Five Percent Potassium Hydroxide for the Treatment of Anogenital Warts: A Systematic Review and Meta-analysis

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ABSTRACT

Background and Objectives. Potassium hydroxide (KOH) is effective and safe as treatment of viral dermatoses. No systematic review has been done reporting its efficacy as a treatment for anogenital warts.

Methods. A systematic literature search for controlled clinical trials using KOH, any drug or ablative procedure measuring the clearance rate was conducted. Analysis was done using RevMan v5.3 software.

Results. Four low quality trials, composed of 197 patients were included but only two qualified for meta-analysis. Two studies compared KOH to cryotherapy while the two other trials compared KOH to intralesional 5-fluorouracil (FU) + salicylic acid (SA) and carbon dioxide (CO_2) laser vaporization. The KOH group showed a higher clearance rate compared to cryotherapy (RR= 1.40, P> 0.05, I^2=39 %) and no recurrence was noted (RR= 0.17, P> 0.05, I^2=0) but the difference is not statistically significant. Isik et al., 2014 and Asadi et al., demonstrated that there was no significant difference among groups receiving KOH, 5-FU+SA and CO_2 laser vaporization in the mean lesion count and size at follow up visits. (P > 0.05).

Conclusions. Potassium hydroxide has comparable efficacy to the present treatment modalities but well-structured RCTs are needed to further support its use.

Key Words: Potassium Hydroxide, Genital Warts, Condyloma Acuminata

INTRODUCTION

Description of the condition

Condylomata acuminata (CA), also known as anogenital warts, are the clinical manifestations of human papillomavirus (HPV) infection (type 6 and 11). These are acquired through direct genital contact with an incubation period of about 6-10 months.[1] They present as asymptomatic grey, flesh-colored to pink papules or nodules on the perineum, genitalia, and anus, varying in size. Among the therapeutic options available, none has emerged as the standard of care. Spontaneous resolution occurs but may take months, and is unpredictable hence, treatment is usually offered.

Description of the intervention

Potassium hydroxide is a strong alkali used for the diagnosis of fungal infections and bacterial vaginosis.[2] It is an effective, safe and well tolerated treatment for different viral dermatoses such as molluscum contagiosum

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in children[3,4] and genital warts in adults.[5] Its efficacy is attributed to its ability to dissolve keratin causing an inflammatory reaction[3,4], thus breaking the induced immunosuppression resulting to clinical cure.[2,4]

Importance of the review

Several studies have reported the efficacy of potassium hydroxide (KOH) solution in genital warts but no systematic review has been done. We aimed to determine the benefits and side effects of KOH to help physicians and patients make informed decisions.

OBJECTIVES

General objective

To determine the efficacy and safety of potassium hydroxide versus placebo, pharmacoactive drug or ablative procedure in achieving clinical clearance of patients diagnosed with condyloma acuminata

Specific objectives

A. To assess and compare the difference in the clearance rate after treatment between potassium hydroxide and control groups
B. To assess and compare the difference in recurrence rate after treatment between potassium hydroxide and control groups
C. To determine the common adverse effects reported by patients and observed by clinicians during therapy

METHODS

Criteria for considering studies for this review

Types of studies

This systematic review included only randomized controlled trials. No exclusions were made with regard to publication status, sample size or language.

Types of participants

Patients diagnosed with condyloma acuminata regardless of age and sex were included. No exclusions were made on duration and severity of condition.

Types of intervention

Studies that used potassium hydroxide as the intervention, regardless of its dosage or period of administration, were included.

Types of outcomes

Studies which reported the primary outcomes of clearance rate and recurrence rate and secondary outcomes such as clinician-observed and patient reported adverse effects, were included.

Search methods for identification of studies

Electronic searches

The MEDLINE, Cochrane Library, Embase, Health Research Development Information Network (HERDIN) electronic databases, Journal of the American Academy of Dermatology (JAAD) and International Prospective Register of Systematic Reviews (PROSPERO) were searched using the following relevant keywords: HPV, genital warts, condyloma acuminata, venereal warts, potassium hydroxide, KOH.

Data collection and analysis

Selection of studies

Studies were selected by the consensus of three independent review authors. Preliminary review of titles and abstracts was done for inclusion by two independent authors. Duplicate articles were identified. Full-text articles were retrieved if inclusion criteria were unclear or could not be identified by preliminary review. The full-text articles were reviewed using a standard eligibility form. A third review author was consulted to resolve any discrepancies or disagreements between the two independent authors. This selection process is shown in Figure 1.

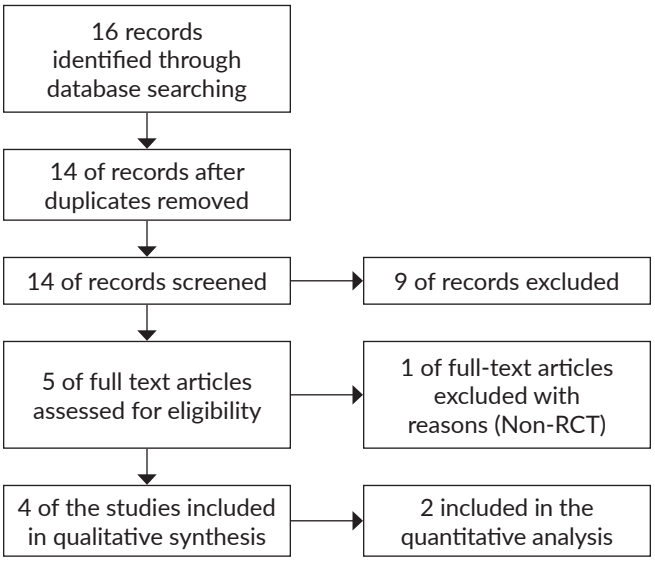

Figure 1. Flow diagram of selection process of included studies.

Data extraction and management

The authors independently extracted data from included studies using a data extraction form patterned after the table from Review Manager (v 5.3), and the following items were extracted: authors, year of publication, design of the trial, inclusion and exclusion criteria, demographic characteristics of the participants, intervention details and the assessed outcomes. Data regarding dropouts and funding sources were also noted.

Quality assessment of included studies

Internal validity of included trials was independently assessed by two review authors using the Cochrane risk of bias tool (Chapter 8, section 8.5). Risk of bias was gauged based on these domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. Included trials were categorized as low risk, unclear risk or high risk. "High methodological quality" was assigned to a study designated with low-risk in all domains; "moderate methodological quality" if one of the domains is reported as having "unclear risk"; "low methodological quality" if any of the domains is "high risk." Any incongruities, such as bias from selection, detection, and significance of dropouts, were settled by discussion between the authors, and resolved by a third review author.

Measurement of treatment effect

Meta-analyses were done using the software Review Manager 5.3.

Dealing with missing data

Authors were contacted via electronic mail for further details on missing data. No response was received, thus only available data were used in the analyses.

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of forest plots and by determining I^2 statistic. Interpretation was based on the Cochrane Handbook for Systemic Reviews of Interventions (Chapter 9, section 9.5). For trials with high heterogeneity, possible reasons for such were explored. Data of trials not included in the meta-analysis were discussed separately.

Assessment of reporting biases

For missing data of studies suspected with reporting biases, especially involving primary outcomes, communication with authors via electronic mail was done. Both fixed and random-effects were taken and compared for the studies displaying heterogeneity.

Data synthesis

Studies were assessed using the PICOM (Population, Intervention, Comparison, Outcome, Methods) format retrieved from the Cochrane Handbook for Systemic Reviews of Interventions. Summary tables for outcomes were created to simplify presentation of study details. Statistical analysis was done using the Review Manager software (version 5.3) provided by The Cochrane Collaboration.

Summary of findings table

A summary of findings was created using the GRADEpro software including the outcomes used in the meta-analysis. Quality of evidence was assessed using the GRADE approach.

RESULTS

Description of studies

Results of the search

A total of 16 records through the electronic searches from The Cochrane Library (n = 2), MEDLINE (n = 6), HERDIN (n = 5) and JAAD (n = 3) was obtained. We identified 2 duplicates and excluded nine clearly irrelevant records through reading the titles and abstracts. We retrieved the full text of the remaining 5 records for further assessment.

Included studies

The four studies, which fulfilled the inclusion criteria, are summarized in Table 1.

Excluded studies

One full text article (Loureiro et al., 2008) screened was excluded because it was an uncontrolled open-label trial.

Design

All of the 4 trials were randomized controlled trials assessing the efficacy of potassium hydroxide solution as a treatment for anogenital warts in comparison to the other therapeutic modalities available.

Two of these studies were self-controlled studies namely Yaghoobi et al., 2013[2] and Asadi et al., 2015.[6] In both studies, treatment of multiple sites was done by dividing the body into two and doing a right/left within-patient comparison. In Yaghoobi et al., 2013, right-sided lesions were treated with potassium hydroxide while left sided lesions were treated with cryotherapy. This is similar to Asadi et al., 2015 where left-sided lesions were treated with potassium hydroxide and right-sided lesions underwent carbon dioxide laser vaporization. Camargo et al., 2014 also compared the efficacy of potassium hydroxide against cryotherapy using two groups of patients diagnosed with genital warts.[7] The fourth included study (Isik et al., 2014) used 5% potassium hydroxide versus the combination of 5-fluorouracil and salicylic acid among patients with condyloma acuminata.[8]

Setting

All of the studies were conducted in single center facility. Yaghoobi et al., 2013 and Asadi et al., 2015 originated from Iran. The former was accomplished in a Dermatology clinic in Ahvaz from March 2009 to March 2010 while the latter in Motahari Clinic from March to August 2014. The third study (Camargo et al., 2014) was carried out among patients at the Department of Dermatology at University of Sao Paulo General Hospital in Brazil within a 10-month period. Isik et al., 2014 recruited patients from the Department of Dermatology at Bulent Ecevit University in Turkey.

Table 1. Characteristic of included studies using the PICOM[a] format

	Yaghoobi et al., 2013	Camargo et al., 2014	Isik et al., 2014	Asadi et al., 2015
Design and Duration	RCT (split study) 8 weeks	RCT 12 weeks	RCT 12 weeks	RCT (split study) 9 weeks
Participants				
Total	36	48	60	70
Age	18-60 yrs. Mean age: 35	18-74 yrs. Mean age: 31.1	>18 yrs. Mean age: KOH group: 37.00 ± 9.5, 5 FU +SA: 33. 70 ± 9.59	15-55 yrs. Mean age: 28.6±7.9
Sex	Male	Male	Male: 41 / Female: 19	Female
Diagnosis	Genital warts	Genital warts	Anogenital warts	Genital warts
Country	Iran	Brazil	Turkey	Iran
Intervention	Right sided lesions- 5% KOH applied twice a day using a cotton tipped stick for 8 weeks	5% KOH applied twice a day using a toothpick with cotton wrap for 12 weeks	5% KOH applied using a cotton applicator stick once a day for 12 weeks	Left sided lesions: 5% KOH applied twice a day using a toothpick with cotton wrap for 9 weeks
Comparator	Left sided lesions- Cotton tipped application of liquid nitrogen for 15-30s until frosting every 2 weeks for 8 weeks	Cryotherapy with liquid nitrogen for 5-20s until a 1mm halo, every 2 weeks for 12 weeks	5 Fluorouracil + Salicylic acid applied once a day using its original applicator	Right sided lesions: Lesions and 2 mm surrounding the normal tissue evaporated with CO_2 laser every 3 weeks for 9 weeks
Outcome	Clearance rate, recurrence rate, adverse events	Clearance rate, recurrence rate, adverse events	Clearance rate, recurrence rate, adverse events	Clearance rate, recurrence rate, adverse events

[a] *Population, Intervention, Comparison, Outcome, Methods*

Sample size

Sample size ranged from 36 (Yaghoobi et al., 2013) to 70 (Asadi et al., 2015). A total of 197 patients were randomized. Only Asadi et al., 2015 provided an adequate description of the sample size estimation.

Participants

The total number of participants for all trials was 197. The age of the participants ranged from 15 to 74 years old. The mean proportion of males to females was 1.4: 1 (115: 82). Two studies (Yaghoobi et al., 2013 and Asadi et al., 2015) were self-controlled, therefore no difference in the baseline characteristics of the included patients in the intervention group and control group. One study (Isik et al., 2014) explicitly mentioned that there were no significant differences in participants in terms of age, sex, duration and number of lesions for the two treatment groups. In contrast, Camargo et al. 2014, did not mention if treatment groups had similar baseline characteristics.

All of the participants were diagnosed with anogenital warts clinically. Informed consents were secured prior to recruitment and participation to the study. Relevant inclusion criteria involved diagnosis of anogenital warts clinically. Exclusion criteria included immune deficiency, presence of concomitant sexually-transmitted diseases (syphilis, HIV, Hep B or C) and regional infection MCV or herpes simplex, pregnancy and lactation.

Intervention

Treatment group: Five percent potassium hydroxide solution

All the included studies used 5% potassium hydroxide as treatment differing only in frequency and duration of application. In three studies namely Yaghoobi et al., 2013, Camargo et al., 2014 and Asadi et al., 2015, five percent potassium hydroxide was applied using a cotton tip stick twice a day for eight, twelve and nine weeks, respectively. Meanwhile, in Isik et al., 2014, treatment with 5% potassium hydroxide was done as once a day application using a cotton applicator stick for twelve weeks. For all studies, treatment was done until complete clearance or until the set duration whichever was earlier.

Control group: cryotherapy; 5-fluorouracil and salicylic acid solution; carbon dioxide laser vaporization

Two trials namely Yaghoobi et al., 2013 and Camargo et al., 2014 used cryotherapy with liquid nitrogen as control group differing only in the time exposure (15-30 seconds until frosting every two weeks versus 5-20 seconds every two weeks, respectively) and duration (eight versus twelve weeks, respectively). Hence, the outcomes for these studies were included in the meta-analysis. Meanwhile, in Isik et al., 2014 and Asadi et al., 2014, 0.5% 5-fluorouracil with 10% salicylic acid solution and carbon dioxide laser vaporization were used as comparator group, respectively.

Outcome detection

In all studies, the primary outcome was measured by getting the percentage of the number of patients who were lesion-free over the total number of patients treated with the interventions at the end of the study period.

Outcomes reported

Primary outcome

Table 2 shows the summary of primary outcomes for the four included studies. Two studies (Yaghoobi et al., 2013

Table 2. Primary outcomes of included studies

	Yaghoobi et al., 2013[a]	Camargo et al., 2014[a]	Isik et al., 2014[b]	Asadi et al., 2015[c]
Study duration	8 weeks	12 weeks	12 weeks	9 weeks
Clinical cure	Total clearance	Total clearance	Total clearance	Total clearance
Clinical improvement	None stated	None stated	Marked moderate, insufficient improvement	Excellent, good, weak, response

[a] *Used dichotomous outcomes (frequency and percentage distribution) only;*
[b] *Clinical efficacy measured as dichotomous outcomes and change in papule counts from baseline to the last follow-up visit*
[c] *Clinical efficacy measured as dichotomous outcomes and mean size of lesions from baseline to the last follow-up visit*

Table 3. Secondary outcomes of included studies with 5% potassium hydroxide solution as intervention

	Yaghoobi et al., 2013	Camargo et al., 2014	Isik et al., 2014	Asadi et al., 2015
Recurrence rate	Frequency of recurrence among free-from-warts patients for 8 weeks	Frequency of recurrence 1 month after treatment completion	Frequency of relapse 1 month after treatment completion	Frequency of recurrence 6 months after treatment completion
Adverse events	Frequency of events Percentage distribution of events	Frequency of events Percentage distribution of events	Frequency of events Percentage distribution of events	Frequency of events Percentage distribution of events

and Camargo et al., 2014) used only dichotomous outcomes (clinic response divided into total clearance and partial or no clearance), while Isiket al., 2014 and Asadi et al., 2015 used both dichotomous (clinical response) and continuous outcomes (lesion count from baseline to last visit and lesion size from baseline to last visit, respectively).

The primary outcome measured in all studies was the total clearance reported as the percentage distribution of patients who achieved such result. Yaghoobi et al., 2013 defined the efficacy of treatment as the total removal of exophytic lesions without any recurrence at the end of 8 weeks. The group receiving 5% potassium hydroxide achieved 84.6% clearance rate whereas 50% clearance rate was observed in the cryotherapy group. Meanwhile, Camargo et al., 2014 defined clearance as those patients who were completely wart-free without any recurrences at the end of the trial reporting a rate of 54.2% versus 50% for groups who received 5% KOH and cryotherapy, respectively. In another study (Isik et al., 2014), a physician global assessment (PGA) of anogenital warts using a 5-point scale was utilized to measure the primary efficacy endpoint which was the change in papule counts from baseline to last visit (week 12 of treatment). The PGA index was graded as 1) excellent improvement indicated by regression of 76– 100%; 2) marked improvement indicated by regression of 51–75%; 3) moderate improvement indicated by regression of 26–50%; 4) insufficient improvement indicated by regression of 0–25%; or 5) deterioration). 70.0% of patients in the KOH group and 76.7% of those in the 5-FU+SA group achieved excellent clearance. Marked improvement was seen in 13.3% of patients in the KOH group and 20.0% of patients in the 5-FU+SA groups. For the last study (Asadi et al., 2015), the size of the lesions was measured pre- and posttreatment using a ruler and response to treatment was defined as follows: "complete response" as complete clearance of the warts, "excellent" if there was 75-99% decrease in the size of the lesions, " good response" as a decrease up to 50-75% of the wart size, and "weak response" as a decrease under 50% in the wart size. Both groups treated separately with 5% KOH solution and carbon dioxide achieved a complete response rate of 88.9%.

Secondary outcomes

Table 3 shows a summary of secondary outcomes for the four included studies.

Recurrence rate: All studies measured and reported the recurrence rate among patients who achieved clearance at the end of the treatment differing only in the duration of the evaluation period posttreatment. For both Camargo et al., 2014 and Isik et al., 2014, surveillance for recurrence was done one month until after completion of treatment whereas for Yaghoobi et al., 2013 and Asadi et al., 2015, a longer evaluation period of 2 months and 6 months posttreatment, respectively, was allotted to determine recurrence. For both Yaghoobi 2013 and Camargo 2014, no recurrence was observed among groups receiving KOH while 7.7% and 10% recurrence rate were reported, respectively, for the groups receiving cryotherapy. Isik et al., 2014 also reported a lower recurrence rate of 7% for KOH group while 10% was reported for the group treated with 0.5% 5-fluorouracil and 10% salicylic acid solution whereas a higher recurrence for KOH group was reported by Asadi et al., 2015 (11.7%) compared to carbon dioxide laser vaporization group (7.9%).

Adverse events: The most commonly reported side effects in all studies were burning sensation with or without erosion/ulceration for both interventions. Pigmentary disturbances were also reported- hypopigmentation for both interventions by Isik et al., 2014 and hyperpigmentation reported by Asadi et al., 2015 in both treatment groups.

Risk of bias in included studies

Figure 2 and Figure 3 illustrate the risk of bias of the included studies.

Selection bias

Only one study adequately described the procedure of randomization via random number generator from a

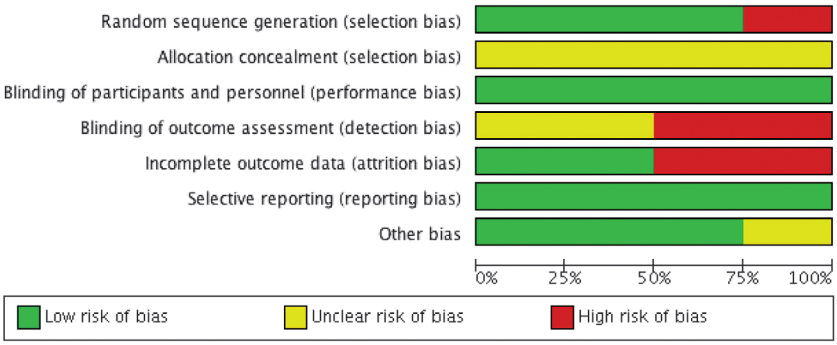

Figure 2. Risk of bias graph: review authors' judgment about each risk of bias item foreach included study.

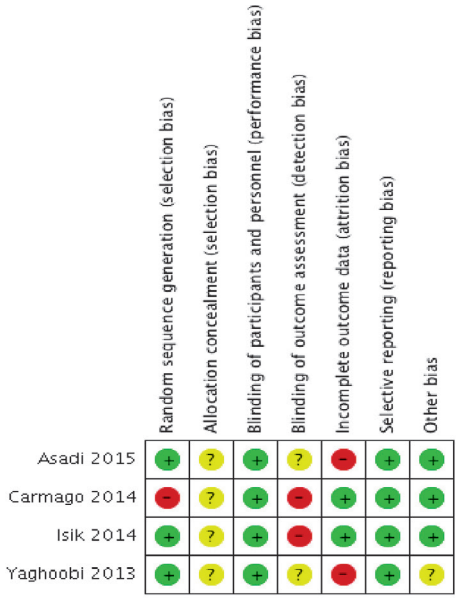

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item.

random table (Isik et al., 2014) thus, assessed as low risk. Studies done by Yaghoobi et al., 2013 and Asadi et al., 2014 were self-controlled classifying them as low risk. Camargo et al., 2014 mentioned random sequence generation using the alternation method, which is not a valid method of randomization classifying it as high risk. Meanwhile, all of the included studies had unclear risk of bias for allocation concealment because it was not stated if the process was done for each study. Selection bias is particularly important in determination of the primary outcome; hence, it is considered in the assessment of the quality of evidence.

Performance Bias and Detection Bias

The studies involved using controls requiring different applications (topical treatment and a laser treatment). In Yaghoobi et al., 2013, Camargo et al., 2014 and Asadi et al., 2015, participants and personnel clearly cannot be blinded from the interventions which are cryotherapy and LASER, respectively; therefore, the absence of blinding did not pose a high risk of performance bias in terms of primary outcome which was complete response rate or clearance rate.

However, blinding of outcome assessment has a great impact on measurement of primary outcome. Two studies (Camargo et al., 2014 and Isik et al., 2014) were open-label studies hence were labeled as high risk. Meanwhile the other two did not specify whether the outcome assessors were blinded hence making it an unclear risk.

Attrition bias

Two studies (Yaghoobi et al., 2013 and Asadi et al., 2015) where both half and half study reported dropouts and those patients were excluded from analysis hence assessed as high risk. On the other hand, Camargo et al., 2014, also reported dropouts but those were considered as failures and were subsequently included in the analysis (intention-to-treat) while Isik et al., 2014, reported no drop out and all patients were included in the analysis. Both studies were assessed as low risk.

Reporting bias

All studies were assessed to have low risk because all the pre-specified primary and secondary endpoints were measured and reported despite the unavailability of full protocols. However, publication bias cannot be ruled out and no funnel plot was done since a minimum of ten studies is needed.

Other bias

Two studies namely Isik et al., 2014 and Asadi et al., 2015 declared no pharmacologic company funding or conflict of interest thus, they were ranked as low risk. Meanwhile, the other two studies (Yaghoobi et al., 2013 and Camargo et al., 2014) did not mention or deny of funding or conflict of interest, hence risk for other biases was unclear.

Data and pooled analysis

Two studies were included in the meta-analysis (Yaghoobi et al., 2013, Camargo et al., 2014). These studies compared potassium hydroxide against cryotherapy. Effect estimates to the right of the vertical line imply benefit from the experimental group (potassium hydroxide). There was a greater pooled clearance rate 1.4 (95% CI: 0.91, 2.16) with large effect size in the potassium hydroxide group compared to cryotherapy at the end of the study period

(Figure 4). The difference is, however, not statistically significant with a *p* value= 0.13 and wide confidence interval crossing the null value.

Both the fixed effect and random effect models were obtained but due to moderate heterogeneity, the random-effect model was the chosen effect measure used and illustrated. The moderate heterogeneity (I^2 = 39%) suggests that the intervention may not consistently have a large effect.

There was also a decreased recurrence rate in the KOH group compared to the cryotherapy group. Effect estimates to the left of the vertical line imply benefit from the experimental group (KOH). There was a lesser pooled recurrence rate 0.17 (95% CI: 0.02, 1.34) with large effect size in the KOH group compared to cryotherapy at the end of the study period (Figure 5). But the difference is not statistically significant with a *p* value= 0.09 and wide confidence interval crossing the null value.

The I^2 turned out zero indicating that the studies were homogeneous in terms of reporting the recurrence rate, thus, the fixed effect model for meta-analysis was used.

DISCUSSION

Summary of the main results

Four randomized controlled trials involving 197 patients clinically diagnosed with anogenital warts were included in this review. This review compared the efficacy and safety of potassium hydroxide solution as a treatment for condyloma acuminata with that of various therapeutic modalities such as cryotherapy with liquid nitrogen, 0.5% 5-fluorouracil + 10% salicylic acid solution and carbon dioxide laser vaporization.

At present, various therapeutic options for anogenital warts are available however none is superior to the others.[8] This is attributed to the inability of these modalities to eliminate HPV from human cells.[7] Thus, the main goal of treatment is directed to removal of clinically visible warts.[8] Destructive therapies and immunomodulatory agents constitute the spectrum of therapies for several decades.[7] Ablative procedures which promote physical destruction of warts are usually clinician administered. These include cryotherapy, electrodessication, surgical excision, laser therapy and chemical destruction using trichloroacetic acid and salicylic acid. Two included trials (Yaghoobi et al., 2013 and Camargo et al., 2014) used cryotherapy with liquid nitrogen as control. Cryotherapy allows clinical clearance by formation of ice crystals leading to dehydration and disruption of cell membrane with consequent cell death.[9] Meanwhile, Asadi et al., 2015 used carbon dioxide laser vaporization as a comparator. Carbon dioxide lasers wavelength (10600 nanometer) is highly absorbed by water (primary chromophore for CO_2 laser) causing conversion of radiant energy to heat. The skin temperature reaches more than 100^{O} C resulting to affected tissue water vaporization until normal tissue architecture is seen.[6] Lastly, Isik et al., 2014 used both the combination of topical chemical ablation (10% salicylic acid) and immunomodulator (0.05% 5-fluorouracil) as positive control. Salicylic acid by virtue of its keratolytic ability increases the penetration and efficacy of 5-fluorouracil[8], which is an antineoplastic

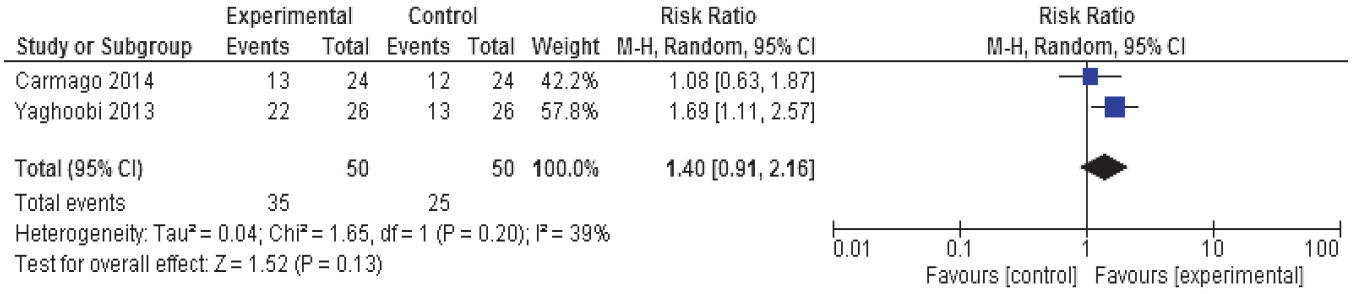

Figure 4. Forest plot of comparison of potassium hydroxide versus cryotherapy for the total clearance rate at the end of the intervention.

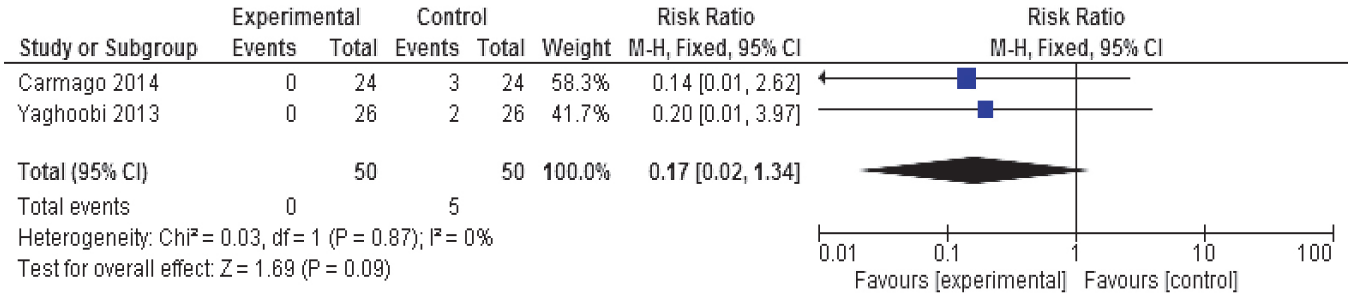

Figure 5. Forest plot of comparison of potassium hydroxide versus cryotherapy for the recurrence rate at the end of the intervention.

antimetabolite that inhibits DNA synthesis, thereby preventing cell replication.

Based on risk of bias assessment following the criteria by the Cochrane Collaboration, the trials were of high risk of bias. When compared to cryotherapy, this review found greater efficacy with potassium hydroxide in terms of clearance rate. However, the pooled analysis showed statistically insignificant difference with high degree of heterogeneity. Possible source of heterogeneity is the dissimilar design, one trial (Yaghoobi 2013) being a self-control study allowing for lesser variations whereas the other study (Camargo 2014) used two distinct groups for each intervention. Another possible cause is the differences in the outcome detection (frequency of follow up and study duration).

Moreover, potassium hydroxide has been demonstrated to have less recurrence than treatment with the controls during the follow up period. But the pooled analysis showed statistically not significant difference with low degree of heterogeneity. This systematic review may not have the statistical power to detect significant difference due to the low number of total participants and the limited number of available randomized controlled trials. Moreover, despite these studies designed as randomized controlled trials, the high risk of bias further decrease our confidence in its effect.

In spite of the lack of significant difference in effecting clinical clearance and decreasing recurrence of potassium hydroxide compared to cryotherapy, one cannot overlook its overall effect and its comparability to this frequently used treatment for anogenital warts. The efficacy of potassium hydroxide is attributed by most studies to its ability to dissolve keratin thereby destroying viral-infected cells and inducing an immune response that is capable of containing the infection preventing further viral proliferation.

Safety of the interventions was measured by documenting the frequency of patient-reported and clinician-observed adverse effects. All treatments were tolerated. No serious or systemic side effects were noted. The most common local adverse effects were burning sensation and erosions or ulcerations, which were minor and transient. Although there were some patients who were excluded due to unattendance during follow-up in three studies (Yaghoobi et al., 2013, Camargo et al., 2014, Asadi et al., 2015), none reported discontinuation of treatment due to adverse effects. Of note is that erosion or ulceration, despite being perceived as a side effect is actually an intended effect to slough off the infected keratinocytes to achieve clinical clearance. The relatively higher frequency of such effect in KOH group (Yaghoobi et al., 2013 90% versus 27% in control, Camargo et al., 2014 50% versus 37.5% in control, Asadi et al., 2015 14.4% versus 6.34%) compared to control group may have also been accounted for the higher clearance rate observed among patients receiving such treatment.

Patient-reported outcomes such as cost and quality-of-life are important outcomes not reported in these trials. However, as compared to the present treatment modalities used as positive controls, potassium hydroxide is readily available, self-administered, and relatively inexpensive allowing a favorable cost-benefit picture for both patients and healthcare system.

Overall completeness and application of evidence

All of the trials were able to address the primary objectives of this review. Efficacy was measured mainly by clinical response documenting the clearance and recurrence rates while safety was measured by reporting of adverse events. Patient-reported symptoms and clinician-observed adverse events may be used for optimal clinical decision-making and future research.

Quality of evidence

None of the included trials were of low risk of bias. In terms of reported outcomes, the quality of evidence was further assessed by exploring inconsistency, indirectness and imprecision as outlined in the GRADEpro software.

Inconsistency

For assessment of efficacy by determining the clearance rate and recurrence rate of anogenital warts after treatment, heterogeneity was significant (I^2= 39%) and the confidence intervals overlap. The observed large variation may be attributed to difference in study design, the difference in intervention and the conduct of studies. One of the two included studies in the meta-analysis was a self-control study (Yaghoobi et al., 2013). The difference with regard to the study duration (8 weeks for Yaghoobi et al., 2013 versus 12 weeks for Camargo et al., 2014) may have also contributed to the perceived inconsistency. Because explanations may be explored, the overall inconsistency was not deemed serious for the authors to downgrade the quality of evidence.

Indirectness

Indirectness was assessed in terms of generalizability and external validity by appraisal of the PICOM format. At the present, there is still no standardized measurement of efficacy and time scales available to assess clearance rate and recurrence rate in the treatment of genital warts. However, the studies included were still able to compare the interventions we are interested in (potassium hydroxide versus placebo or any pharmacoactive drug), delivered to the population we are interested in (patients with anogenital warts) and measured the outcome (clearance and recurrence rate) important for clinical decision-making. Therefore, the quality of evidence for this outcome was assessed as not serious and the quality of evidence was not downgraded.

Imprecision

Despite the effect estimates favoring the treatment group for efficacy in studies comparing potassium hydroxide and cryotherapy, the limited sample size and wide

overlapping confidence intervals present in all included trials were graded as serious. Therefore, effect estimates were imprecise and lowered the quality of evidence.

CONCLUSION

Implication for practice

The reviewed trials were diverse in methods, and the evidence provided by these studies was weak. In spite of the limited evidence, five percent KOH, an inexpensive and tolerable procedure can be used as a treatment for anogenital warts. Moreover, it has comparable efficacy to the present treatment modalities.

Implications for research

Type of study

Future trials should be randomized controlled trials with adequate methods of randomization, allocation concealment and blinding. Blinding of outcome assessors has a great impact on measurement of primary outcome because the efficacy of the treatment was measured through evaluation of clearance rate and recurrence rate, which depend on the clinician's standpoint. Hence, future researches must at least employ such blinding. Within-patient analyses may be considered to allow lesser variation and greater statistical power if a large sample size cannot be obtained.

Outcome

Currently, there are still no standard time scales available to measure clearance rate and recurrence rate in the treatment of genital warts. This review highlights the need for high quality randomized controlled trials, with adequate research design comparing various concentration of topical KOH and other drugs in the treatment of condyloma acuminata, with follow up adjusted for the evaluation of the outcomes: clinical clearance, adverse effects, treatment failures, and recurrence of lesions. Moreover, patient-reported outcomes such as the quality-of-life and satisfaction must be included as secondary outcomes.

Disclaimer

The views expressed in this article are the authors' own and do not reflect the views of the institution.

Statement of Authorship

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