

Local treatments for cutaneous warts: systematic review

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Abstract

Objective To assess the evidence for the efficacy of local treatments for cutaneous warts.

Methods Systematic review of randomised controlled trials.

Main outcomes measures Total clearance of warts and adverse effects such as irritation, pain, and blistering.

Study selection Randomised controlled trials of any local treatment for uncomplicated cutaneous warts. All published and unpublished material was considered, with no restriction on date or language.

Results 50 included trials provided generally weak evidence because of poor methods and reporting. The best evidence was for topical treatments containing salicylic acid. Data pooled from six placebo controlled trials showed a cure rate of 75% (144 of 191) in cases compared with 48% (89 of 185) in controls (odds ratio 3.91, 95% confidence interval 2.40 to 6.36).

Some evidence for the efficacy of contact immunotherapy was provided by two small trials comparing dinitrochlorobenzene with placebo. Evidence for the efficacy of cryotherapy was limited. No consistent evidence was found for the efficacy of intralesional bleomycin, and only limited evidence was found for the efficacy of topical fluorouracil, intralesional interferons, photodynamic therapy, and pulsed dye laser.

Conclusions Reviewed trials of local treatments for cutaneous warts were highly variable in methods and quality, and there was a paucity of evidence from randomised, placebo controlled trials on which to base the rational use of the treatments. There is good evidence that topical treatments containing salicylic acid have a therapeutic effect and some evidence for the efficacy of dinitrochlorobenzene. Less evidence was found for the efficacy of all the other treatments reviewed, including cryotherapy.

Introduction

Viral warts are common, benign, and usually self limiting skin lesions that occur usually on the hands and feet.¹ Extragenital warts in people who are immunocompetent are harmless and usually resolve spontaneously within months or years owing to natural immunity. A policy of not treating them is often advised. However there is considerable social stigma associated with warts on the face and hands, and they

can be painful on the soles of the feet and near the nails. Many patients request treatment for their warts.

Many local treatments are used for warts, but knowledge on the absolute and relative efficacy of these is incomplete. We systematically reviewed randomised controlled trials of any local treatment for uncomplicated warts to assess the evidence for their efficacy.

Methods

We searched Medline (from 1966 to May 2000), Embase (from 1980 to August 2000), and the Cochrane controlled trials register (March 1999) with standardised search strategies.² We manually searched cited references from identified trials and recent review articles. We contacted pharmaceutical companies and experts in the specialty. All studies in which participants were randomised to different interventions were included.

The reviewers assessed the quality of the methods from concealment of allocation, blinding of outcome assessment and handling of withdrawals, and drop-outs.³ They also considered the adequacy of sample size, comparability of treatment groups at baseline, overall quality of reporting, and handling of data. Trials clearly showing adequate concealment, blinding, and intention to treat analysis were classified as high quality.

The main outcome examined was the complete clearance of warts. Because of the overall heterogeneity of the trials we used a random effects model.

Results

Fifty trials were identified from 45 papers. Further details of included and excluded trials are available in the Cochrane Library and on bmj.com.⁴ Only two trials were classified as high quality.^{5,6} Accordingly, evidence from these studies was generally weak. Moreover, the heterogeneity of the methods, particularly the unit of analysis used, hindered the pooling of data for many treatments; in some trials warts were randomised rather than patients (see commentary). Despite this, some useful pooling of data was possible.

Placebo

Seventeen trials with placebo groups used individuals as the unit of analysis. The average cure rate of placebo preparations was 30% after an average period of 10 weeks.

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The full version of this article appears on bmj.com

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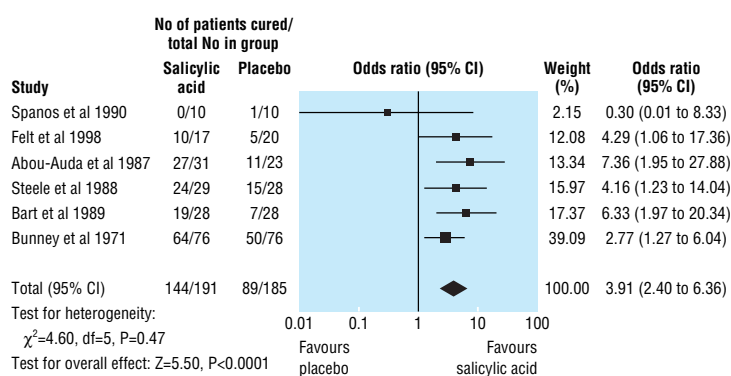


Fig 1 Cure rates in trials comparing topical salicylic acid with placebo for treatment of cutaneous warts

Salicylic acid

Thirteen trials assessed topical salicylic acid. Various preparations were used, with salicylic acid ranging from 15% to 60%; only one trial used 60% salicylic acid, most using standard preparations of between 15% and 26% with or without lactic acid.

Data pooled from six placebo controlled trials showed a cure rate of 75% in cases compared with 48% in controls (odds ratio 3.9, 95% confidence interval 2.4 to 6.4; fig 1).

In one placebo controlled trial one of 29 patients treated with a mixture of monochloroacetic acid and 60% salicylic acid developed cellulitis.⁵ Minor skin irritation was reported occasionally in some of the other trials, but generally there were no major harmful effects of topical salicylic acid.

Cryotherapy

Sixteen trials assessed cryotherapy. Most of these studied different regimens rather than comparing cryotherapy with other treatments or placebo. Pooled data from two small trials including cryotherapy and placebo or no treatment showed no significant difference in cure rates (odds ratio 0.8, 0.2 to 4.2). In two other larger trials no significant difference in efficacy was found between cryotherapy and salicylic acid (1.2, 0.7 to 1.8; fig 2).

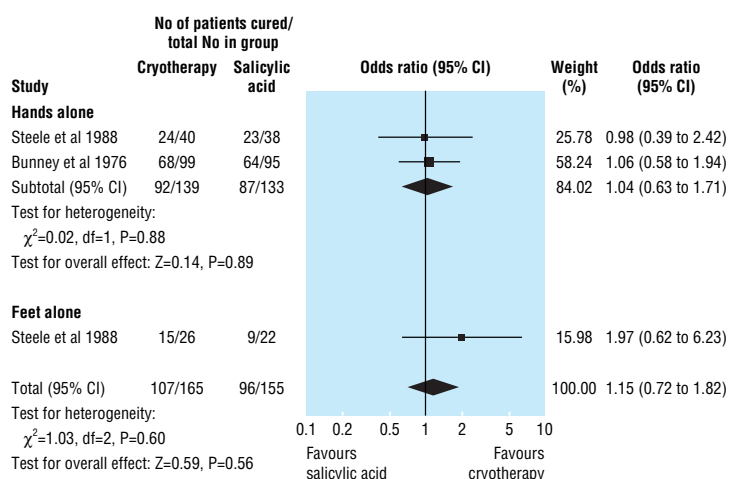


Fig 2 Cure rates in trials comparing cryotherapy with salicylic acid for treatment of cutaneous warts

Pooling of data from four trials showed “aggressive” cryotherapy (various definitions) to be significantly more effective than “gentle” cryotherapy, with cure rates of 52% (159 of 304) and 31% (89 of 288), respectively (3.7, 1.5 to 9.4).⁷⁻¹⁰ Reporting of side effects was less complete, but pain and blistering seemed to be more common with aggressive cryotherapy. Pain or blistering was noted in 64 of 100 (64%) participants treated with an aggressive (10 second) regimen compared with 44 of 100 (44%) treated with a gentle (brief freeze) regimen (2.3, 1.3 to 4.0).⁸ Five participants withdrew from the aggressive group and one from the gentle group because of pain and blistering.

Three trials examined the optimum treatment interval.¹¹⁻¹³ No significant difference was found in long term cure rates between treatment at 2, 3, and 4 weekly intervals. In one trial pain or blistering was reported in 29%, 7%, and 0% of those treated at 1, 2, and 3 weekly intervals, respectively.¹¹ The higher rate of adverse effects with a shorter interval between treatments might have been a reporting artefact due to participants being seen soon after each treatment.

Only one trial examined the optimum number of treatments.¹⁴ This trial showed no significant benefit of prolonging 3 weekly cryotherapy beyond 3 months (about four freezes) in participants with warts on the hands and feet.

Topical immunotherapy with dinitrochlorobenzene

Two small trials comparing the potent contact sensitiser dinitrochlorobenzene with placebo showed some evidence for the efficacy of the active treatment.^{15 16} Pooled data showed cure rates of 80% and 38%, respectively).

No precise data were found on adverse effects in either of these trials. One trial found that six of 20 participants treated with 2% dinitrochlorobenzene became sensitised only after a second application.¹⁵ All of them subsequently experienced major local irritation with or without blistering when they were treated with 1% dinitrochlorobenzene. None withdrew from the study.

Intralesional bleomycin

No consistent evidence was found for the effectiveness of intralesional bleomycin in five trials.¹⁷⁻²¹ Four of the trials, with widely varying results, used warts rather than individuals as the unit of analysis and could not be meaningfully pooled.¹⁷⁻²¹ Cure rates in all five studies ranged from 16% to 94%. Two trials showed higher cure rates with bleomycin than with placebo, one showed no significant difference between bleomycin and placebo, and one showed higher cure rates with placebo than with bleomycin.

None of these trials provided precise data on adverse affects. One trial reported adverse events in 19 of 62 (31%) participants but did not specify what the adverse events were or their distribution between the active treatment and placebo groups.¹⁹ Three of the other four trials reported pain in most participants.^{17 18 21} In two of the five trials, local anaesthetic was used routinely before the injection of bleomycin. One trial reported pain in most participants irrespective of dose.¹⁸ In another trial, two of 24 participants receiving bleomycin withdrew either because of the pain of the injections or because of pain after the injections.¹⁷

Fluorouracil and intralesional interferons

As treatments for ordinary warts, fluorouracil and intralesional interferons are more of historical interest, with most of the trials reviewed from the 1970s and '80s. Evidence provided by all the trials was limited by the heterogeneity of the methods and design. Overall, neither treatment was strikingly effective.

Photodynamic therapy

Four trials reported varying success with different types of photodynamic therapy.^{6 22-24} One well designed trial in 40 adults reported cure in 56% of warts treated with aminolaevulinic acid photodynamic therapy compared with 42% treated by placebo photodynamic therapy.⁶ Topical salicylic acid was also used for all participants.

Two trials provided no data on adverse effects. In one trial, burning and itching during treatment and mild discomfort afterwards was reported universally with aminolaevulinic acid photodynamic therapy.²³ All participants with plantar warts were able to walk after treatment. In another study severe or unbearable pain during treatment was reported in about 17% of warts with active treatment and about 4% of with placebo photodynamic therapy.⁶

Other treatments

One trial of 40 patients treated by pulsed dye laser showed no significant difference in cure rates between four treatments at monthly intervals and "conventional" treatment with either cryotherapy or cantharidin, a potent irritant.²⁵

Six trials of more obscure local treatments (two trials of ultrasonography, one of silver nitrate, one of topical thuja, one of 0.05% tretinoin cream, and one of heat) were not included in the review.⁴

No randomised trials were identified that studied the efficacy of carbon dioxide laser, surgical excision, curettage or cautery, formaldehyde, podophyllin, or podophyllotoxin.

Discussion

Most of the trials reviewed concerning local treatment for cutaneous warts were of low quality. We had difficulty reviewing the research systematically because of the heterogeneity of study design, methods, and outcome. This hindered the pooling of data.

A large number of important variables distinguished these trials from one another (see bmj.com). Some used subgroup analysis to allow for these variables (for example, warts on the hands or feet). Others excluded particular subgroups such as mosaic plantar warts or participants with multiple warts. Few trials made a distinction between plane warts and common warts.

In view of this heterogeneity and the low quality of most of the trials, the descriptive synthesis and pooled data in our review should be interpreted with caution.

Implications for practice

A dearth of high quality evidence prevents the rational use of treatments for common warts. Simple topical treatments containing salicylic acid seem to be both effective and safe. No clear evidence was found that any of the other treatments have a particular advantage of either higher cure rates or fewer adverse effects.

What is already known on this topic

A wide range of local treatments is available for treating warts

No one treatment is strikingly effective and little is known about the absolute and relative efficacy of these treatments

What this study adds

High quality research on the efficacy of various local treatments for warts is lacking

Evidence, which is generally of a poor quality, shows a beneficial effect of topical salicylic acid and contact immunotherapy with dinitrochlorobenzene

Little evidence exists for the efficacy of cryotherapy and no consistent evidence for the efficacy of all the other treatments reviewed

Although it is widely believed that cryotherapy may succeed when topical salicylic acid has failed, there was no clear evidence to support this. Indeed some evidence shows that at best cryotherapy is only equal in efficacy to topical salicylic acid.

Intralesional bleomycin is a popular third line treatment with some dermatologists, but evidence for its efficacy is limited. Topical immunotherapy with agents such as dinitrochlorobenzene is best confined to specialist centres at present in view of its adverse effects. Photodynamic therapy and the use of pulsed dye lasers may hold promise for the future.

Contributors: See bmj.com

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Commentary: Systematic reviewers face challenges from varied study designs

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Relatively minor conditions, without serious consequences and with little associated pain, offer an ideal environment for randomised trials. A good example is warts. Warts are common, and there should be little resistance from patients to participating in a trial of relatively short duration as it would be clear that they could switch to a different treatment shortly. Yet the systematic review of treatments for warts by Gibbs and colleagues shows surprisingly few trials of most treatments. Also interpretation was made more difficult because of the variation in study design.

Some medical conditions affect multiple parts of the body simultaneously, with important implications for the design of randomised trials. The symmetrical cases of eyes and teeth are well known.^{1,2} A more complex situation arises with multiple lesions, such as bed sores, leg ulcers, or warts. For example, in one trial 232 warts from 45 patients were individually randomised, with 19 of the warts (8%) present in one patient.³ It is likely that an individual's warts will respond to a treatment in a similar way. Thus it is not valid to analyse results for each wart with standard methods of analysis. An analysis that ignores the design will tend to give overoptimistic results. The statistical issue here is identical to that of a cluster randomised trial,⁴ with the patient as the "cluster."

Several design options exist. Firstly, each patient could simply be randomised to a single treatment and each patient's outcome summarised across all of his or her warts. (A variation would be to treat just one wart per patient.) Secondly, individual warts could be randomised, if possible ensuring that each patient has at least one wart in each treatment group. The analysis should take account of the clustering.⁵ Thirdly,

treatment could be restricted to two warts for each patient, randomly allocating these to the two treatment arms. A simple paired analysis can then be done, making this design an attractive option.

It would seem preferable to take advantage of the multiple lesions to compare treatments within patients. However, an important additional consideration is a possible systemic effect. The simultaneous use of two treatments within the same patient assumes that their effects are independent. For example, an active treatment with some systemic effect would influence the outcome of warts treated with placebo, so that an effective treatment might seem ineffective. This possibility should always be considered. A further question is whether there might be qualitative differences between patients with few and many warts.

For systematic reviewers, a set of trials using a mixture of different designs of varying validity is certainly challenging. All of the methodological issues mentioned are of course in addition to the standard assessments of trial quality. It is helpful to provide details of the design used and assess whether the analysis was statistically correct. These aspects should help to determine which studies to include in any meta-analysis.

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One hundred years ago Increase in the morphine habit

Our attention has been drawn to an article in one of the popular weekly journals entitled, "Morphine Tea Parties given by Women." The fashion, which is said to have originated in Paris, consists of the formation of what may be termed a morphine club. A number of ladies meet about 4 O'clock every afternoon, tea is served, servants are sent out of the room, the door is locked, the guests bare their arms, and the hostess produces a small hypodermic syringe with which she administers an injection to each person in turn. If one injection is not sufficient to satisfy any particular guest, a second or even a third is given. Whether this is merely a piece of sensational journalism or whether it represents unexaggerated fact we have no convenient means of ascertaining;

probably, however, it is only too true that alcoholism, morphinism, cocaineism, and other supposed means of getting beyond a monotonous daily life are becoming increasingly prevalent among women, and it is also only too true that there is no ruin so utter as a woman's ruin from such causes. Opium as a reliever of pain may still be regarded as "the gift of the gods;" but for those who use it for its mental effect it is fraught with the utmost danger, none the less because the one motive may merge so easily into the other, and none the less because of the ease with which the subject of a single administration may stumble into an enthralling habit, for the greater the relief from one the greater is the danger from the other. (BMJ 1902;i:473)