treatment-related adverse events.
Supplementary Figure 5. Net heat plot of recurrence.
Supplementary Figure 6. Net split of complete clearance (a), recurrence (b), adverse events (c) and patients with severe adverse events or patients who withdrew because of treatment-related adverse events (d).

1 Table 1. Results of P-score analysis in terms of each outcome

Treatment	P-score for complete clearance (ranking)	P-score for recurrence (ranking)	P-score for adverse events (ranking)	P-score for severe adverse events* (ranking)
Idoxuridine 0.5% cream	**0.93 (1)**			
Interferon alpha cream	**0.90 (2)**		0.71 (6)	
Idoxuridine 0.25% cream	**0.81 (3)**			
Imiquimod 2% cream	**0.80 (4)**		0.25 (14)	
Polyhexamethylene biguanide cream	**0.79 (5)**	0.56 (7)		0.14 (15)
Podophyllin 2.0% solution	0.74 (6)		0.11 (17)	0.17 (14)
Podophyllin 0.5% solution	0.74 (7)	0.11 (16)	0.14 (16)	0.29 (13)
Podophyllotoxin 0.5% solution	0.69 (8)	0.55 (8)	0.32 (12)	0.62 (6)
Podophyllotoxin 0.3% cream	0.66 (9)	0.41 (10)	0.31 (13)	**0.62 (5)**
TCA with podophyllin 25%	0.62 (10)			
Cidofovir gel	0.63 (11)			**0.72 (3)**
Podophyllotoxin 0.25% solution	0.62 (12)	0.28 (15)		
SB206 12% gel	0.54 (13)		0.46 (10)	**0.65 (4)**
Podophyllotoxin 0.5% cream	0.54 (14)	0.60 (6)	0.32 (11)	0.51 (7)
Podophyllotoxin 0.15% cream	0.48 (15)	0.39 (11)	0.16 (15)	**0. 84 (2)**
Imiquimod 5% cream	0.47 (16)	**0.69 (4)**	0.61 (7)	0.40 (11)
Podophyllin 20%–25% solution	0.40 (17)	0.48 (9)	0.47(9)	0.50 (8)
TCA	0.39 (18)			
Imiquimod 3.75% cream	0.27 (19)	0.34 (13)	**0.72 (5)**	
Podophyllotoxin 0.5%	0.21(20)	0.32 (14)	0.51 (8)	

solution or cream				
Sodium nitrite with citric acid cream	0.20 (21)		**0.80 (3)**	0.31 (12)
Imiquimod 2.5% cream	0.17 (22)	0.39 (12)	**0.76 (4)**	
Imiquimod 1% cream	0.14 (23)	**0.78 (1)**	**0.86 (2)**	
Sinecatechins 15% ointment	0.13 (24)	**0.71 (3)**		0.40 (10)
Sinecatechins 10% ointment	0.09 (25)	**0.65 (5)**		0.44 (9)
Placebo	0.00 (26)	**0.75 (2)**	**0.98 (1)**	**0.90 (1)**

Abbreviations: TCA, trichloroacetic acid

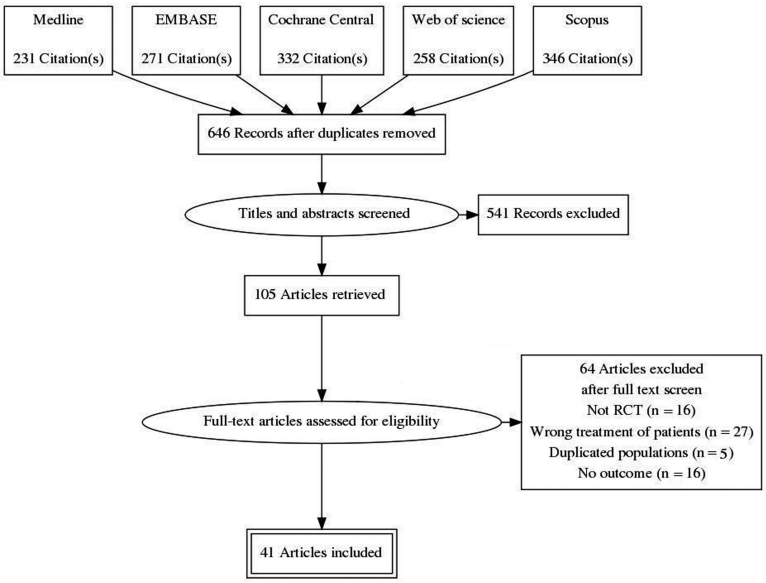
* Severe adverse events or treatment-related adverse events that led to patient withdrawal

The top five best treatments for each column were highlighted in bold type.

Table 2. Severe adverse events or adverse events that led to patient withdrawal for each agent

Topical treatment, the number of events/safety population (%)
Polyhexamethylene biguanide, 21/94 (22.34%) severe erythema
Podophyllin 2.0% solution, 4/106 (3.77%) unspecified adverse events that led to withdrawal
Podophyllin 0.5% solution, 2/103 (1.94%) unspecified SAEs
Sodium nitrite with citric acid, 7/73 (9.59%) unspecified adverse events that led to withdrawal
Imiquimod 5% cream, 8/20 (40%) severe erythema and erosion
Sinecatechins 15% ointment, 111/397 (27.96%) unspecified severe local reactions
Sinecatechins 10% ointment, 107/400 (26.75%) unspecified severe local reactions
Podophyllin 20%–25% solution, 6/117 (5.13%) unspecified severe local reactions, 1/117 (0.85%) severe erythema and swelling and 1/117 (0.85%) papule enlargement that led to withdrawal
Podophyllotoxin 0.5% cream, 8/311 (2.57%) unspecified adverse events that led to withdrawal, 2/311 (0.64%) foreskin swelling that led to withdrawal, 1/311 (0.32%) severe tenderness and 1/311 (0.32%) unspecified SAEs
Podophyllotoxin 0.5% solution, 6/331 (1.81%) erythema with inflammation and erosion, 5/331 (1.51%) severe erosion, 5/331 (1.51%) unspecified SAEs, 4/331 (1.21%) severe pain and erythema, 1/331 (0.30%) severe inflammation, 1/331 (0.30%) erythema that led to withdrawal, 1/331 (0.30%) penile swelling that led to withdrawal, 1/331 (0.30%) burning and itching with nausea that led to withdrawal and 1/331 (0.30%) marked pruritus that led to withdrawal
Podophyllotoxin 0.3% cream, 5/31 (16.13%) unspecified SAEs
SB206 12% gel, 1/30 (3.33%) severe intolerability
Cidofovir gel, 1/19 (5.26%) ulceration
Podophyllotoxin 0.15% cream, 2/30 (6.67%) unspecified SAEs
Placebo, 9/602 (1.50%) unspecified severe local reactions

Abbreviations: SAE, severe adverse event



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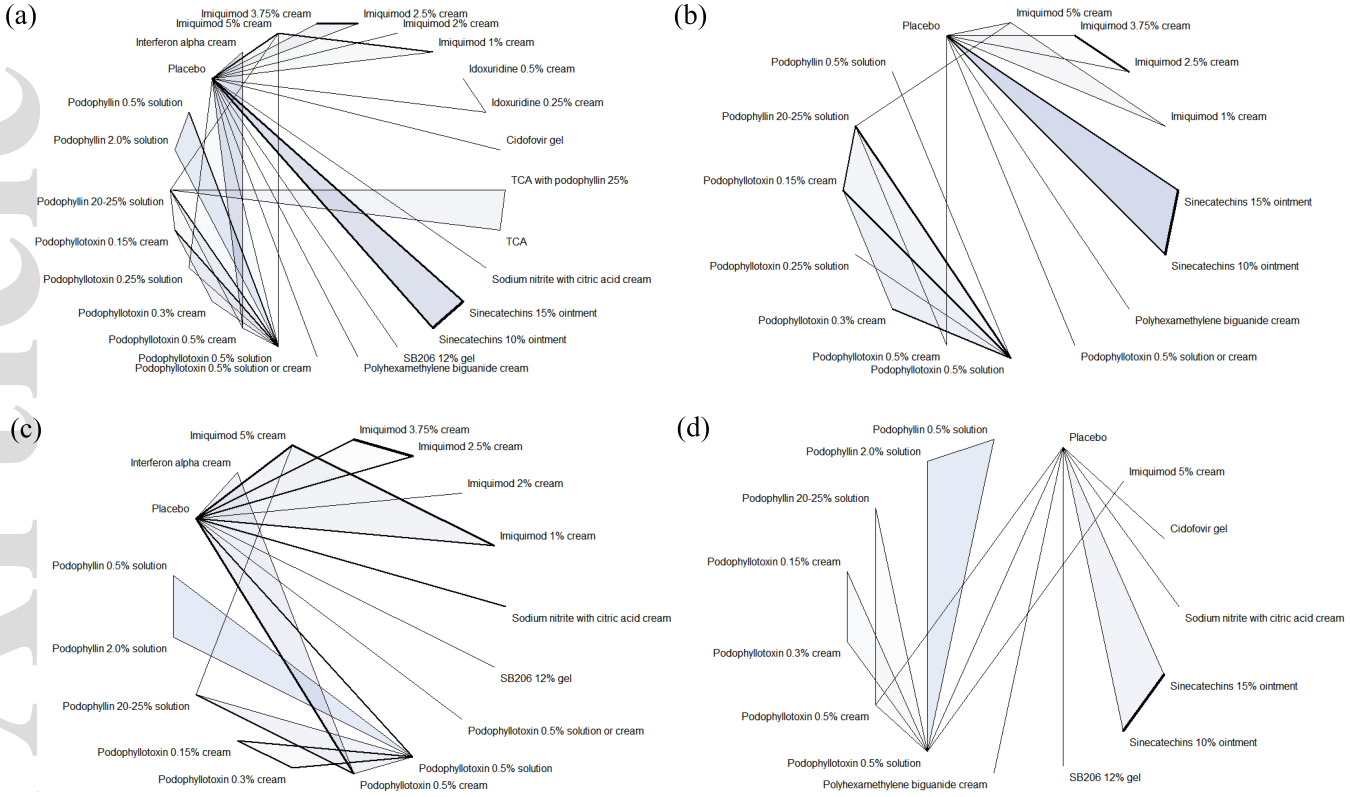

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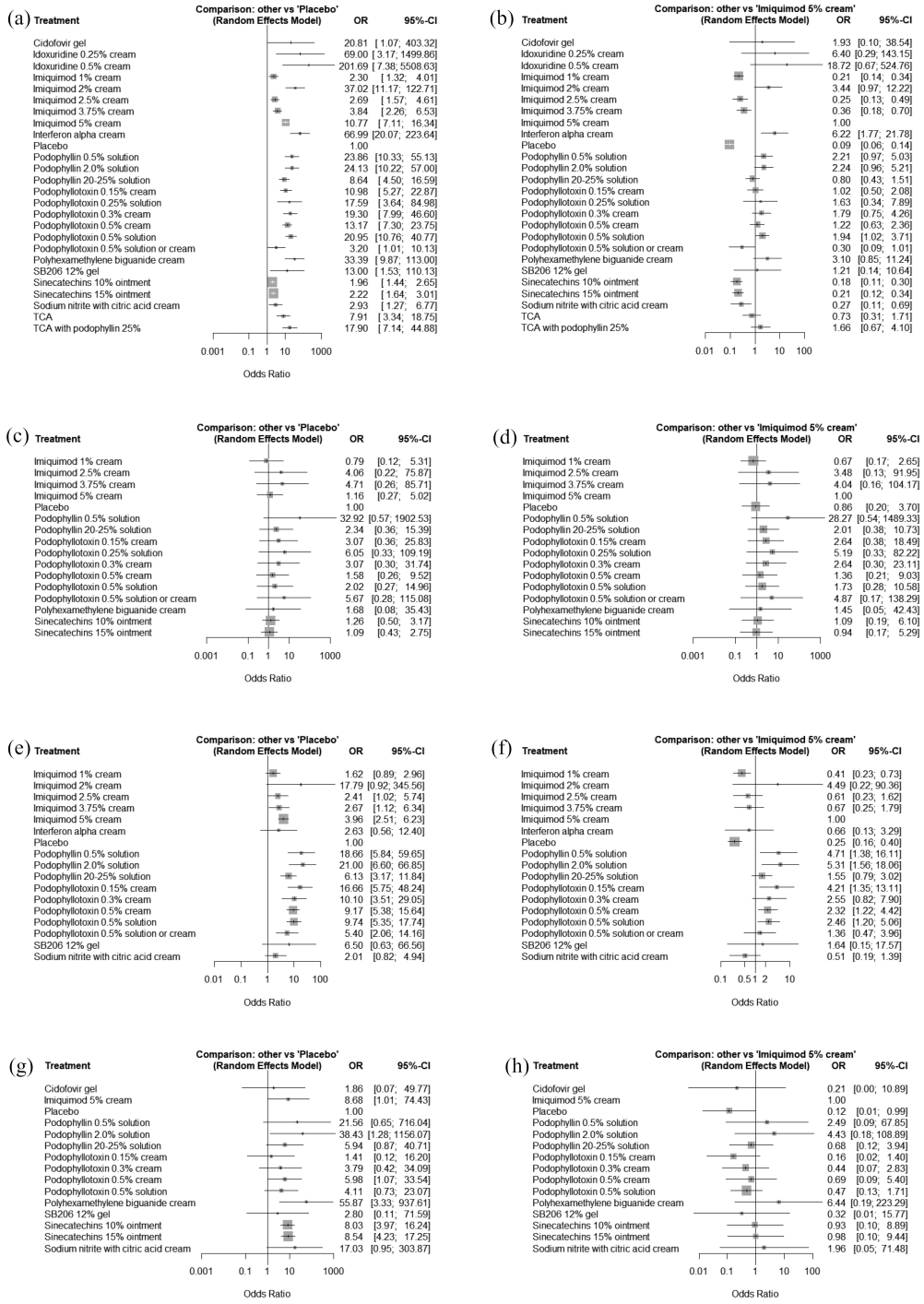

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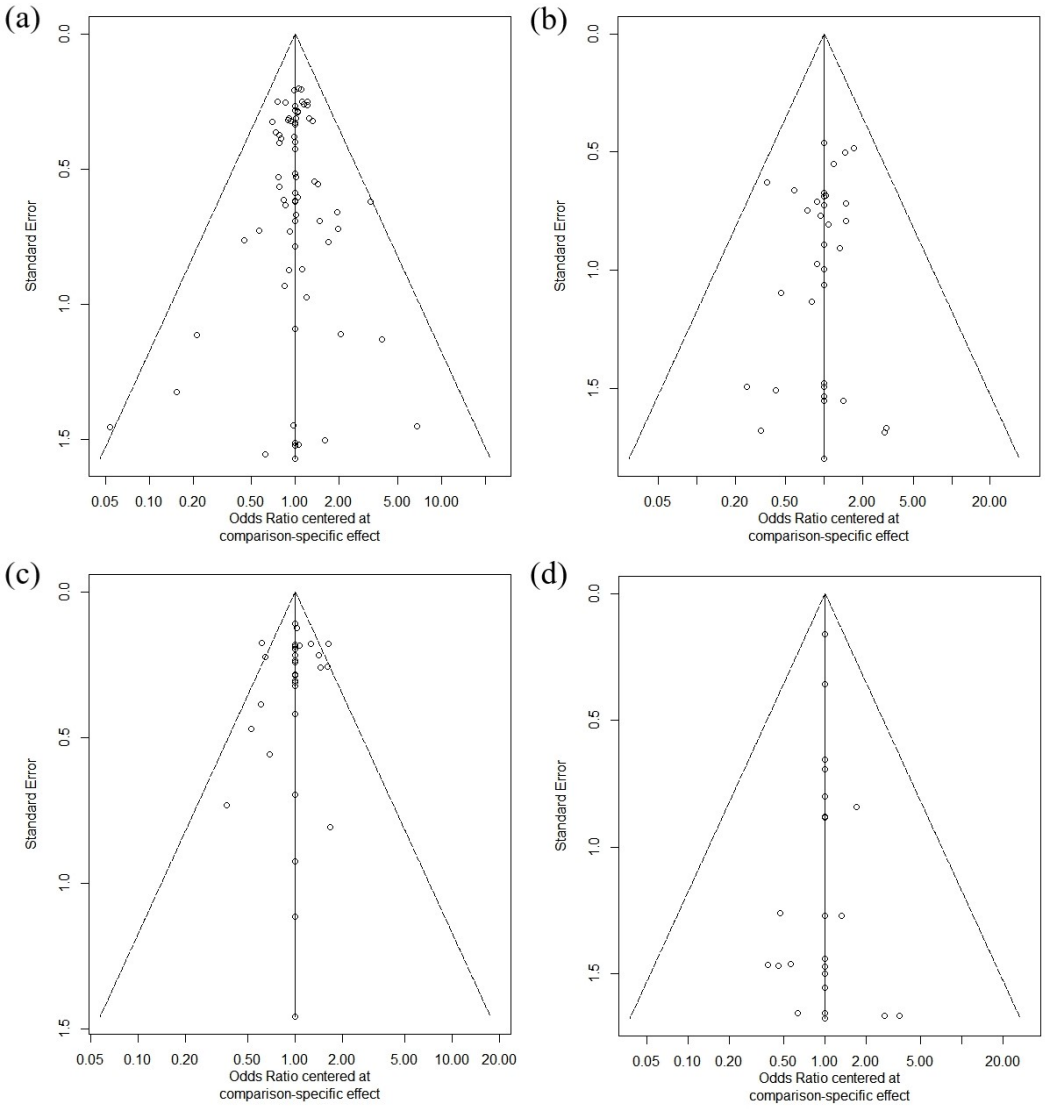

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