

## Review Article

# Comparison of Cryotherapy and Topical Salicylic Acid in Common Warts: A Systematic Review and Meta-Analysis

Dipika Chaudhary <sup>1,2</sup>, Yan Sun <sup>1,2</sup> and Xinghua Gao <sup>1,2</sup>

<sup>1</sup>Department of Dermatology, The First Hospital of China Medical University, Shenyang, China

<sup>2</sup>NHC Key Laboratory of Immunodermatology, Ministry of Education Key Laboratory of Immunodermatology, National Joint Engineering Research Center for Diagnosis and Treatment of Immunologic Skin Diseases, The First Hospital of China Medical University, Shenyang, China

Correspondence should be addressed to Yan Sun; sunyan805@163.com and Xinghua Gao; gaobarry@hotmail.com

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**Background.** Common warts are most common complaint among children and adults caused by human papillomavirus (HPV). Cryotherapy and topical salicylic acid are common therapies. **Objective.** To compare the efficacy and safety of cryotherapy and topical salicylic acid in common warts. **Methods.** Randomized controlled trials (RCTs) comparing cryotherapy and topical salicylic acid treatment in patients with common warts were searched by using PubMed, Embase, Google Scholar, and Cochrane Database of Systematic Reviews up to Oct 20, 2021. The keywords were “common warts/verruca,” “cryotherapy,” and “salicylic acid.” The language was restrained to English. No age or gender limitation was conducted. The outcomes were complete remission of all warts at different observation times, recurrence rates, and side effects. Study-specific effect sizes were pooled by using the fixed-effects model and the Mantel–Haenszel method.  $I^2$  was used to assess heterogeneity of studies. **Results.** Seven articles involving 976 patients randomized into the cryotherapy group or salicylic acid group were included. Of whom, 487 patients received cryotherapy, while 489 received salicylic acid treatment. With the fixed-effects model, the pool effect of complete clearance of warts at 12 weeks comparing cryotherapy and salicylic acid was not statistically significant (RR = 0.99 (0.84–1.17),  $I^2 = 0\%$ ). **Conclusion.** Comparable efficacy of cryotherapy and topical salicylic acid was conducted in common wart treatment. More high-quality pieces of evidence with more samples are needed to confirm the results for further recommendations.

## 1. Introduction

Common warts are widespread benign skin conditions caused by human papilloma virus (HPV) [1, 2]. They frequently affect the hands as well as feet but also in other sites. They are widespread in general population, estimated to affect approximately 7–12% populations worldwide [3]. There are more than 200 types of HPV identified, most of which are DNA viruses infecting epithelial cells [4]. They affect any area on the skin and mucous membrane and are transmitted by direct or indirect contact. Although warts disappear spontaneously without treatment in 15–63% of cases in years [1], patients usually seek treatments to avoid physical discomfort and debilitating appearance.

There are several treatment options available for common warts, including cryotherapy, topically applied treatments, surgical curettage, and local hyperthermia [5]. Topical salicylic acid is the first-line treatment choice of common warts, and further treatment with cryotherapy is indicated as second-line therapy without clearance of warts [6]. Cryotherapy is usually applied on lesions at intervals of 2–4 weeks by using liquid nitrogen, which works by freezing tissue, damaging intended cells and their vascular supply, and is also expected to stimulate the immune system which leads to resolution of warts [4]. Salicylic acid is comparatively cheaper, readily available, and self-applicable topical treatment. It is effective for warts with limited adverse effects but requires daily application for several weeks [4]. Local

hyperthermia is a patent device held by our team. It destroyed HPV-infected tissue by antigen-presenting cells, T cells, and natural killer cells at 44°C [7]. Our previous study including 1027 patients showed comparable complete clearance rates of plantar warts by local hyperthermia and cryotherapy (50.9% vs. 54.3%) 3 months after treatment [8].

Several studies reported cryotherapy and topical salicylic acid treatment in common warts. But the results were controversial. Therefore, we conducted the present systemic review and meta-analysis in order to compare the efficacy as well as safety of cryotherapy and topical salicylic acid in common warts.

## 2. Methods

The procedure followed the recommendations for the Preferred Reporting Items for Systematic Review (PRISMA) [9] and the Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Collaboration, 2011).

**2.1. Search Strategy.** Randomized controlled trials (RCTs) of cryotherapy and topical salicylic acid treatment in common warts of healthy, nonimmunocompromised adults, and/or children were searched by using PubMed, Google Scholar, Embase, and Cochrane Database of Systematic Reviews up to Oct 20, 2021. The keywords were “common warts/verruca,” “salicylic acid,” and “cryotherapy.” The language was restrained to English. No age or gender limitation was conducted.

**2.2. Study Selection and Data Extraction.** All studies with cure rates of both cryotherapy and salicylic acid treatments were selected by screening abstracts or even full text. Studies with recurrent/recalcitrant warts, genital warts, immunocompromised patients (such as agammaglobulinemia), impaired healing (such as diabetics), cold intolerance (such as cold urticaria or Raynaud’s syndrome), blood dyscrasias of unknown origin, cryoglobulinemia, cryofibrinogenemia, and connective or autoimmune disease were excluded. Guidelines, review articles, commentary, salicylic acid, or cryotherapy used as adjuvant therapy and treatments other than salicylic acid and cryotherapy were also omitted. Relative data, including the first author, year of publication, size/number of warts, age/gender of patients, and treatment procedure, were extracted by screening the full text. Two reviewers, Dipika Chaudhary and Anupama Bishwokarma, performed the procedure independently and discussed as well as consulted with a third reviewer, Archana Shrestha, with disagreements.

**2.3. Quality Assessment.** Qualities of all the studies included were evaluated using the revised Cochrane risk-of-bias tool (RoB, version 2) for randomized trials. RoB 2 is designed into a fixed set of domains of bias, aimed at focusing various traits of trial designing, conducting, and reporting. There are 5 domains in RoB: biases as a result of the randomization process, biases owing to deviations from intended interventions, biases as a result of missing outcome data, biases

in the measurement of the outcome, and bias during selection of the reported result. In each domain, there are a series of questions (signaling questions) focused on obtaining information regarding features of the trial, which are significant to the risk of bias. For each domain, a response (yes, probably yes, probably no, no, or no information) was defined according to each study. Then, the quality was evaluated by the algorithm as a low risk, some concerns, or a high risk [10].

**2.4. Outcomes.** Complete remission of all warts was described as the complete restoration of normal skin. The outcomes were complete remission of all warts at different observation times, recurrence rates, and side effects.

**2.5. Statistical Analysis.** All of the statistical analysis was conducted by using R version 4.0.3 (the R Foundation for Statistical Computing, Vienna, Austria) [11]. Study-specific effect sizes were pooled by using the fixed-effects model [12] and the Mantel–Haenszel method.  $I^2$  was used to assess heterogeneity of studies. The forest plot, funnel plot, and pooled relative risk (RR) were conducted by using the “meta” package [13]. Robustness was performed by leave-one-out sensitivity analysis in the “metainf” function of the meta package.

## 3. Results

**3.1. Eligible Studies.** A total of 617 studies were retrieved. After screening titles as well as abstracts of the yielded studies, 208 duplicates and 269 studies which failed to meet the inclusion criteria were excluded. Thus, the remaining 140 articles were selected for full-text review. Subsequently, 133 studies with recurrent warts/recalcitrant warts, genital warts, guidelines or review articles, commentary, salicylic acid, or cryotherapy used as adjuvant therapy or treatments other than salicylic acid and cryotherapy were excluded. At last, 7 studies were selected for the following meta-analysis [14–20] (Figure 1).

**3.2. Basic Characteristics and Interventions of the Studies Included.** A total of 976 patients with common warts were treated with either cryotherapy or salicylic acid. Their age ranged from 4 to 79 years old. Sample size ranged from 70 [18] to 240 [14] (Table 1).

A total of 487 patients were treated with cryotherapy, which was performed 4–6 sessions at hospital with an interval of 2–3 weeks. The other 489 patients were treated with 20–50% salicylic acid, which was applied topically by themselves every day for a maximum of 8–12 weeks. The follow-up periods were 6 weeks for 1 study [17], 12 weeks for 5 studies [14–17, 19], and 6 months for the other one [20] (Table 2).

**3.3. Quality Assessment.** Only one study was categorized as a low risk [18], whereas all other studies had a high-risk publication bias [14–17, 19, 20]. Out of the 7 studies, low risk

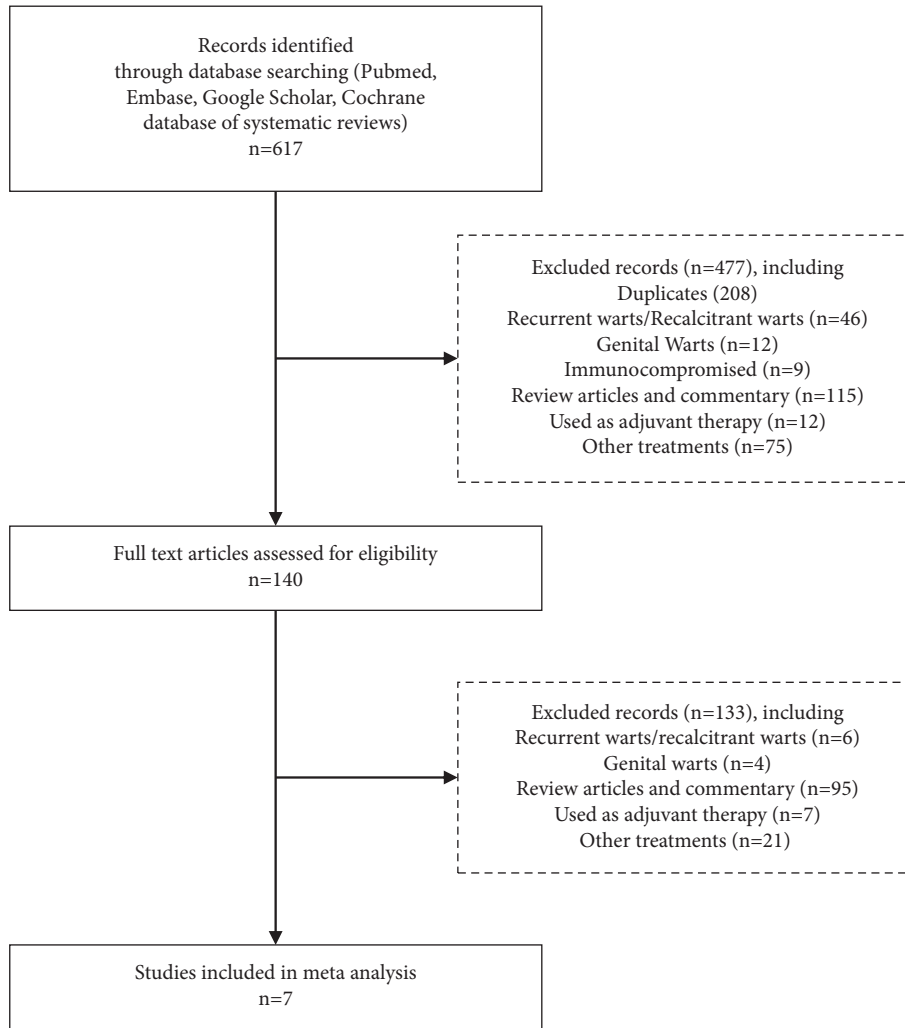


FIGURE 1: Flowchart of the selection procedure.

TABLE 1: Basic characteristics of the included studies.

Study	Year	Size of warts (cm in diameter)	No. of warts	No. of people		Mean age		Gender (male/female)	
				Cryotherapy	Salicylic acid	Cryotherapy	Salicylic acid	Cryotherapy	Salicylic acid
Bunney	1976	—	—	99	95	—	—	—	—
Steele	1988	0.3–0.9	5	66	60	—	—	—	—
Bruggink	2010	<1	<6, ≥6	80	84	—	—	35/45	30/54
Cockayne	2011	—	3.7	117	123	30.1	30.2	30/84	50/73
Rosniza	2017	>1, 0.5–1, <0.5	3.63	39	41	37.87	34.44	17/22	18/23
Muhamad	2018	—	—	35	35	22.54 ± 8.729	26.91 ± 11.44	15/20	15/20
Qamar	2018	<1, 1–1.5	2.48 ± 1.35	51	51	24.63 ± 5.30	25.80 ± 6.69	—	—

was reported in 3 studies in the randomization process [15, 17, 18], 3 studies in deviations from intended interventions [14, 15, 18], 5 studies in missing outcome data

[14, 17–20], 1 study in measurement of the outcome [18], and all studies in selection of the reported results [14–20] (Figure 2).

TABLE 2: Interventions and outcomes of the included studies.

Study	Year	Treatment		Duration		Percentage recovered		Side effect		Recurrence rate (%)		Outcomes
		Cryotherapy	Salicylic acid	Cryotherapy	Salicylic acid	Cryotherapy	Salicylic acid	Cryotherapy	Salicylic acid	Cryotherapy	Salicylic acid	
Bunney	1976	4-5 sessions	Daily self-application of SA/LA paint for 12 weeks	3 weeks apart	Daily up to a maximum of 12 weeks	67.3	68.6	—	—	—	—	Cure rate at 12 weeks
Steele	1988	Up to 6 sessions	Daily self-application of SA/LA paint for 12 weeks	1 week apart	Daily up to a maximum of 12 weeks	Hand warts = 62.5 Plantar warts = 57.7	Hand warts = 60.5 Plantar warts = 40.9	—	—	0/66 (0%)	2/60 (3.33%)	Cure rate at 6 months
Bruggink	2010	Up to 6 sessions	Patient self-application with 40% SA	Once every 2 weeks	Daily until warts are completely gone	39	24	2/80	9/84	—	—	Complete clearance rate at 13 weeks
Cockayne	2011	Up to 4 sessions	Patient self-application with 50% SA	2-3 weeks apart	Daily up to a maximum of 8 weeks	13.6	14.3	14/28	13/28	2/117 (1.7%)	2/123 (1.6%)	Complete clearance rate at 12 weeks
Rosniza	2017	Maximum of 4 sessions	Self-application of 20% SA	2 weeks apart	Daily up to a maximum of 12 weeks	33.3	26.8	—	—	—	—	Complete clearance rate at 12 weeks
Muhamad	2018	Up to 5 sessions	Self-application with 40% SA	2-3 weeks apart	Daily up to a maximum of 8 weeks	66.7	80	—	—	—	—	Complete clearance rate at 12 weeks
Qamar	2018	Up to 3 sessions	Self-application of 40% SA	2 weeks apart	Daily up to a maximum of 6 weeks	56.9	66.7	—	—	—	—	Complete clearance rate at 6 weeks

SA/LA = salicylic acid/lactic acid; SA = salicylic acid.



FIGURE 2: Quality assessments of the included studies.

3.4. Outcome Assessments

3.4.1. Complete Remission Rate of All Warts at 6 Weeks.

One study reported the complete remission rate of all warts between cryotherapy and salicylic acid treatment at 6 weeks [17]. The complete remission rate was comparable in the salicylic acid group (66.7%) and the cryotherapy group (56.9%) ( $p = 0.415$ ).

3.4.2. Complete Remission Rate of All Warts at 12 Weeks.

Four studies compared the complete remission rate of all warts treated by cryotherapy or salicylic acid at 12 weeks [14, 16, 18, 19]. With the fixed-effects model, there was not any statistical significance between the two groups, RR=0.99 (0.84–1.17) with a heterogeneity of  $I^2 = 0\%$  (Figure 3).

3.4.3. Complete Remission Rate of All Warts at 13 Weeks.

One study reported the complete remission rate of all warts between cryotherapy and salicylic acid treatment at 13 weeks [15]. The cure rate was observed to be higher in the cryotherapy group (39%) than that in the salicylic acid group (24%) ( $p < 0.05$ ). The relative risk between cryotherapy and salicylic acid was 1.6 (95% CI: 1.0–2.6).

3.4.4. Complete Remission Rate of All Warts at 24 Weeks.

Only 1 study reported the complete remission rate of all warts between cryotherapy and salicylic acid treatment at 24 weeks [20]. For common warts in hands, the complete remission rate was 62.5% in the cryotherapy group and 60.5% in the salicylic acid group ( $p < 0.05$ ); for those in feet, the complete remission rate was 57.7% in the cryotherapy group and 40.9% in the salicylic acid group ( $p < 0.05$ ).

3.4.5. Recurrence Rate.

Two studies mentioned the recurrence rate at 6 months [18, 20]. In Cockayne’s study, 4 patients reported recurrence of warts in their original positions, and the recurrence rate was comparable between the cryotherapy group (1.7%, 2/117) and the salicylic acid group (1.6%, 2/123) [18]. In Steele’s study, only 2 patients (3.33%, 2/60) had recurrence of warts in the salicylic acid group, which had a higher recurrence rate than that in the cryotherapy group (0%, 0/66) [20].

3.4.6. Side Effects.

Two studies reported side effects between cryotherapy and salicylic acid on warts [15, 18]. In Cockayne’s study, patients after cryotherapy suffered from more side effects than those after topical salicylic acid treatment. The side effects included pain, scarring, blistering, crust, pigmentation, and irritation. A total of 28 adverse events

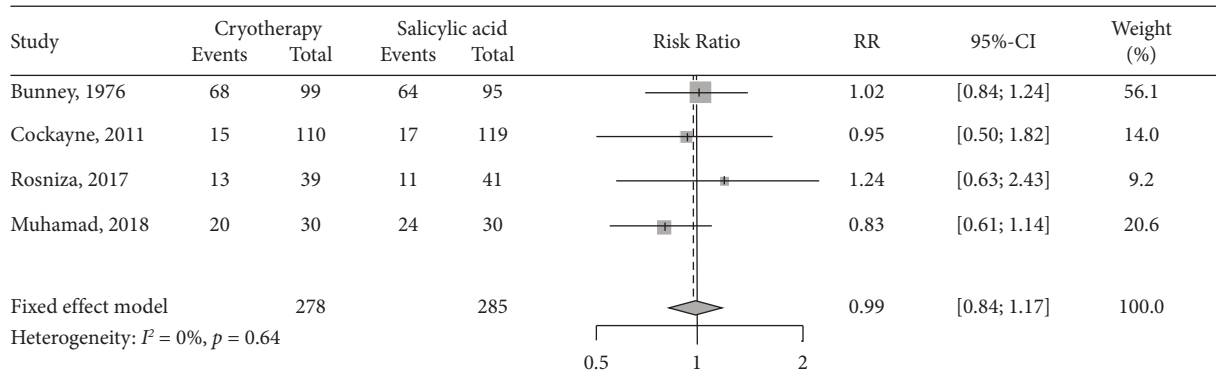


FIGURE 3: Comparison of complete clearance of common warts at 12 weeks between cryotherapy and salicylic acid. The forest plot was generated using the “meta” package of R.

were reported, including 1 serious one (not related to the treatment in the salicylic acid group) and 27 nonserious ones. For the remaining 27 reported events, 14 were in the cryotherapy group (2 related events of blisters, 7 were unrelated, and 5 unlikely to be related) and 13 were in the salicylic acid group (9 unrelated and 4 unlikely to be related) [18]. In Bruggink’s study, more patients treated with salicylic acid (54%) reported significant treatment burden than those with cryotherapy (31%) ( $p = 0.040$ ), such as pain, blistering, and scarring [15].

**3.5. Leave-One Out Sensitivity Analysis.** The leave-one out sensitivity analysis was conducted by eliminating one study at a time in sequential order, pooled RR was recalculated for the remaining studies, and the effect of removing each study based on the  $I^2$  statistic was evaluated. It showed how an individual study affected the overall estimate of the rest ones [21]. The pooled RRs did not change significantly, ranging from 1.0487 (95% CI: 0.9183; 1.1976) to 1.1455 (95% CI: 0.9694; 1.3536).  $I^2$  indicated small heterogeneity among studies, varied from 0.0% to 20.3% (Table 3).

**3.6. Publication Bias.** The publication bias of the 7 studies was shown in the funnel plot (Figure 4). The points were few but scattered symmetrically, which indicated lower publication bias. We could not use Egger’s test to evaluate the potential publication bias because fewer studies were involved in meta-analysis (<10) [22].

## 4. Discussion

Cryotherapy commonly uses liquid nitrogen with a temperature of  $-196^\circ\text{C}$ , which works by either necrotic destruction of HPV-infected keratinocytes or local inflammation triggering cell-mediated response [6]. The efficacy varies in mode of application, treatment intervals, and freeze times. Increased efficacy is conducted by aggressive cryotherapy, accompanied with higher risks of side effects, such as pain, scarring, blistering, crust, pigmentation, and irritation [23]. Hyperpigmentation or hypopigmentation may occur, especially in dark-skinned patients [18]. Moreover, side effects are more common in treatment

regimens with a shorter interval. Therefore, preventive measures must be taken during application of cryotherapy adjacent to the cutaneous nerves, nail apparatus, and tendons, as well as in patients with arterial or venous circulation impairment.

Topical salicylic acid is a keratolytic agent which gradually destroys the epidermis infected by virus, and the mild irritation may activate an immune response. The concentration preparation may vary from 10% to 60%. The available preparations over the counter are 17% salicylic acid combined with a flexible collodion base or as 20%, 40%, and 50% in Vaseline ointment [6]. Before each application of topical salicylic acid, warts should be soaked in warm water for approximately 5 minutes, and then, the dead tissues should be removed using a file. Patients should be very careful when paring in order to avoid abrading the adjacent normal skin, as it may spread the disease.

Both treatments are destructive therapy. As we know, there were 4 studies with meta-analysis reported the comparison of effectiveness and cost between cryotherapy and topical salicylic acid in common warts. All of them showed no significant difference in efficacy [4, 24, 25]. Our findings were consistent with those of previous ones, but the number of patients and studies included were more than theirs. Nowadays, topical salicylic acid is first-line therapy, while cryotherapy is second-line therapy for common warts [18]. Therefore, we suggest that both topical salicylic acid and cryotherapy should be the first choice for common warts according to the present results.

Furthermore, salicylic acid is convenient and cheap but requires daily application up to 8 weeks. Therefore, patient compliance plays a major role. Moreover, all salicylic acid can cause chemical burns so it should not be applied to poor healing areas such as neuropathic feet, except for few very low-strength ones. Thus, they are forbidden to apply on the face because of risk of irritant burning [26]. Since both salicylic acid and cryotherapy have a higher probability of adverse reactions and recurrence, photodynamic therapy might be a better choice with better efficacy, fewer adverse reactions, and lower recurrence rates [27]. The mechanism might be associated with antiviral activity, local immunity, and reactive oxygen species [28]. Therefore, patients could choose either treatment as their convenience.

TABLE 3: Leave-one out sensitivity analysis.

	RR	95% CI	<i>p</i> value	Tau <sup>2</sup>	Tau	<i>I</i> <sup>2</sup> (%)
Omitting Bunney, 1976	1.1455	[0.9694; 1.3536]	0.1104	0.0084	0.0915	19.0
Omitting Steele, 1988	1.0974	[0.9515; 1.2657]	0.2017	0.0095	0.0973	20.3
Omitting Bruggink, 2010	1.0487	[0.9183; 1.1976]	0.4830	0.0000	0.0000	0.0
Omitting Cockayne, 2011	1.1174	[0.9818; 1.2720]	0.0930	0.0093	0.0962	21.5
Omitting Rosniza, 2017	1.0961	[0.9615; 1.2495]	0.1699	0.0089	0.0942	20.3
Omitting Muhamad, 2018	1.1413	[0.9921; 1.3129]	0.0644	0.0000	0.0000	0.0
Omitting Qamar, 2018	1.0923	[0.9475; 1.2592]	0.2238	0.0080	0.0892	17.1
Pooled estimate	1.1040	[0.9700; 1.2565]	0.1339	0.0028	0.526	7.4

RR = relative risk; CI = confidence interval.

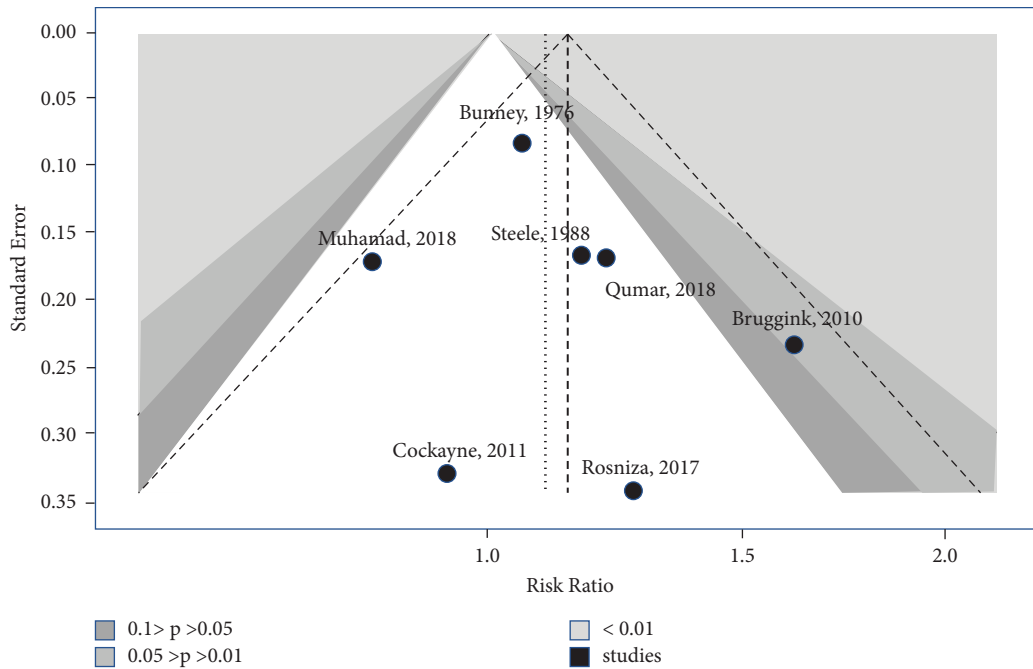


FIGURE 4: Publication bias of the included studies. The funnel plot was generated using the “meta” package of R. The vertical axis represents the standard error, and the horizontal axis represents the risk ratio of all the included studies.

However, there were some limitations in this review. On the one hand, although the funnel plot was symmetrically distributed, it was difficult to conclude that publication bias was absent because only 7 RCTs were included. On the other hand, the individual study quality assessment indicated a high risk of publication bias, except for one. Therefore, we acknowledge that our meta-analysis could have been affected by publication bias, with inclusion of disproportionately higher number of studies with hypothesized outcomes. Moreover, topical salicylic acid was self-administered by patients themselves so it was bound to have some variations in compliance, as it would reduce the efficacy compared to treatments applied by health professions.

### 5. Conclusion

The present study concluded a comparable efficacy of cryotherapy and topical salicylic acid for the treatment of common warts. More pieces of evidence with higher

qualities and sample sizes are needed to confirm the results for further recommendations.

### Data Availability

The data used to support the findings of this study are included within the article; further inquiries can be directed to the corresponding author upon request.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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