Cryotherapy versus salicylic acid for treating plantar warts: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the efficacy of cryotherapy and salicylic acid for treating plantar warts

METHODS

Three independent reviewers systematically searched through electronic databases including Cochrane library, Pubmed, Trip Database and Scopus. We also sought for additional studies using a hand searching to explore other unidentified studies on the databases to identify all relevant randomized controlled trials comparing cryotherapy to topical salicylic acid in term of clearance of plantar warts.

RESULTS

We identified and included two randomized controlled trials with 309 participants with plantar warts. The clearance of plantar warts at 3 months was interpreted that using cryotherapy was no statistically significant difference from using topical salicylic acid (RR 0.94; 95% CI 0.51 to 1.49, fixed-effect model, I^2=0) and at 6 months (RR 1.07; 95% CI, 0.79 to 1.46, fixed-effect model, I^2=0).

CONCLUSION

Clearance of plantar warts was not different between using cryotherapy and topical salicylic acid at 3 and 6 months.

INTRODUCTION

Plantar warts are caused by human papillomavirus especially type 1, 2, 27, and 57.[1-6] About 33% of primary schoolchildren have cutaneous warts and 20% have plantar warts.[7] Nearly 90% of them were located on pressure points such as the base of heels, longitudinal arch, metatarsal arch, or base of toes.[8] Patients with plantar warts seek for treatment for a variety of reasons, including discomfort, prevented from doing sports, interfering with work, bleeding and pain.[9-11,24] Treatments for plantar warts comprise salicylic acid, trichloroacetic acid, topical cidofovir, cryotherapy, hyperthermia therapy, laser, or debridement.[12-28]

There were two relevant studies; one of them mentioned that cryotherapy was statistically better than salicylic acid in the clearance of common warts.[25] However, both studies described no significant difference regarding the clearance of plantar warts between the two treatments.[24-25] We will conduct a systematic review in order to compare the clearance of plantar warts of the two treatments that might be clearer with larger sample size.

METHODS

SEARCH STRATEGIES

Without language restrictions, three independent reviewers systematically searched through electronic databases including Cochrane library, Pubmed, Trip Database and Scopus using the term "plantar warts" or "verruca plantaris" together with either "cryotherapy" or "salicylic acid". We applied MeSH searching to identify studies on Pubmed and Cochrane library. Furthermore, we sought for additional studies using a hand searching to explore other unidentified studies on the databases. All of the procedures above were described as individually searching by reviewers.

INCLUSION CRITERIA

STUDY DESIGN

Randomized controlled trial (RCT).

PARTICIPANTS

Plantar warts

INTERVENTIONS

Cryotherapy

COMPARISON

Topical salicylic acid

OUTCOMES

The clearance of plantar warts

EXCLUSION CRITERIA

We excluded records that were not be indicated as studies, then we removed the duplicated and ongoing studies. The rest of them were excluded using the following criteria (i) studies which plantar warts were not mentioned, (ii) studies which cryotherapy or salicylic acid were not indicated or were combined with other interventions known as treatments for plantar warts. The three reviewers individually identified and agreed to have two relevant studies after the inclusion and exclusion criteria to be included in the analysis

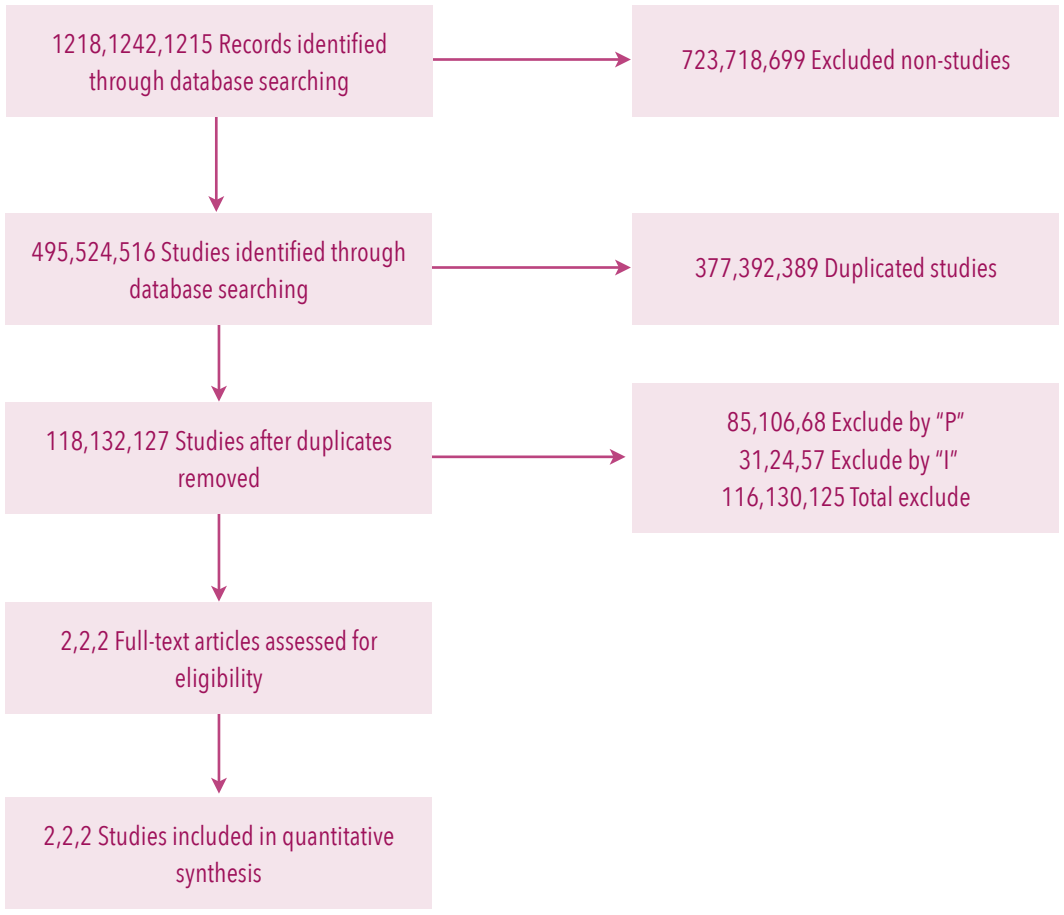

Figure 1. Represents inclusion and exclusion journal in this systematic review
Three numbers in each box are results from each process from each reviewer.

QUALITY OF REPORTING AND RISK OF BIAS

We used Jadad score to assess the quality of the included RCT comprising the evaluations of randomization, blinding methods and adequate description of withdrawals and drop-outs. In addition to this, we used Cochrane risk of bias to present the risk of bias demonstrated as random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias by classifying them to be three degrees which were low risk, high risk, and unclear risk of bias.

DATA EXTRACTION

We extracted the data from the included studies regarding the author, a number of patients, patient's age, duration of both treatments, duration of studies, interventions described as strength of salicylic acid as well as procedures of using

Table 1. Characteristics of 2 studies eligible for inclusion

Studies	Trial duration (months)	Number of patients with plantar warts	Age (Years)	Intervention	Clearance of plantar warts at 3 months Number of event/ Number in group (%)	Clearance of plantar warts at 6 months Number of event/ Number in group (%)
Cockayne et al	39	229	Median range 24.3 (12.2-75.3)	cryotherapy with liquid nitrogen by health care professional vs 50% Salicylic acid self-applied plantar warts every day.	Cryotherapy 15/110 (13.6%) Salicylic acid 17/119 (14.3)	Cryotherapy 33/98 (33.7%) Salicylic acid 29/95 (30.5%)
Bruggink et al	9	80	Range 4-79	cryotherapy with liquid nitrogen every 2 weeks by health care professional vs 40% Salicylic acid self-applied plantar warts every day.	Cryotherapy 11/37 (29.7.%) Salicylic acid 14/43 (32.6%)	Cryotherapy 18/37 (48.6%) Salicylic acid 20/42 (47.6%)

cryotherapy and outcomes in term of clearance of plantar warts from each study.

DATA ANALYSES

We calculated and described the results as the relative risk (RR) and 95% confidence interval (CI) by using Review Manager 5.3 statistical software to analyze the clearance of plantar warts between cryotherapy and salicylic acid at 3 and 6 months. We calculated I2 to show the heterogeneity among studies. Moreover, the results from a meta-analysis of our systematic review were described by forest plot. We used fixed-effect models for combining data in a meta-analysis. The publication bias was demonstrated in funnel plots.

RESULTS

STUDY CHARACTERISTICS

The searching results were totally identified as 1218, 1242 and 1215 records by the reviewers I, II and III, respectively (Figure 1). We identified 494, 523 and 515 records as studies, which 375, 390 and 387 of them were duplicates. There were 119, 133 and 128 studies remained after duplicate removed. We later excluded 117, 131, 126 studies because of being related to our exclusion criteria. The remaining two trials were included in the meta-analysis.[24-25] Both studies were compared topical salicylic acid to cryotherapy in term of clearance of plantar warts. The characteristics of 309 participants

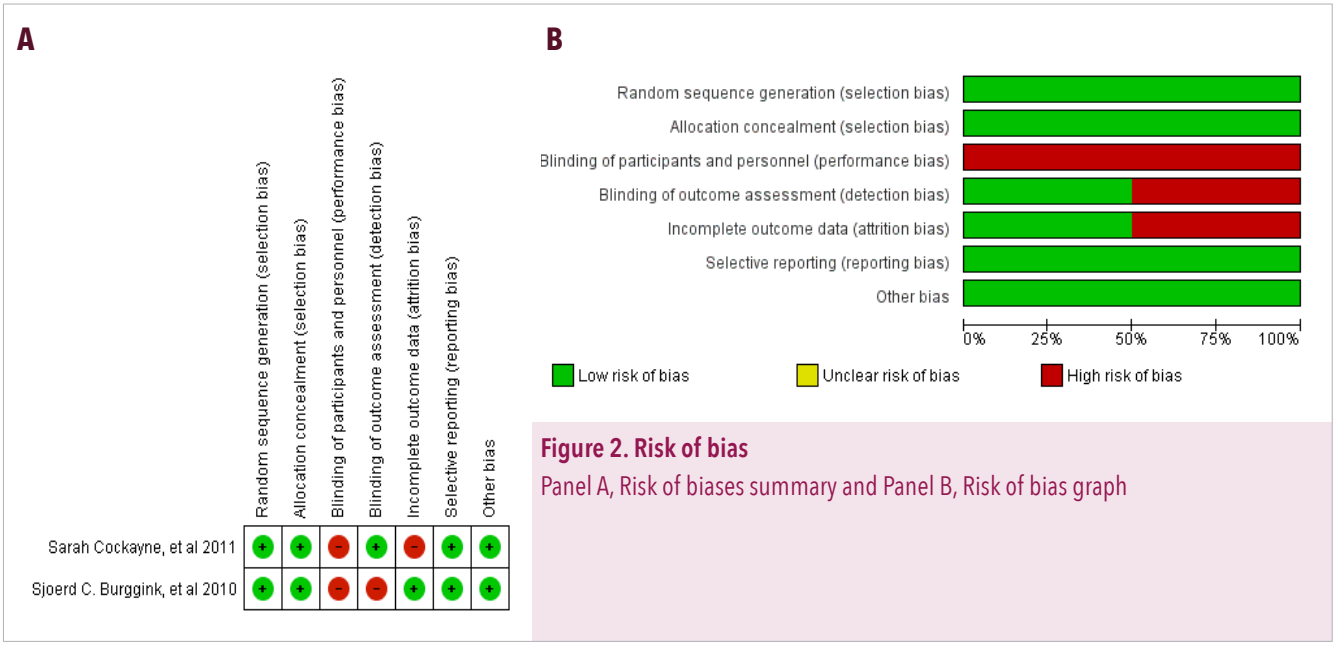

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

with plantar warts in two RCTs are presented in Table 1.

ASSESSING THE QUALITY AND RISK OF BIAS

The quality of the two studies, Cockayne et al's study and Bruggink et al., 2010's study, was assessed using Jadad score and Cochrane Collaboration's tool was used to assess risks of bias. The former study had 2 points from the Jadad score (Table 3) because patients and physicians were not blinded and the dropouts were not described clearly at the end of the study. The later study had 3 points from the Jadad score because the study lacked only double-blinded method. The risk of bias using the tool of both studies is summarised in Figure 2.

RANDOM SEQUENCE GENERATION

Both studies reported the methods of random sequence.

ALLOCATION CONCEALMENT

The former study reported treatment allocation processed by telephoning or accessing a secure web randomization program, whereas, the latter study used opaque, sealed envelopes that were number based on computerization list delivered by an independent statistician.

BLINDING OF PARTICIPANT AND PERSONAL

Both studies were described as high risk of bias because the former study was an open trial and the later study mentioned those uncured patients in the 13th week could switch to other treatments by their own.

BLINDING OF OUTCOME ASSESSMENT

The former study evaluated the clearance of plantar warts using blinded digital photograph assessors which were considered as a low risk of bias. Evaluation of clearance of plantar warts of the later

Table 2. Meta-analysis of clearance of plantar warts comparing cryotherapy to salicylic acid at 3 and 6 months.

	Number of event/Number in group (%)		Relative risk	95% confidence interval	P Value
	Cryotherapy	Salicylic acid			
Clearance of plantar warts at 3 months	26/147(17.7)	31/162(19.1)	0.94	0.59-1.49	0.78
Clearance of plantar warts at 6 months	51/135(37.8)	49/137(35.8)	1.07	0.78-1.45	0.68

Table 3. Jadad score

	Cockayne et al	Bruggink et al
Was the study described as randomized ?	1	1
Was the method used to generate the sequence of randomization described and was it appropriate?	1	1
Was the study described as double blind ?	0	0
Was the method of double blind described and was it appropriate ?	0	0
Was there a description of withdrawals and dropouts ?	0	1
Score	2	3

study was considered as a high risk of bias because they could know the intervention.

INCOMPLETE OUTCOME DATA

The former study was a high risk of bias because they describe nothing about missing patients at 6-month evaluation. The later study described clearly of all missing data which were low risk of bias.

SELECTIVE REPORTING

Both studies were low risks of bias because all results were totally reported.

OTHER POTENTIAL SOURCES OF BIAS

No other sources of bias were mentioned in both studies. We described them as low risk of bias.

THE PRIMARY OUTCOME

THE CLEARANCE AT 3 MONTHS

Comparing cryotherapy to topical salicylic acid, the clearance of plantar warts at 3 months was interpreted that using cryotherapy was no statistically significant difference from using topical salicylic acid (RR 0.94; 95% CI 0.51 to 1.49, fixed-effect model, $I^2=0$) (Figure 3).

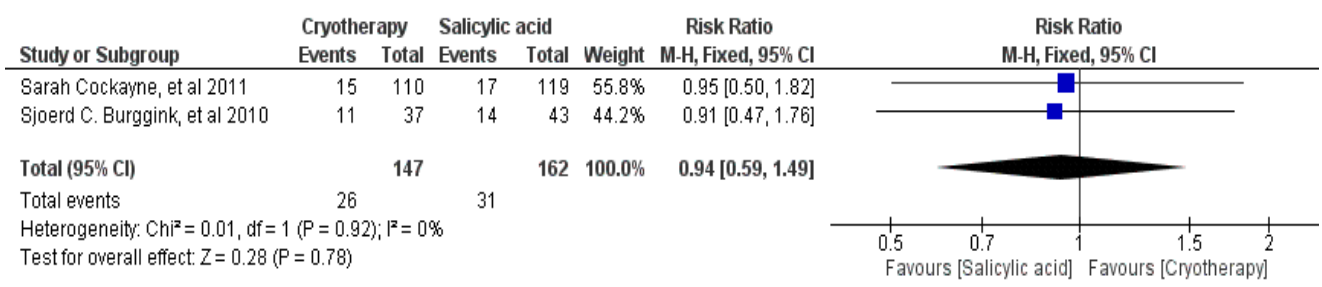

Figure 3. Forest plot: cryotherapy versus salicylic acid, outcome: 1.1 Clearance of plantar warts at 3 months

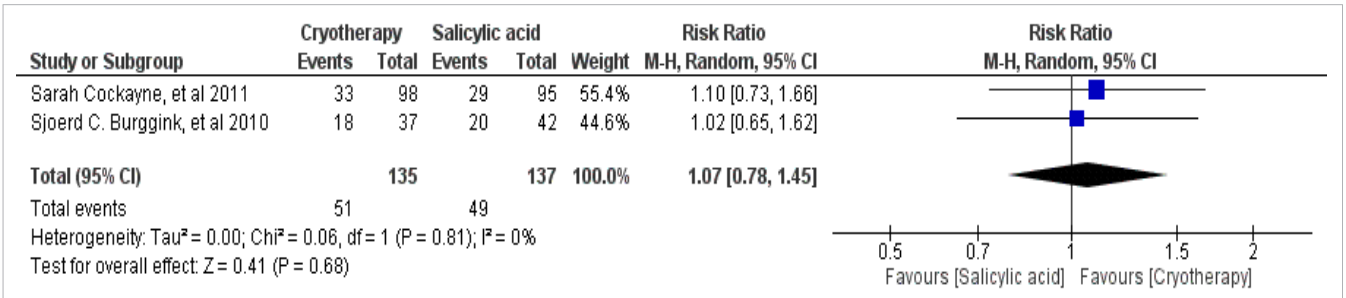

Figure 4. Forest plot: cryotherapy versus salicylic acid, outcome: 1.2 Clearance of plantar warts at 6 months

THE SECONDARY OUTCOME

THE CLEARANCE AT 6 MONTHS

Comparing cryotherapy to topical salicylic acid, the clearance of plantar warts at 6 months was interpreted that using cryotherapy was no statistically significant difference from using topical salicylic acid (RR 1.07; 95% CI, 0.79 to 1.46, fixed-effect model, I^2=0) (Figure 4).

ADVERSE EFFECT

Bruggink et al., 2010 reported that 62 participants had adverse effects. The pain was reported 84% as the most common side effect of cryotherapy while skin irritation was reported 53% as the most common side effect of salicylic acid. The other side effects were described in the table below.

PUBLICATION BIAS

The funnel plots of clearance of plantar warts at 3 and 6 months were not adequately interpreted the publication bias because our systematic review had only two RTCs that we could not detect the distribution of the studies properly (Figure 5-6).

DISCUSSION

SUMMARY OF EVIDENCE

In our systematic review, two RCTs were identified with 309 patients with plantar warts were included in the analysis and we found no statistically significant difference in clearance of plantar warts between cryotherapy and topical salicylic acid at 3 and 6 months. High homogeneity was observed. Both studies were conducted in patients aged 4

Table 4. Adverse effects reported at 13th week in Bruggink et al., 2010's study.

Type of side effect	Cryotherapy (n=37) Number of patients	Salicylic acid (n=40) Number of patients
Pain	31	4
Blistering	16	5
Scarring	1	-
Skin irritation	6	21
Skin pigmentation	3	2
Bleeding after filing	-	1
Crust	1	-
Other minor side effect	4	4

years or older. Meta-analysis of the adverse effects were not performed as only one study reported the effects by Bruggink et al., 2010, another study did not describe adverse effects clearly but only non-serious effects were mentioned by Cockayne et al. In our review, the funnel plots of the outcomes were summarised However, we did not estimate publication bias as the number of the included studies was too few.

STRENGTH AND LIMITATIONS OF THE REVIEW

To our knowledge, this is the first systematic review comparing cryotherapy to topical salicylic acid in the clearance of plantar warts. We conducted this review with the compliance to the Cochrane handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist, our search was comprehensive, no study likely to be missed. Moreover, I^2 was calculated as 0%. Thus,

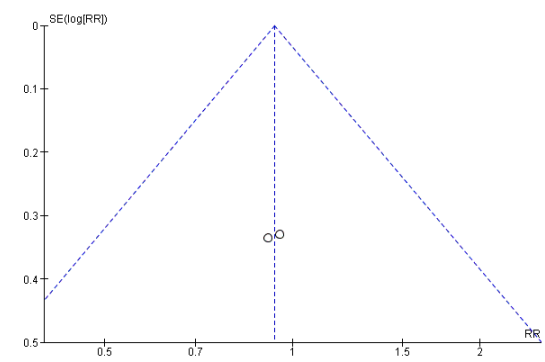

Figure 5. Funnel plot: cryotherapy versus salicylic acid, outcome: 1.1 Clearance of plantar warts in 3 months

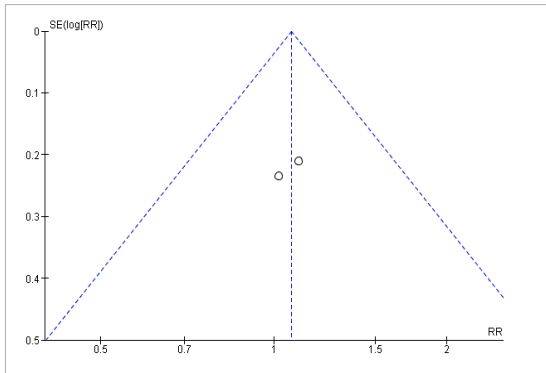

Figure 6. Funnel plot: cryotherapy versus salicylic acid, outcome: 1.2 Clearance of plantar warts in 6 months

our results are reproducible with high confidence for generalizability to other settings.

Our study had some limitations. The first limitation was the small number of participants because we found only two RCTs that followed our robust inclusion and exclusion criteria. The quality of the two RCTs was varied. Randomization and methods were adequately described in both trials. However, the study by Cockayne et al did not describe dropouts after 13th week clearly. Thus, the exact outcomes of both benefit and harm were not clearly identified due to the dropout. The third limitation was the blinding outcome bias as only the study by Cockayne et al, the assessors were blinded. The last limitation of our study was indicated as no description of double-blinded methods as both physicians and patients obviously knew one's intervention.

COMPARISON TO OTHER STUDIES

In our systematic review, there was no statistically significant difference in clearance of plantar warts between cryotherapy and salicylic acid at 3 and 6 months in patients aged 4 and over. Our findings were congruent to that of two prior studies that compared cryotherapy with salicylic acid plus lactic acid in patients with plantar warts and palmar warts.[23,26] Furthermore, Bruggink et al., 2015 described no difference between using cryotherapy and monochloroacetic acid in the clearance of common warts.[13] However, KaÇar et al's study described that salicylic acid plus cantharidin-podophyllotoxin was better than cryotherapy in the clearance of plantar warts.[28]

In our opinion, we could not suggest that chemical therapies were superior to physical therapies by evidence of referral studies mentioned above.[23,26,28] Although, one of them stated that combined chemical therapy was better than cryotherapy alone but no treatment would be indicated as the most effective one because the proper treatment needed to be considered carefully in every single case.

CONCLUSION AND IMPLICATION

There was no statistically significant difference between cryotherapy and topical salicylic acid in the clearance of plantar warts at three and six months. Despite no difference between cryotherapy and salicylic acid in term of clearance of plantar warts, we prefer salicylic acid to cryotherapy because of its affordability and availability, especially in developing countries. For the further upcoming studies, we suggest a large number of participants and a longer follow-up trial evaluate the differences in term of clearance of plantar warts as well as their recurrence between cryotherapy and topical salicylic acid.

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COMPETING INTERESTS: This study has no competing on interest.
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