Topical treatments for cutaneous warts (Review)

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[Intervention Review]

Topical treatments for cutaneous warts

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ABSTRACT

Background

Viral warts are common and usually harmless but very troublesome. A very wide range of local treatments are used.

Objectives

To assess the effects of different local treatments for cutaneous, non-genital warts in healthy people.

Search strategy

We searched the Cochrane Skin Group Specialised Register (March 2005), the Cochrane Central Register of Controlled Trials (*The Cochrane Library Issue* 1, 2005), MEDLINE (1966 to March 2005), EMBASE (1980 to March 2005) and a number of other biomedical databases. The references of all trials and selected review articles were also searched. In addition, we contacted pharmaceutical companies involved in local treatments for warts and experts in the field

Selection criteria

Randomised controlled trials of local treatments for cutaneous non-genital viral warts in immunocompetent (healthy) people.

Data collection and analysis

Data was extracted and two authors independently selected the trials and assessed methodological quality.

Main results

Sixty trials were identified that fulfilled the criteria for inclusion. The evidence provided by these studies was generally weak due to poor methodology and reporting.

In 21 trials with placebo groups that used participants as the unit of analysis, the average cure rate of placebo preparations was 27% (range 0 to 73%) after an average period of 15 weeks (range 4 to 24 weeks).

The best available evidence was for simple topical treatments containing salicylic acid, which were clearly better than placebo. Data pooled from five placebo-controlled trials showed a cure rate of 117/160 (73%) compared with 78/162 (48%) in controls, which translates to a risk ratio of 1.60 (95% confidence interval 1.16 to 2.23), using a random effects model.

Evidence for the absolute efficacy of cryotherapy was surprisingly lacking. Two trials comparing cryotherapy with salicylic acid and one comparing duct tape with cryotherapy showed no significant difference in efficacy.

Evidence for the efficacy of the remaining treatments reviewed was limited.

Authors' conclusions

There is a considerable lack of evidence on which to base the rational use of topical treatments for common warts. The reviewed trials are highly variable in method and quality. Cure rates with placebo preparations are variable but nevertheless considerable. There is certainly evidence that simple topical treatments containing salicylic acid have a therapeutic effect. There is less evidence for the efficacy of cryotherapy, but reasonable evidence that it is only of equivalent efficacy to simpler and safer treatments. The benefits and risks of topical dinitrochlorobenzene and 5-fluorouracil, intralesional bleomycin and interferons, photodynamic therapy and other miscellaneous treatments remain to be determined.

PLAIN LANGUAGE SUMMARY

Topical treatments for skin warts

Viral warts are one of the most common skin diseases. They are caused by the human papilloma virus and most commonly found on the hands and feet. While warts are not harmful and usually go away in time without any treatment, they are unattractive and can be painful. Warts can be removed with wart paints containing salicylic acid. These are cheap and readily available, but slow to work. Cryotherapy, usually using liquid nitrogen, is often considered more effective than wart paints but is more expensive. The review of trials found that there was not enough evidence to compare treatments and that there was not enough evidence to support the use of cryotherapy (freezing) over wart paints as initial treatment for viral warts. More research is needed.

BACKGROUND

Description of the condition

Biology

Cutaneous viral warts, caused by the human papilloma virus (HPV), are an extremely common problem with most people experiencing them in one form or another at some time in their lives (Sterling 2004). HPV (of which 80 types have now been characterised and several others reported) are DNA viruses, which infect epithelial cells (cells that form the outer layer of the skin or the lining of body cavities). Viral replication only takes place in fully differentiated epithelium and the subsequent proliferation results in a clinically evident warty papule or plaque.

The clinical appearance of warts is variable and depends to some extent on the type of HPV involved and the anatomical site. HPV can also remain dormant within epithelial cells without visible disease. Any epithelial surface can be affected and different types of HPV tend to favour particular anatomical sites. The most common infections are with HPV type 2 on the hands and feet. HPV types 1, 4, 27 and 57 are also frequently found in common warts. Plane or flat warts which are clinically distinct from common warts and usually occur on the distal limbs and face are caused by HPV types 3 or 10. Genital warts, caused by a different group of HPV types (6,16,18,31,32,42 to 44 and 51 to 55) are also very common, but do not fall within the remit of this review.

Epidemiology

There are very few precise epidemiological data on viral warts. Most prevalence surveys have tended to use selected subsets of the population such as dermatology outpatients or school children. Two large studies of populations with a complete age range in the USA and Russia produced widely different prevalence figures for viral warts of 0.84% (Johnson 1978) and 12.9% (Beliaeva 1990) respectively. The much-cited 1978 Lambeth study of skin disease found an overall prevalence of warts of 32.8/1000 in the 15 to 74 years age range (Rea 1976). Two studies of school populations found prevalences of 3.9 to 4.7% in the 11 to 16 year age range (Williams 1993) and 12% in 4 to 6 year olds and 24% in 16 to 18 year olds (Kilkenny 1998). This wide variation in prevalence figures is probably due to a combination of true variation between samples and populations, variations of study design and age-related effects.

Despite the scarcity of robust data, it is generally agreed that in the general population viral warts are uncommon in infancy, in-

creasingly common in childhood (reaching a peak in the teenage years) and sharply declining in prevalence thereafter. Young people in institutions are at greater risk, particularly for plantar warts (found on the sole of the foot) in communal 'bare foot' areas such as changing rooms and swimming pools (Johnson 1995). Fishmongers, butchers and other meat handlers are also known to be at greater risk of acquiring large and numerous hand warts (Keefe 1994).

Natural history

Non-genital warts in healthy people are quite harmless and usually resolve spontaneously due to natural immunity within months or years. The rate of resolution probably depends on a number of factors including host immunity, HPV type and the site of infection. One well known study in an institutional population showed that two thirds resolved within a two year period (Massing 1963) but the rates of cure in placebo and no treatment groups of some of the trials reviewed here clearly show a more rapid rate of resolution. In view of this, and because there are probably no universally effective treatments for warts, many clinicians and health planners suggest, if possible, avoiding the treatment of viral warts (Bridger 1996; Ordoukhanian 1997). On the other hand some viral warts persist for many years and untreated warts represent a pool of HPV infection within the community. Moreover many people find warts either unsightly (especially on the hands or face) or painful (especially on the soles of the feet and near the nails) and there is considerable social stigma and hence morbidity associated with visible warts (Ciconte 2003). Therefore, although in theory a policy of not treating warts is logical, in practice many people present to health professionals and are treated.

Description of the intervention

Treatment

The ideal treatment for viral warts should be simple, cheap, effective and free of side effects. The usual first line treatment of wart paints containing salicylic acid and/or lactic acid fulfil these criteria but are slow to work, somewhat laborious and require a degree of perseverance. However, they are readily available and cheap. Cryotherapy, usually with liquid nitrogen, is another first line treatment (particularly for facial warts where topical treatments are contraindicated) or a second line treatment if topical treatments have been ineffective. A number of freezes at intervals of two to four weeks are usually employed. In industrialised countries this treatment is usually available in both primary and secondary care but is expensive essentially because of the cost of clinic time.

Other substances sometimes used topically are:

- glutaraldehyde;
- formaldehyde;
- podophyllin;
- podophyllotoxin;
- 5-fluorouracil;
- silver nitrate;
- cantharidin.

Very resistant warts are sometimes treated with 'third line' treatments such as:

- topical or systemic immunotherapy;
- intralesional bleomycin injections;
- surgical excision;
- curettage and cautery.

These treatments are more specialised and generally carry a higher risk of side effects. They are also more expensive and, generally speaking, more uncomfortable.

OBJECTIVES

Primary objective

(1)To assess the effects of commonly used treatments for warts, with a particular focus on:
(i) the efficacy of common topical treatments and cryotherapy versus placebo or no treatment; and
(ii) a comparison of the efficacy and safety of cryotherapy versus simple topical treatments accepting a 20% relative difference in cure rate as clinically significant.

Secondary objectives

(1) To compare the effects of different methods of cryotherapy (length of freeze, number and frequency of freezes).
(2) To evaluate the effects of other topical treatments such as topical 5-fluorouracil (5-FU) and dinitrochlorobenzene (DNCB), intralesional bleomycin and interferons and photodynamic therapy (PDT) against placebo.
For all of these analyses, where possible, to carry out subgroup analysis comparing:
(1) warts on the hands versus warts on the feet;
(2) ordinary versus refractory warts.
For the purposes of this review we have defined refractory warts as those that have not cleared with a standard course of treatment. Ordinary warts, are defined as warts that have not been treated.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of local treatments for non-genital viral warts.

Types of participants

People with clinically observed viral warts.

Types of interventions

All local treatments aimed at eradicating viral warts. Local treatments are defined here as all topical, intralesional and surgical treatments, including cryotherapy but not including systemic or psychological treatments.

Types of outcome measures

Primary outcomes

(1) Clinical cure at the end of the treatment period. Clinical cure is defined as complete disappearance of elevated/warty skin.
(2) Participant satisfaction/dissatisfaction.
(3) Quality of life measures.

Secondary outcomes

(1) Adverse events such as blistering, pain and scarring.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases using the search strategies shown in the Appendices. Cochrane Skin group Specialised Register (March 2005) Appendix 1; The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) Issue 1, 2005 Appendix 2; MEDLINE (OVID) (March 2005) Appendix 3; EMBASE (OVID) (March 2005) Appendix 4. For the original version of this review we searched a number of other electronic databases in 1999. These included A-med and the Science Citation Index which yielded one additional trial each. No additional trials were found from other databases. These databases were not searched for the update in 2005. We handsearched a number of databases of planned or ongoing trials were searched for the current update; www.nottingham.ac.uk/ongoingskintrials, www.controlled-trials.com, www.clinicaltrials.gov, www.nrr.nhs.uk/search.htm and www.actr.org.au.

Searching other resources

Reference searches

The references of all reviewed trials and selected review articles (Burns 1992; Miller 1996; Benton 1997; Combemale 1998; DTB 1998; Buckley 1999; Wetmore 1999; Dyall-Smith 2000; Kuykendall-Ivy 2003; Micali 2004; Zschocke 2004) on wart treatments were also searched.

Correspondence

We contacted key clinicians and researchers around the world were contacted in an attempt to locate unpublished data and the relevant pharmaceutical companies (suppliers of cryotherapy products and topical wart treatments) were contacted and asked for published and unpublished data (please see Table 1; Table 2).

Table 1. Pharmaceutical companies contacted

Name	Response	Additional RCTs?
Smith & Nephew	Yes	No
Stiefel	Yes	No
Dermal	Yes	No
Pickles	Yes	No

Table 1. Pharmaceutical companies contacted (*Continued*)

Norgine	Yes	No
Typharm	Yes	No
Bray	Yes	No
Dermapharm	Yes	No
Brymill	Yes	No
Cryomed	Yes	No
3M	Yes	Yes

Table 2. Clinicians and researchers contacted

Name	Response	Additional RCTs?
Elliot Androphy (USA)	Yes	No
Richard Barlow (UK)	Yes	No
John Berth-Jones (UK)	Yes	Yes
John Bourke (Eire)	Yes	Yes
Mary Bunney (UK)	Yes	No
Kiyofumi Egawa (Japan)	Yes	No
Reinhard Hopfl (Austria)	Yes	No
Peter Hutchinson (UK)	No	No
Martin James (UK)	Yes	No
Martin Keefe (UK)	Yes	No
Takeji Nishikawa (Japan)	No	No
Bruce Pollock (UK)	Yes	No
Ida-Marie Stender (Germany)	No	No
Steven Tyring (USA)	Yes	No

Table 2. Clinicians and researchers contacted (*Continued*)

M Ramam (India)	Yes	No
Claire Benton (UK)	Yes	No

Adverse events

We did not perform a separate search for adverse events, however, we did consider adverse events which were reported in the included trials.

Translation

No language restrictions were placed on this review and we translated and included papers outside the English language.

Data collection and analysis

Selection of studies

We obtained and examined the full text of all trials identified as possible RCTs from titles and abstracts. If obviously not RCTs, we excluded them immediately, but if there was any doubt two authors (SG and IH) independently assessed the trials for inclusion and discussed until agreement about inclusion or exclusion was reached. All studies that contained evidence demonstrating that they were RCTs were included.

Assessment of risk of bias in included studies

Assessment of methodological quality of included studies

The assessment of methodological quality was based on a subjective judgement of the criteria generally agreed to be most discriminatory for RCT quality - concealment of allocation, blinding of outcome assessment and handling of withdrawals and dropouts (Juni 1999):
(a) the method of generation of the randomisation sequence;
(b) the method of allocation concealment - it was considered 'adequate' if the assignment could not be foreseen;
(c) who was blinded or not blinded (participants, clinicians, outcome assessors);
(d) how many participants were lost to follow up in each arm;
(e) whether participants were analysed in the groups to which they were originally randomised (intention to treat principle).

In addition the quality assessment also included:
(f) the adequacy of sample size,
(g) comparability of treatment groups at baseline,
(h) overall quality of reporting and handling of data were also taken into consideration.
Trials that clearly explained the methods of concealment of allocation, blinding of outcome assessment and handling of withdrawals and dropouts, with intention to treat analysis if at all possible, were classified as high quality. Those that mentioned randomisation without an explanation of method and were unclear about blinding of outcome assessment and the handling of withdrawals and drop outs were classed as low quality. Those classed as medium quality were intermediate in terms of their clarity of explanation and methodology with respect to these three main criteria.

Data synthesis

We examined the data from the included studies in more detail and drew up a descriptive synthesis with pooling of dichotomous data where it was felt the trials were sufficiently homogeneous in design, methodology and outcome. For the parallel group designed trials, risk ratios with 95% confidence intervals (CI) were used as the main measure of effect. Where data were pooled, the DerSimonian and Laird random effects model was used because of anticipated heterogeneity between the trials reviewed. Where appropriate, numbers needed to treat (NNT) for cure rate outcomes and numbers needed to harm (NNH) for adverse events are reported together with 95% CI. For the within-participant trials, the statistical analysis technique used together with the resulting p value from the original publications are reported since data could not be extracted from the publication to allow for conditional effect measures to be calculated.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
The included trials fell into eight broad therapeutic categories:

- 13 trials of salicylic acid and other topical agents (Analysis 1);
- 17 trials of cryotherapy (Analysis 2);
- 5 trials of intralesional bleomycin (Analysis 3);
- 5 trials of 5-fluorouracil (Analysis 4);
- 6 trials of interferons (Analysis 5);
- 2 trials of dinitrochlorobenzene (DNCB) (Analysis 6);
- 5 trials of photodynamic therapy (PDT) (Analysis 7);
- 1 trial of the pulsed dye laser (Analysis 8);
- 7 trials of miscellaneous interventions (Analysis 24).

Even within these therapeutic categories making comparisons and pooling of data was problematic for reasons discussed below, as the populations, types of warts treated and methods of using the treatments varied widely between different trials.

Results of the search

One hundred and twenty four published papers were identified from searches that possibly contained relevant RCTs.

Included studies

Two papers (Bunney 1976a; Berth-Jones 1992a) included eight and two separate trials respectively. Five and two of these respectively were included, bringing the total number of included trials in the review up to 60. Please see Characteristics of included studies.

Excluded studies

Both authors (SG and IH) independently examined and 72 were excluded (Characteristics of excluded studies).

Risk of bias in included studies

The authors used a subjective measure of quality classifying trials as high, medium or low quality based on the three main criteria mentioned above (concealment of allocation, blinding of outcome assessment and handling of withdrawals and dropouts) together with overall quality of reporting and handling of data. There was little disagreement about trial quality and where there was a difference in rating further discussion resolved this by consensus and there was no need to involve a third party.
In general the methodological quality of trials was rated as poor. Of the 60 included trials 46 (77%) were classified as low quality. Only three trials (Steele 1988ii; Stender 2000; Fabbrocini 2001) were classified as high quality. The remaining 11 trials were of intermediate quality.

Allocation

The randomisation process in general and concealment of allocation in particular are the most important and sensitive indicators that bias has been minimized in a clinical trial (Schulz 1995). The method of randomisation was not described at all or was at best unclear in the majority of trials reviewed. In only nine of the trials (Hursthouse 1975; Bunney 1984; Vance 1986; Erkens 1992; Parton 1994; Steele 1988ii; Stender 2000; Focht 2002; Gustafsson 2004) had the trial authors demonstrated clearly that concealment of allocation was adequate.

Blinding

Many of these trials were designed within a clinical service where blinding of outcome assessment is difficult. Moreover many of the physical treatments such as cryotherapy and intralesional bleomycin make it impossible to disguise the effects of treatment unless participants are assessed some time after treatment has been given. Nonetheless in any trial of wart treatments it would be possible to have a completely independent person to assess the outcome of interventions at a set period after treatment. Unfortunately blinding of outcome assessment was clearly demonstrated in only 32 of the studies.

Incomplete outcome data

One of the chief problems with wart treatment trials is the high rate of attrition and this is an important potential source of bias. In many of the trials analysis of outcome was carried out only in those participants who completed the trial and in seven trials (Bunney 1973; Munkvad 1983; Hayes 1986; Abou-Auda 1987; Lee 1990; Marroquin 1997; Zhang 1999) the reporting of numbers of recruited and/or completing participants was entirely obscure. Intention-to-treat analysis was used in only 7 of the 37 trials where it could have been employed (Hansen 1986; Veien 1991; Erkens 1992; Artese 1994; Berth-Jones 1994; Larsen 1996; Stender 1999; Stender 2000).
A number of trial authors took pains to show that the numbers of dropouts and withdrawals were not significantly different in the treatment and control groups but this does not exclude bias, as the reasons for attrition may be different in the two groups (e.g. side effects in the treatment group and lack of response in the placebo group). Many authors did all they could to retain participants in their trials chiefly by writing or telephoning them. Results gathered in this way are clearly less reliable than if participants are seen but if participants telephoned or wrote to report cure or lack of cure then these results were accepted.

Selective reporting

Ten trials (Rossi 1981; Munkvad 1983; Bunney 1984; Hayes 1986; Martinez 1996; Marroquin 1997; Stender 1999; Stender

2000; Fabbrocini 2001; Iscimen 2004) used warts rather than individuals as the unit of analysis. Making statistical inferences from such data is problematic (Altman 1997) but the trials were included as it was felt that they did nevertheless provide some evidence of efficacy about the treatments being investigated. Unfortunately data on individual participants could not be extracted from these trials and pooling of data was not possible. Seven studies (Hursthouse 1975; Veien 1977; Wolff 1980; Bunney 1984; Lee 1990; Niimura 1990; Iscimen 2004) used individuals as their own controls with active treatment and placebo treatment divided in a random fashion between the left and right side of the body. These trials were also included and separate analyses performed but the data were not pooled with the non-paired data from other trials.

Other potential sources of bias

Human papilloma virus can remain dormant in epithelial cells without any visible abnormality, and the effects of wart treatments, especially if they work in synergy with natural immunity, may take some time to become apparent. A questionnaire survey of wart treatments looking at long term outcome (Keefe 1990) showed disappointing results with an impressive 83% of participants thinking they were cured initially but only 57% were clear of warts after a median follow up of 19 months. For these reasons it seems sensible that the result of any treatment for common warts should be assessed after a reasonable interval to allow for gradual resolution of warts or equally gradual recurrence of disease. In 12 of the reviewed trials (Hursthouse 1975; Wolff 1980; Rossi 1981; Schmidt 1981; Bunney 1984; Sonnex 1988; Lee 1990; Spanos 1990; Perez 1992; Martinez 1996; Marroquin 1997; Stender 1999) the period of assessment was six weeks or less. Most clinicians would agree that this period is inadequate to properly assess cure of warts and would suggest follow up at about six months as more realistic. Moreover in some trials it was unclear whether the period before assessment was measured from the beginning or the end of the treatment period. Lack of clarity on this point and a short assessment interval clearly reduce the weight of evidence provided by the data.

Effects of interventions

(1) Salicylic acid and other topical treatments (13 trials; Analyses 1, 9, 11, 16 and 17)

Efficacy

Thirteen trials looked at the efficacy of simple topical agents containing salicylic acid (SA) and lactic acid (LA), salicylic acid only or lactic acid only. The pooled data from five trials that compared these treatments with placebo, showed them to be clearly superior in terms of cure rate. The results were 117/160 (73%) compared with 78/162 (48%) in controls, which translates to a 60% increase in the risk ratio (RR) 1.60 (95% confidence interval (CI) 1.16 to 2.23; Analysis 9.1) and a number needed to treat (NNT) of 4 (95% CI 3 to 7). The treatment period for these trials varied from 6 to 12 weeks and assessment of outcome was normally at the end of the treatment period.

One trial (Steele 1988ii) involving 57 adults and children with simple plantar warts, was classified as having a high methodological quality. This trial used an aggressive topical treatment combining trichloroacetic acid crystals with 60% salicylic acid in an ointment base. This was applied in a specially devised occlusive dressing and left in place for one week. The placebo preparation contained sodium sulphate crystals laced with acetic acid so that it had a similar odour. The outcome was assessed at 6 weeks and 6 months with active treatment and placebo cure rates of 66% versus 18% and 83% versus 54% respectively. The risk ratio for 6 months was 1.54 (95% CI 1.05 to 2.27; Analysis 9.1).

Two trials (Bunney 1976b; Steele 1988i) that compared cryotherapy (weekly and 3 weekly respectively) with topical SA/LA on hand and foot warts (Analysis 11) showed no convincing difference in efficacy between the treatments (RR 1.04, 95% CI 0.88 to 1.22; Analysis 11.1). A trend towards both treatments together being more effective than either treatment alone was reported (RR 1.24, 95% CI 1.07 to 1.43 for cryotherapy + SA/LA versus SA/LA alone; Analysis 16.1) and RR 1.20, 95% CI 0.99 to 1.45; Analysis 17.1 for cryotherapy + SA/LA versus cryotherapy alone), all using a random effects model.

The other seven trials compared different products containing SA or compared SA with other topical treatments such as glutaraldehyde and anthralin. The limited evidence provided by these different trials failed to show a convincing advantage of any particular delivery system for SA (please see Characteristics of included studies and Analysis 1, non-numerical data on trials of salicylic acid)

Adverse events

In one trial (Steele 1988ii) that compared a mixture of monochloroacetic acid and 60% SA with placebo, one of the 29 participants in the active treatment group developed cellulitis. Minor skin irritation was reported occasionally in some of the other trials but generally no significant harmful effects of topical SA were identified.

Conclusion

Established but modest efficacy when compared to placebo

(2) Cryotherapy (17 trials; Analyses 2, 10 to 17, 23 and 24)

Efficacy

Seventeen trials of cryotherapy were included with cryotherapy being the main focus in 13 trials.
Four trials (Hansen 1986; Sonnex 1988; Berth-Jones 1994; Connolly 1999) examined the benefit of 'aggressive' versus 'gentle' cryotherapy (comparison 15). Although these trials were in different populations, on different types of warts and used different definitions of aggressive and gentle (see below), it was felt that the results could be usefully combined for analysis.

- Berth-Jones 1994 - double versus single freeze
- Connolly 1999 - 10 second freeze versus a gentle freeze
- Hansen 1986 - 2 minutes versus 15 seconds with a cryoprobe
- Sonnex 1988 - 20 or 30 second freeze with local anaesthesia versus 10 or 15 second freeze (hands and feet respectively)

Pooling of data showed aggressive cryotherapy to be significantly more effective, with cure rates of 159/304 (52%) versus 89/288 (31%), which translates to a 90% increase in the cure rate (RR 1.90, 95% CI 1.15 to 3.15; Analysis 15.1) and a NNT of 5 (95% CI 3 to 7). Unfortunately, reporting of side effects was less complete and pooling of data on pain and blistering was not possible. The impression from those trials that did comment on adverse effects was that, not surprisingly, pain and blistering were more frequent with aggressive cryotherapy.
There were three trials (Bourke 1995; Bunney 1976a; Larsen 1996) examining the optimum treatment interval that showed no significant difference in long term cure rates between treatment at two, three and four weekly intervals (Analyses 12,13 and 14). The frequency of pain and blistering was higher with shorter treatment intervals although this may have been due to seeing participants sooner after treatment. Generally, data on side effects were sketchy.
The two trials (Bunney 1976b; Steele 1988i) that compared cryotherapy (weekly and three weekly respectively) with topical SA/LA on hand and foot warts (Analysis 11) have already been discussed under 'trials of salicylic acid and other topical agents'.
Only one trial (Berth-Jones 1992b) examined the important question of the optimum number of treatments and this showed no significant benefit of prolonging three weekly cryotherapy beyond three months (approximately four freezes) in a large population of adults and children with warts on the hands and feet.
Two small trials (Wilson 1983; Gibson 1984), both classified as low quality by the authors, contained a cryotherapy and placebo group and both included another topical treatment (DNCB and acyclovir respectively). Pooled data from these trials showed, surprisingly, no advantage of cryotherapy over placebo (RR 0.88, 95% CI 0.26 to 2.95; Analysis 10.1). One of these trials (Gibson 1984) showed an unusually low cure rate (1/11) for cryotherapy consisting of four double freezes at intervals of two weeks and the other (Wilson 1983) showed a relatively high cure rate (8/20) in its placebo group after four months of 'treatment'.
A more recently published trial (Focht 2002), classified as medium quality by the authors, compared occlusive treatment with duct tape and cryotherapy in 61 children and young adults. The duct tape was applied for six and a half days every seven days and cryotherapy given for ten seconds every two to three weeks up to a maximum of six times. Cure rates in the intention to treat population were 22/30 (71%) and 15/31 (46%) respectively, which translates to a 52% increase in cure rate in the participants using the duct tape (RR 1.52, 95% CI 0.99 to 2.31; Analysis 22.1). The trial was relatively small, and some would say that ten seconds of cryotherapy is inadequate. An unspecified number of outcome assessments were carried out over the telephone and it is not entirely clear how long after the treatment period this was done. Despite these weaknesses (Abramovits 2003; Buccolo 2003) this properly randomised and blinded trial adds weight to the argument that simpler and safer treatments are likely to be at least as effective as cryotherapy and possibly more so.

Adverse events

Only two trials had precise data on adverse events. In one trial (Connolly 1999) pain and/or blistering in was noted in 64/100 (64%) participants treated with an 'aggressive' freezing regime (10 seconds) compared to 44/100 (44%) of those treated with a 'gentle' regime (brief freeze) regime. This translates to a 45% significant increase in pain and/or blistering in the 'aggressive' group (RR 1.45, 95%CI 1.12 to 2.31), and a number needed to harm (NNH) of 5 (95% CI 3 to 15). Five participants withdrew from the aggressive group and one from the gentle group due to pain and blistering. In the other trial (Bourke 1995) pain and/or blistering was reported in 29%, 7% and 0% of those treated at 1, 2 and 3 weekly intervals respectively. The higher percentage of reported adverse effects with a shorter interval between treatments might have been a reporting artefact due to participants being seen sooner after each treatment. Pain (ranging from mild to severe) was reported in all 25 cryotherapy participants by Focht et al (Focht 2002).

Conclusion

Inconclusive evidence concerning the relative merits of cryotherapy compared with placebo and other simpler and safer treatments.

(3) Intralesional bleomycin (5 trials; Analyses 3 and 18)

Efficacy

Evaluation of four of the five included trials of intralesional bleomycin was hampered by the fact that they used warts rather than participants were used as the unit of analysis. The results of these four trials (Rossi 1981; Munkvad 1983; Bunney 1984; Hayes

1986) varied widely with cure rates between 16% and 94% of warts and should be interpreted with considerable caution. The trials used different concentrations, delivery systems and total doses of bleomycin but none of these factors seem to correlate with their rates of success. Two of the four trials that compared bleomycin with placebo showed no significant difference in cure rates. One of these (Perez 1992), the only trial that used participants as the unit of analysis, demonstrated a cure rate of 15/16 (94%) that was not significantly different from the 11/15 (73%) achieved with placebo injections of saline, (RR 1.28, 95% CI 0.92 to 1.78; Analysis 18.1).

Adverse events

No precise data on adverse effects were provided in any of the trials. Munkvad et al (Munkvad 1983) reported 'adverse events' in 19/62 (31%) of all participants but did not specify what the adverse events were or their distribution between the active treatment and placebo groups. Three of the other four trials (Rossi 1981; Bunney 1984; Hayes 1986) reported that pain was experienced by most participants. In two of the five trials (Rossi 1981; Perez 1992) local anaesthetic was used routinely prior to the injection of bleomycin. Hayes et al reported pain in most participants irrespective of dose. In the trial by Bunney et al in which all 24 participants received bleomycin, one withdrew because of the pain of the injections and one because of pain following injections.

Conclusion

Insufficient evidence of efficacy.

(4) Topical 5-fluorouracil (4 trials; Analysis 4)

Efficacy

The two trials that compared 5-FU with placebo showed it to be superior with cure rates in the order of 50%, but one trial (Hursthouse 1975) used a left/right within-participant design preventing meaningful pooling of data: cure rates of (45%) versus (13%). The other (Schmidt 1981) used a preparation of 5-FU and salicylic acid combined: cure rates of 46% versus 19%. In one trial (Bunney 1973) involving 95 participants, 2 different concentrations of 5-FU were compared with standard topical SA/LA for mosaic plantar warts. The cure rates for all 3 treatments were close to 50% and not significantly different.

Adverse events

The Hursthouse study (Hursthouse 1975) noted onycholysis (nail detachment) in 11 of 64 participants using 5-FU especially when it was used for warts near the nails. The Artese study (Artese 1994) said that local irritation was noticed by most participants with no precise figures. This may have been due to SA or the combination of SA and 5-FU. The other two studies did not mention adverse effects.

Conclusion

Limited evidence of efficacy, but no discernible evidence of any advantage over other, simpler topical treatments.

(5) Intralesional interferons (6 trials; Analyses 5 and 19)

Efficacy

Of the six trials, four were with interferon alpha and one each with interferon beta and gamma. The latter two trials both used a within-participant design. Four of the six trials involved refractory warts. Pooled data from three of the IFN alpha trials failed to show any significant advantage over placebo (RR 0.87, 95% CI 0.56 to 1.33; Analysis 19.1), random effects model.

Adverse events

The Varnavides study (Varnavides 1997) that used a relatively low dose alpha interferon noted flu-like symptoms that lasted for a few hours in all participants in the active treatment group and 1.5% of the placebo group. The Lee study (Lee 1990) reported flu-like symptoms in 71% and 26% of participants in the high and low dose groups respectively. In another study (Vance 1986) 5 of 100 participants (all in the high dose interferon group) dropped out due to 'extraneous reactions', 2 due to local pain and 3 due to flu-like symptoms. Redness and itching alone was reported in 7 of 64 warts in the Niimura study (Niimura 1990).

Conclusion

Insufficient evidence of efficacy.

(6) Topical dinitrochlorobenzene (DNCB) (2 trials; Analyses 6 and 21)

Efficacy

Pooled data from the 2 small trials (Analysis 21) (Wilson 1983; Cancino 1989) comparing DNCB with placebo showed DNCB to be more than twice as effective at curing than placebo (RR 2.12, 95% CI 1.38 to 3.26; Analysis 21.1) and a NNT of 2 (95% CI 2 to 4). Cure rates for the DNCB group were 32/40 (80%) and 15/40 (38%) for the placebo group.

Adverse events

There were no precise data concerning adverse effects in either of these trials. Rosado-Cancino et al commented that 6/20 participants treated with DNCB (30%) sensitised only after the second application of 2% DNCB to the warts. All of them subsequently experienced significant local irritation with or without blistering when they were treated with 1% DNCB. None withdrew from the study.

Conclusion

Limited evidence of efficacy

(7) Photodynamic therapy (PDT) (5 trials; Analyses 7 and 22)

Five RCTs of PDT were included in the review.

Efficacy

The two older trials from the 1970s used different dyes with dimethylsulphoxide (DMSO) and different light sources. Neither had a placebo group although one (Veien 1977) used a left/right within-participant design and reported complete resolution of the placebo half in the 40% of participants whose warts responded to treatment. The other (Stahl 1979) showed equally disappointing results with PDT and topical SA with creosote.

Two more recent studies from the same group evaluated PDT with aminolaevulinic acid (ALA) for refractory warts. Both trials used warts as the unit of analysis. The first trial (Stender 1999), described as a pilot study, compared a number of different light sources with 4 treatments of cryotherapy and showed PDT to be superior, with cure rates of up to 73% of warts compared with 20% in the cryotherapy group. The second study (Stender 2000) was one of only two studies in the whole review classified as having a high methodological quality. This trial involved 45 adults with refractory warts and compared ALA-PDT with placebo-PDT and showed cure rates of 64/114 (56% of warts) and 47/113 (42% of warts) respectively, which is statistically significant with $p < 0.05$ using the chi-squared test. All warts were also treated with paring and topical salicylic acid ('Verucid'). Wart area was also measured photographically and shown to be significantly more reduced in the active group compared to the placebo group.

The most recently published PDT trial (Fabbrocini 2001), also classified as high quality by the authors, involved 67 participants with refractory warts and compared ALA-PDT three times with placebo PDT. All participants received keratolytic ointment under an occlusive dressing for seven days prior to PDT. Cure rates were higher in the active treatment group two months after the last treatment (48/64 [75%] of warts vs 13/57 [23%] of warts). Unpublished figures of the cure rates at 22 months were 45/64 [71%] vs 13/57 [23%] respectively and, using participants as the unit of analysis, 26/34 [76%] vs 13/33 [42%] respectively.

Methodological heterogeneity prevented pooling of any of these data.

Adverse events

Only three trials commented on adverse events. Precise data were provided by one trial only (Stender 2000) in which severe or unbearable pain during treatment was reported in an average of 17.0% of warts with active treatment and an average of 4.2% of warts with placebo PDT. In another trial using the group of participants (Stender 1999), burning and itching during treatment and mild discomfort afterwards were reported universally with ALA PDT. All participants with plantar warts were able to walk after treatment. One trial (Fabbrocini 2001) reported a burning sensation or slight pain at the time of treatment and moderate swelling with mild erythema 24 hours afterwards in participants with ALA-PDT. No treatments were suspended because of pain.

Conclusion

Limited evidence of efficacy for photodynamic therapy

(8) Pulsed dye laser (Analysis 8)

Efficacy

One trial (Robson 2000) of the pulsed dye laser involving 40 participants showed no significant difference in cure rates between 4 pulsed dye laser treatments at monthly intervals and 'conventional treatment' with either cryotherapy or cantharidin (66% vs 70% of warts respectively)

Adverse events

No significant adverse effects were reported in either treatment group.

(9) Miscellaneous treatments (Analysis 24)

This group contains a heterogeneous collection of trials of less commonly used local treatments, none of which are of any great relevance to everyday practice. For most of these trials the data speak for themselves but two recently published trials warrant further brief comment.

Sandra Johnson and Thomas Horn's group in the USA have published a number of trials (Johnson 2001; Johnson 2004) of intralesional antigen injection for warts (a form of local immunotherapy designed to elicit an immune reaction in warts injected with candida, mumps or trichophyton antigens). Their recent paper in Archives of Dermatology (Horn 2005) is the first published RCT of this type of treatment. Unfortunately the design of the trial was made more complex by the addition of intralesional interferon.

This resulted in four treatment arms (antigen with and without IFN and placebo with and without IFN) rather than two, which would have given much clearer data. Up to five injections were given at three weekly intervals into the largest wart on each participant. Blinding involved only the participants and not the investigators, introducing a source of potentially significant bias. The main outcome reported was > 75% reduction in wart surface area at the end of treatment, of questionable relevance to participants. No long term follow up appears to have been carried out. Two hundred and one participants with refractory warts completed the trial and 57/95 participants (60%) injected with antigen with or without additional interferon experienced the resolution of at least one wart compared with 25/106 (24%) of participants injected with saline or IFN alone. The number of participants who experienced complete clearance of all warts was a little difficult to ascertain from the study but it appears to have been 21/95 (22%) in the treatment groups and 11/106 (10%) in the 'placebo' groups. For an elaborate and presumably fairly painful and expensive treatment this does not appear to be a treatment with any striking advantages.

The second trial (Gustafsson 2004) appeared in the pages of a very prominent journal and consisted of an RCT comparing aphalactalbumin-oleic acid (ALOA) with placebo . This employed the topical application of an unusual hybrid molecule (consisting of a combination of alpha-lactalbumin from human breast milk and oleic acid) said to be lethal to a wide range of transformed cells but harmless to normal ones. The trial appears to have been properly randomised and double blind but the analysis focuses on the main outcome of > 75% reduction in wart volume rather than the more relevant complete clearance of warts. Unfortunately the trial defaulted to an open label design after three months making the long-term follow up data unconvincing. Closer inspection of the reported data shows that although beautiful diagrams demonstrate the active treatment reducing wart volume over time and 100% of participants in the treatment group experiencing > 75% reduction in wart volume, only 21% of lesions in the treatment group resolved completely and only a modest 9/20 (45%) participants with active treatment experienced the resolution of at least one wart compared with 3/20 (15%) in the placebo group RR 3.0, 95% CI 0.95 to 9.48; Analysis 24.1, an unconvincing difference given the size of the trial and consequently wide confidence intervals. The number of participants whose warts completely cleared is not clear from the data. None of this seems to support the trial authors' rather optimistic conclusion that 'ALOA has potential as a novel therapeutic tool in the treatment of papillomas and other tumours'.

Other local treatments

Imiquimod

Topical imiquimod, a novel immunomodulator drug, is an established treatment for genital warts. Two dose-finding RCTs for non-genital warts were obtained from 3M, the manufacturers of imiquimod, but permission to publish the data was declined.

Surgery (curettage and excision)

Surgical excision and curettage with cautery have certainly been recognised treatments for common warts in the past, but fewer dermatologists advocate these treatments now due to the morbidity of the procedure, particularly scarring, and the anecdotal experience of high rates of recurrence. No controlled trials or RCTs that evaluated these treatments were identified.

Glutaraldehyde, formaldehyde, podophyllin, podophyllotoxin and cantharidin.

No RCTs studying these treatments were identified by our searches.

DISCUSSION

Overall completeness and applicability of evidence

Characteristics of 'wart clinic' populations

A number of trials from the 1970s (notably those of Mary Bunney and colleagues in the UK) seemed to show high cure rates with relatively simple treatments. By the 1990s more participants in the UK with common warts were being treated in primary care and people referred to secondary care were much more likely to have refractory warts. Cure rates achieved with cryotherapy in secondary care seem to have been lower. Thus participant groups studied in secondary care in the 1990s probably represented an entirely different sort of population than those studied 20 years previously. Similar changes or differences in referral practice may well have affected trials in other parts of the world. In 25 of the trials, no comment was made about whether the warts being treated were ordinary or refractory.

With all of these potentially confounding factors varying across the range of trials reviewed the descriptive synthesis and pooling of data in this review should be tempered with a degree of caution.

Quality of the evidence

As well as the fact that the majority of the trials reviewed were of low quality an additional difficulty with this review was heterogeneity of study design, methodology and, to a lesser extent, outcome. Such heterogeneity represents a formidable hindrance to the pooling of data and descriptive synthesis of information. Within these trials there were a large number of important variables distinguishing them one from another:

Participant factors

- age of participants: spontaneous and therapeutic cure rates are probably higher in children than in adults
- site of lesions: plantar warts tend to be more resistant to treatment than warts at other sites
- length of history and previous treatment: generally speaking warts of short duration are more likely to clear with or without treatment and longstanding warts with a history of lack of response to previous treatments are likely to represent HPV infection in a host with an impaired immune response to the virus.
- type of lesion: e.g. mosaic plantar warts differ in response to treatment from simple plantar warts as do plane warts from common warts

Some trials stratified their treatment arms to allow for these variables (e.g. hand warts and warts on the feet) but others did not, simply pooling data and reporting the results in single treatment and control groups. Other trials excluded particular sub-groups such as mosaic plantar warts or participants with multiple warts, making these trials subtly different. Very few trials made a distinction between plane warts and common warts.

Treatment factors

- topical treatments: different concentrations, formulations and methods of application of salicylic acid and other topical agents
- cryotherapy: different delivery systems, methods, regimens and interpretations of techniques for administering cryotherapy
- intralesional treatments: different concentrations, vehicles, intervals between treatments and numbers of injections
- trial period: different periods of treatment and different periods before assessment of outcome.

Potential biases in the review process

Statistical heterogeneity

The heterogeneity of study design and methodology described above meant that not many data could be pooled and subjected to meta-analysis. Where data were pooled, a random effects model was used for all comparisons. Only 2 of the 14 comparisons in the review involved more than 3 trials and statistical heterogeneity of outcome was therefore not a commonly encountered problem. One of the six trials comparing topical treatments containing salicylic acid with placebo (Spanos 1990) showed outcomes at variance with the other five (analysis 9). This was primarily a study of hypnosis compared with topical treatment and placebo and involved small numbers of participants. Outcome assessment was carried out at six weeks and the cure rates in the topical treatment and placebo groups were both very low. Sensitivity analysis excluding this one study from the meta-analysis did not alter the direction of the estimate or make a significant difference to the size of effect.

Publication bias and trial size

The limited nature of meta-analyses in the review already mentioned prevented any formal evaluation of publication bias with funnel plots but such bias can be discerned in some of the treatment categories with smaller studies showing greater treatment effects than larger studies. This can be seen in the comparison of aggressive versus gentle cryotherapy (analysis 15). Reservations about methodological heterogeneity in this comparison have already been mentioned but this particular forest plot shows a striking inverse relationship between size of trial and size of effect. Given our reservations about the quality and overall heterogeneity of trials reviewed it is suggested that greater credence is given to the trials with larger numbers of people treated despite the fact that they may show smaller treatment effects.

AUTHORS' CONCLUSIONS

Implications for practice

There is a dearth of sound evidence to govern the rational use of treatments for common warts.

Simple topical treatments containing salicylic acid appear to be both effective and safe. There is no clear evidence that any of the other treatments have a particular advantage in terms of higher cure rates and/or fewer adverse effects.

Cure rates were highly variable between the different trials even within the same therapeutic group. This probably reflects the heterogeneity of the trials in terms of the particular 'population' of warts being studied, and the design and methods of the trials themselves.

The most important finding of this review is the lack of evidence that cryotherapy is any more effective than simple topical treatments. Traditionally cryotherapy has been seen as a routine second-line treatment to be used if simple topical treatments fail. Cryotherapy may indeed succeed where topical treatments have failed, but there is no firm evidence to support this view and some evidence against it.

Intralesional bleomycin is a popular third line treatment with some dermatologists but evidence for its efficacy is both limited and inconsistent.

Topical 5-FU, DNCB, intralesional interferons, photodynamic therapy and intralesional antigen would be viewed as experimental by most dermatologists. The limited available evidence suggests that although these treatments may have a therapeutic effect none of them have any significant advantage over simpler and safer treatments.

Implications for research

There is an urgent need for better quality randomised controlled trials on the routine treatments for common warts, particularly cryotherapy. The problem of cutaneous warts lends itself well to randomised controlled trials because it is so common and also non-life threatening. It is therefore disappointing that among the large number of published trials of wart treatments only a minority are properly randomised and in the majority of these the methodology and reporting leave a great deal to be desired. It would not be too difficult to design trials on the treatment of warts with proper, concealed randomisation procedures, blinding of outcome assessment and intention to treat analysis with additional attention to sub-groups such as site, length of history and previous treatment. The most urgent need is for a trial to compare topical salicylic acid, cryotherapy and placebo. This could be carried out in primary care on ordinary, new warts using salicylic acid daily with some sort of occlusion for three to four months and vehicle alone for the placebo group. Cryotherapy could be used for a similar period at three weekly intervals and then the outcome assessed blindly at six months. The more hazardous second and third line treatments such as bleomycin, DNCB and photodynamic therapy could be compared with placebo in a secondary care setting on refractory warts. Such trials would provide a firmer basis for a more rational approach to this very common problem.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abou-Auda 1987

Methods	1° care multicentre blind ITT -
Participants	?100 - 46 (54 analysed) adults & children ordinary hands & feet
Interventions	15% SA patch vs placebo patch
Outcomes	'Successful treatment' at 12w
Notes	Measured 'successful treatment' rather than cure number of withdrawals and dropouts not clear

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Artese 1994

Methods	2° care open ITT +
Participants	300 - 6 adults & children ordinary hands & feet
Interventions	5FU+SA/LA vs cautery
Outcomes	Cure at 75d
Notes	No statistical analysis on results

Risk of bias

Item	Authors' judgement	Description

Artese 1994 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Auken 1975

Methods	?2° care multicentre blind ITT -
Participants	240 - 55 adults & children ns hands & feet
Interventions	LA/SA(Verucid) vs 'conventional' (=anything else or no treatment)
Outcomes	Cure at 3m
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bart 1989

Methods	2° care blind ITT -
Participants	61 - 8 adults ordinary hands only
Interventions	SA patch vs placebo patch
Outcomes	Cure at 12w
Notes	

Risk of bias

Item	Authors' judgement	Description

Bart 1989 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Berman 1986

Methods	2° care blind ITT na
Participants	8 - 0 adults refractory site not stated
Interventions	I/L IFN alpha (0.1 mls of 1millionU/ml X9) vs placebo
Outcomes	Cure at 8w
Notes	No apparent 'systemic' effect on untreated warts

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Berth-Jones 1992a

Methods	2° care open ITT -
Participants	400 - 77 adults & children mixed hands & feet
Interventions	3 weekly cwb cryo+SA/LA with vs without paring
Outcomes	Cure at 3m
Notes	Cure rates expressed as percentages only

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Berth-Jones 1992b

Methods	2° care open ITT -
Participants	155 - 40 adults & children refractory hands & feet
Interventions	3 weekly cwb cryo vs no cryo
Outcomes	Cure after a further 3m
Notes	2nd part of above study. Systemic inosine pranobex also used for some participants with no apparent impact

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Berth-Jones 1994

Methods	2° care open ITT +
Participants	300 - 93 adults & children ordinary/refractory hands & feet
Interventions	3 weekly cwb cryo+SA/LA: double vs single freeze
Outcomes	Cure at 3m
Notes	High attrition rate

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bourke 1995

Methods	2° care open ITT +/-
Participants	225 - 143 adults & children ordinary/refractory hands & feet
Interventions	cwb cryo +SA/LA: 1 vs 2 vs 3 week interval between freezes
Outcomes	Cure after 12 treatments
Notes	V high attrition rate and cure rates only given as %

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bunney 1971

Methods	2° care blind ITT -
Participants	382 - 86 adults & children ns feet only
Interventions	SA/LA vs collodion vs callusolve vs 50% podophyllin
Outcomes	Cure at 12w
Notes	lower cure rates for mosaic as apposed to simple plantar warts with all treatments 58% vs 75%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bunney 1973

Methods	2° care blinding unclear ITT -
Participants	95 analysed ns ns feet -mosaic
Interventions	2%5FU vs 5%5FU vs SA/LA vs 5%idoxuridine
Outcomes	Cure at 12w
Notes	Report of trial very brief

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bunney 1976a

Methods	2° care open ITT -
Participants	100 - 28 adults & children ns hands only
Interventions	Cwb cryo: 2 vs 3 vs 4 weekly intervals between freezes
Outcomes	Cure at 12w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bunney 1976b

Methods	2° care open ITT -
Participants	389 - 95 adults & children ns hands only
Interventions	3 weekly cwb cryo vs SA/LA vs both
Outcomes	cure at 12w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bunney 1976c

Methods	2° care blind ITT -
Participants	156 -18 adults & children ns feet (simple plantar)
Interventions	SA/LA vs SA/LA + polyoxyethylene
Outcomes	Cure at 12w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bunney 1976d

Methods	2° care blind ITT -
Participants	94 - 13 adults & children ns feet (mosaic plantar)
Interventions	10% glutaraldehyde vs SA/LA
Outcomes	Cure at 12w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bunney 1976e

Methods	2° care blind ITT -
Participants	110 -17 adults & children ns feet (mosaic plantar)
Interventions	40% SA vs SA/LA
Outcomes	Cure at 12w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bunney 1984

Methods	2° care blind ITT na L/R study
Participants	24 - 0 adults refractory hands
Interventions	0.1% bleomycin vs saline X2 if necessary
Outcomes	Cure at 6w
Notes	Main unit of analysis warts rather than patients Participants switched to active treatment after 6 weeks

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Cancino 1989

Methods	2° care open ITT na
Participants	40 - 0 children refractory any site
Interventions	DNCB vs placebo
Outcomes	Cure (time period not stated)
Notes	Period of trial unclear

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Connolly 1999

Methods	2° care open ITT -
Participants	200 - 54 adults & children ns hand & feet
Interventions	cg cryo: 10s freeze vs 'gentle' freeze
Outcomes	Cure at 8w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Erkens 1992

Methods	1° care open ITT +
Participants	93 - 18 adults & children ordinary hands
Interventions	Monthly cwb cryo vs bimonthly histofreezer
Outcomes	Cure at 2.5m
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Fabbrocini 2001

Methods	2° care blind ITT na
Participants	67 - ? adults refractory feet
Interventions	ALA PDT vs placebo PDT (weekly up to 3 times) all patients had 10% urea / 10% SA under occlusion first
Outcomes	Cure at 2m and 22m
Notes	Warts used as unit of analysis. Cure rates reported at 2 months only despite long follow up

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Felt 1998

Methods	2° care open ITT -
Participants	61 - 10 children ordinary anywhere
Interventions	Relaxation imagery vs SA vs no treatment
Outcomes	Cure at 6 - 18m
Notes	Only one index wart treated in each child

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Flindt-Hansen 198

Methods	2° care open ITT -
Participants	72 - 14 adults & children ns hands & feet
Interventions	Anthralin vs LA/SA
Outcomes	Cure at 2m
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Focht 2002

Methods	2° care blind ITT -
Participants	61 - 10 adults & children ordinary hands & feet
Interventions	Duct tape occlusion vs 2-3 weekly cryo (max X6)
Outcomes	Cure at 2m
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gibson 1984

Methods	2° care blind (creams) ITT -
Participants	52 - 5 adults & children ns feet
Interventions	Topical aciclovir vs placebo vs 2 weekly cg cryo/glutarol
Outcomes	Cure at 8w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Gustafsson 2004

Methods	2° care blind ITT na
Participants	40 - 0 adults & children refractory hands & feet
Interventions	Alpha-lactalbumin-oleic acid vs placebo
Outcomes	>75% reduction in wart volume at 2m
Notes	Trial converted to open label after first 3 months

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hansen 1986

Methods	1° care open ITT +
Participants	77 - 17 adults/children ordinary feet
Interventions	Cryoprobe: 2 mins vs 15 s
Outcomes	Cure at 9w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hayes 1986

Methods	2° care blind ITT na
Participants	26 - ? adults refractory hands
Interventions	Bleomycin: 0.25 vs 0.5 vs 1.0 U per wart up to 3X at 3w intervals
Outcomes	Cure at 3m
Notes	Main unit of analysis warts rather than participants number of dropouts not disclosed

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Horn 2005

Methods	2° care investigator open ITT -
Participants	233 - 32 age group ns mostly refractory site ns
Interventions	Intralesional skin test antigens vs placebo
Outcomes	>75% reduction in surface area of warts during trial only
Notes	Only one index wart treated per patient. No medium or long term follow up

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hursthouse 1975

Methods	2° care blind ITT - L/R study
Participants	66 - 2 adults & children ns hands & feet
Interventions	5%5FU cream vs placebo
Outcomes	Cure at 4w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Iscimen 2004

Methods	2° care open ITT not clear within patient
Participants	79 - 3 adults ns any site
Interventions	Intralesional 5FU/lidocaine/epinephrine vs saline
Outcomes	Complete response at 1m and 6m
Notes	Main unit of analysis warts rather than patients

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Khan 1999

Methods	2° care blind ITT na
Participants	30 - 0 adults & children ns feet
Interventions	Topical Thuja vs placebo
Outcomes	Resolution at 1m and 3m
Notes	Conference abstract only

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Khan 2000

Methods	2° care blind ITT na
Participants	30 - 0 adults & children ns feet
Interventions	Comparison of 3 different fractions of Thuja applied topically
Outcomes	Resolution
Notes	Conference abstract only. Timescale not clear.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Larsen 1996

Methods	2° care (multicentre) open ITT +
Participants	185 - 41 adults & children ordinary hands
Interventions	cwb cryo: 2 vs 3 vs 4 weekly intervals between freezes
Outcomes	Cure at 6m
Notes	Study done on one index wart per participant only

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lee 1990

Methods	2° care blind ITT - L/R study
Participants	74 - ? adults & children refractory hands & feet
Interventions	IFN gamma: high dose (5millionU/ml) vs low dose (1millionU/ml) vs placebo
Outcomes	Cure at 4w
Notes	Number of withdrawals and dropouts not clear from text

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Marroquin 1997

Methods	1° care open ITT na within patient study
Participants	30 - ? adults & children ns hands & feet
Interventions	Jatropha sap vs cryo (X1 only) vs petrolatum
Outcomes	Cure at 30d
Notes	Main unit of analysis warts rather than participants Only 3 warts per participant treated Results poorly reported

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Martinez 1996

Methods	1° care open ITT -
Participants	124 - 3 adults & children ordinary anywhere
Interventions	Dimethyl ether propane (DMEP) vs cwb cryo
Outcomes	Cure 15d after last treatment
Notes	Main unit of analysis warts rather than participants

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Munkvad 1983

Methods	2° care blind ITT na
Participants	62 - ? adults ns hands & feet
Interventions	1% bleomycin: in saline vs in oil vs saline alone vs oil alone using dermajet
Outcomes	Cure at 3m
Notes	Main unit of analysis warts rather than participants

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Niimura 1990

Methods	2° care blind ITT - L/R study
Participants	80 - 16 adults & children ns hands & feet
Interventions	IFN beta (0.1 mls of 1millionU/ml weekly) vs placebo
Outcomes	Cure at 10w
Notes	One wart per participant injected

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Parton 1994

Methods	1° care open ITT na
Participants	49 - 0 children ordinary feet
Interventions	Abrasion vs SA
Outcomes	Mean time to cure
Notes	Cure rate not reported (100% cure rate implied by text) Brief report

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Pazin 1982

Methods	2° care blind ITT na
Participants	1 - 0 adult refractory hands & feet
Interventions	IFN alpha vs placebo (various regimes and doses)
Outcomes	Cure at 15.5w
Notes	Also received IFN systemically with no apparent benefit

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Perez 1992

Methods	2° care blind ITT -
Participants	37 - 6 adults & children ns hands & feet
Interventions	0.1% bleomycin vs saline X2 if necessary
Outcomes	Cure at 30d
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Robson 2000

Methods	2° care blind ITT -
Participants	40 - 5 adults mixed hands & feet
Interventions	Pulsed dye laser (585 nm) vs 'conventional' treatment (cryotherapy or cantharidin). All participants used SA.
Outcomes	Cure at approx 16w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rossi 1981

Methods	2° care blind ITT na
Participants	16 - 0 adults & children refractory ns
Interventions	bleomycin 0.1% vs placebo (saline) X 1
Outcomes	Cure at 1m
Notes	Main unit of analysis warts rather than participants

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Schmidt 1981

Methods	2° care blind ITT -
Participants	60 - 5 adults ns hands & feet
Interventions	5FU/SA vs vehicle alone
Outcomes	Cure (presumably at 6w)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sonnex 1988

Methods	2° care open ITT na
Participants	31 - 0 adults refractory hands & feet
Interventions	Cg cryo: aggressive (with LA) vs standard cryo
Outcomes	Cure at 4w
Notes	Published as abstract only

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Spanos 1990

Methods	2° care blind ITT na
Participants	40 - 0 adults ns hands & feet
Interventions	Hypnosis vs SA vs placebo vs nil
Outcomes	'Loss of warts' at 6w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Stahl 1979

Methods	2° care open ITT -
Participants	149 - 29 adults & children ordinary hands & feet
Interventions	Methylene blue/DMSO PDT vs SA/creosote
Outcomes	Cure at 8w
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Steele 1988i

Methods	1° care open ITT -
Participants	207 - 18 adults & children ordinary hands & feet
Interventions	Weekly cwb cryo vs SA/LA vs both
Outcomes	Cure at 6m
Notes	Multiple and mosaic plantar warts excluded side effects not assessed

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Steele 1988ii

Methods	1° care blind ITT na
Participants	57 - 0 adults & children ordinary feet (simple plantar)
Interventions	Monochloracetic acid crystals + 60%SA vs placebo
Outcomes	Cure at 6w and 6m
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Stender 1999

Methods	2° care open ITT + within patient
Participants	30 - 2 adults refractory hands & feet
Interventions	PDT with white (X3 & X1), red (X3) and blue (X3) light vs cryotherapy (X4)
Outcomes	Cure at 4 - 6w
Notes	Warts used as unit of analysis Results in % only No placebo group, SA also used in all groups

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Stender 2000

Methods	2° care blind ITT + within patient
Participants	45 - 5 adults refractory hands & feet
Interventions	20% ALA/red light PDT vs placebo
Outcomes	Cure at 18w
Notes	Warts used as unit of analysis SA also used in both groups

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Vance 1986

Methods	2° care multicentre blind ITT -
Participants	111 - 11 adults ns feet only
Interventions	IFN alpha: high dose 10millionU/ml) vs (low dose 1millionU/ml) vs placebo
Outcomes	Cure at 12w
Notes	One wart per participant injected

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Varnavides 1997

Methods	2° care blind ITT -
Participants	51 - 9 adults refractory hands & feet
Interventions	IFN alpha (10 IU/ml weekly X12) vs placebo
Outcomes	Cure at 24w
Notes	One wart per participant injected

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Veien 1977

Methods	2° care blind L/R study ITT -
Participants	56 - 6 adults & children refractory hands & feet
Interventions	PDT with proflavine/DMSO or neutral red/DMSO PDT vs placebo PDT (all X8)
Outcomes	Cure at 8w
Notes	Placebo half also cured in all responders and no placebo response in all non-responders

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Veien 1991

Methods	2° care open ITT +
Participants	250 - 80 adults & children ns feet (simple plantar)
Interventions	SA/LA with occlusion vs SA/LA
Outcomes	Cure at 17w
Notes	Results expressed as percentage only Higher cure rates in children noted

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wang 2002

Methods	2° care blinding unclear ITT ?
Participants	126 - ? adults & children ordinary hands & face
Interventions	Topical Chinese herbal meds + 0.1% retinoic acid vs retinoic acid alone
Outcomes	Cure after 3 courses of treatment
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wilson 1983

Methods	2° care open ITT na
Participants	60 - 0 adults ordinary hands
Interventions	DNCB vs cryo vs no treatment
Outcomes	Cure at 4m
Notes	Published as abstract only

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wolff 1980

Methods	2° care blind ITT - L/R study
Participants	30-6 adults & children ordinary hands & feet
Interventions	5FU/SA vs placebo
Outcomes	Cure at a mean of 4.4 weeks
Notes	Unpublished study. Follow up period not clear

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Zhang 1999

Methods	2° care blinding unclear ITT ?
Participants	107 - ? ages? ordinary feet
Interventions	Chinese herbal medicine decoction vs electrocautery knife
Outcomes	Recovery after 3 courses of treatment
Notes	Data from brief translation of paper

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

METHODS
All studies, apart from L/R and within patient studies, were parallel group randomized controlled trials.

1° and 2° care refer to the setting of the trial, blinding refers to outcome assessment only, ITT = intention to treat analysis: + = done, - = not done, na = not applicable, ? = not clear
L/R = left/right comparison study
Participants
300 - 6: 300 participants randomized with 6 dropouts/withdrawals, ns: not stated
Interventions
cryo: cryotherapy with liquid nitrogen, cwb: cotton wool bud cryo, cg: cryogun or cryospray
SA: topical salicylic acid, LA: topical lactic acid
DNCB: dinitrochlorobenzene
MCAA: monochloracetic acid
PDT: photodynamic therapy
ALA: aminolaevulinic acid
DMSO: dimethylsulphoxide
LA: local anaesthetic
Outcomes
d: day, w: week, m: month
Quality (column 6) is based purely on concealment of allocation A: adequate, B: unclear, C: inadequate. For the authors quality grading of trials please consult the additional data in comparisons tables 01 - 08.

Characteristics of excluded studies *[ordered by study ID]*

3M 2000a	Details not published at the request of 3M
3M 2000b	Details not published at the request of 3M
Ahmed 2001	Controlled clinical trial of cryogun versus cotton-bud cryo with quasi-randomisation
Allenby 1977	Case series using various concentrations of glutaraldehyde
Amer 1988	Within-patient, open controlled clinical trial of intralesional bleomycin. No randomisation
Anderson 1963	Controlled clinical trial of formalin soaks versus oral and topical placebos. Allocation to treatment was alternate
Androphy 1984	Controlled clinical trial of intralesional and systemic alpha interferon in patients with an abnormal immune response to HPV. No randomizations
Baggish 1985	Randomized controlled trial of laser treatments but on genital and peri-anal warts i.e. in the genital area and not 'common warts'
Behl 1970	Non randomized trial of 25% milkweed in various vehicles
Benton 1991	RCT of systemic inosine pranobex
Blancas 2002	No mention of randomizations. Not clear whether a local or systemic treatment.
Bleiker 1997	Controlled clinical trial of cryogun versus cotton bud cryotherapy with alternate allocation of treatment

(*Continued*)

Borovoy 1996	Case series of treatment with the pulsed dye laser
Braatz 1974	Randomized control trial of a ultrasound but not the focus of this review
Breitbart 1979	Double-blind, within-patient controlled clinical trial of topical 5-fluorouracil. No mention of randomizations.
Coskey 1984	Case series of warts in children treated with a combination of SA, podophyllin and cantharidin
Crow 1954	Non-randomized trial of carbon dioxide snow and curettage and cautery
El-Tonsy 1999	Probable randomized trial of carbon dioxide laser but no clinical outcomes measured.
Epstein 1958	Case series using cantharidin
Goihman-Yahr 1978	Controlled clinical trial of topical DNCB. Open left/right study with no randomizations.
Goncalves 1975	Non randomized, left/right study of 10% SA with and without 5% 5-fluorouracil
Gunther 1973	Non-randomised left/right study of 0.1% retinoic acid and petroleum jelly on warts, verrucous naevi and lichenified eczema
Halasz 1998	Non-randomised trial using 70% pyruvic acid with and without 2% 5-fluorouracil
Hirose 1994	Case series using 20% glutaraldehyde
Jacobsen 1997	Case series using the pulsed dye laser
Johnson 2001	Quasi-randomised study of intralesional mumps or candida antigens versus cryotherapy
Johnson 2004	Large case series (n = 260) of intralesional injection of candida, mumps and trichophyton antigens
Jung 1971	Controlled clinical trial of caustic and surgical removal of warts with and without oral amantadine. No mention of randomizations.
Kainz 1995	Randomized controlled trial of a systemic homeopathic treatment rather than a local treatment (poster presentation: data subsequently published formally [twice] with different authors named)
Kainz 1996	Randomized controlled trial of a systemic homeopathic treatment (see also Kainz 1995 and Smolle 1998)
Kang 1999	Systemic treatment
Kassis 1989	Randomized controlled trial of ultrasound. Not a focus of this review
Khan 1998	Small case series of 30 participants treated with topical Thuja.
Kubeyinje 1996	Randomized control trial of 0.05% tretinoin cream. Not a focus of this review.

(*Continued*)

Labrecque 1992	RCT of 3 systemic homeopathic treatments (thuya, antimony and nitric acid)
Lahti 1982	Controlled clinical trial of topical tuberculin jelly. No mention of randomizations.
Larsen 1995	Large case series of participants (n = 241) treated with diphencyprone
Locke 1970	Description of treatment with intralesional sodium tetradecyl sulfate. Percentage success reported but no numbers (!) Not an RCT obviously
Lyell 1951	A histological study of a case series of 102 participants
Ma 2000	Controlled clinical trial
Manchanda 1997	RCT of various systemic homeopathic treatments
Marchant 1974	Open clinical trial of various topical treatments including 70% salicylic acid for plantar warts. No mention of randomisation.
McEwan 1983	Conference abstract of RCT of interferon subsequently published in 1986 with Vance as first author
McKnight 1968	Case series using 5% formaldehyde soaks
Meyer-Rohn 1978	Not RCT
Oram 1991	Controlled clinical trial of intralesional interferon. No randomisation.
Parish 1988	Case series using 26% SA
Peng 2001	Randomised trial of systemic treatment (intramuscular fractionated BCG)
Peng F 2001	Randomised trial of systemic treatment (intramuscular fractionated BCG)
Pueyo 1990	Within-patient clinical trial of intralesional alpha interferon. Only 3 of 9 patients received placebo. No mention of randomizations or blinding.
Pyrhonen 1975	Non-randomised trial and immunological study or 173 patients using curettage and cautery or keratolytic treatments (presumably SA)
Savage 1961	Non randomized trial of systemic treatments (no treatment, chlorpromazine, propantheline and aspirin)
Schreiner 1995	Possible randomised trial of topical 0.025% tretinoin gel, topical 100,000 IU/g interferon beta gel and both treatments combined. A letter addressed to the authors requesting clarification of randomisation procedure was not answered.
Shah 1991	Non-randomized, within-patient design trial of DNCB
Shumer 1983	Double-blind controlled clinical trial of intralesional bleomycin with alternate allocation of treatment.

(*Continued*)

Smolle 1998	Randomized control trial of a systemic homeopathic treatment for warts with added data of a separate and unrelated study of the effects of the lunar phase on postoperative outcome (see also Kainz 1995 and Kainz 1998)
Sobh 1991	Controlled clinical trial of intralesional bleomycin. Open left/right study with no randomisation.
Sollitto 1996	Case series using intralesional bleomycin
Stender 1996	Case series of 4 using ALA PDT
Stern 1992	Randomized control trial of localized heat therapy. Not a focus of this review.
Stevens 1975	Randomized control trial of transfer factor. Systemic rather than local treatment.
Takigawa 1985	Controlled clinical trial of placebo tape vs tape impregnated with bleomycin
Tucker 2003	Single case report of successful treatment of a plantar wart with 5% imiquimod cream under occlusion combined with 40% salicylic acid
Vickers 1961	One retrospective and one prospective non-randomised trial of curettage and 3% - 10% formalin soaks
Xhao 2000	Controlled clinical trial
Xhao X 2000	Controlled clinical trial
Xia 2001	Controlled clinical trial
Xia Q 2001	Controlled clinical trial
Yazar 1994	Randomized controlled trial of topical silver nitrate. Not a focus of this review.
Yu 2000	Mixture of systemic and local treatments- oral Chinese herbal medicine + topical aciclovir vs i.m. vitamin B, oral and topical aciclovir
Zhu 1995	Non randomised trial of acupuncture with and without moxibustion

Characteristics of ongoing studies *[ordered by study ID]*

Berth-Jones

Trial name or title	Double blind, placebo-controlled randomised treatment of warts using diphencyprone
Methods	
Participants	Patients referred for secondary care

Berth-Jones (*Continued*)

Interventions	Diphencyprone vs placebo
Outcomes	
Starting date	February 2000
Contact information	
Notes	

Bilsland

Trial name or title	A comparison of pulse dye laser and cryotherapy for plantar warts
Methods	
Participants	
Interventions	Laser and cryotherapy
Outcomes	
Starting date	July 1998
Contact information	
Notes	

Day

Trial name or title	Cryotherapy versus SA/MCAA for the treatment of verrucae: a randomised-controlled trial
Methods	
Participants	Referred patients with plantar warts
Interventions	Cryo and SA/MCAA combination
Outcomes	
Starting date	October 2003
Contact information	
Notes	

Eekhof

Trial name or title	Randomised controlled trial of the treatment of warts in general practice
Methods	
Participants	Patients presenting to primary care
Interventions	3 arms: Cryotherapy, salicylic acid and no treatment
Outcomes	
Starting date	March 2006
Contact information	
Notes	

Foulds

Trial name or title	Comparative study of treatment of viral warts with pulse tuneable dye lasers and liquid nitrogen
Methods	
Participants	Patients referred for secondary care
Interventions	Laser and cryotherapy
Outcomes	
Starting date	June 1995
Contact information	
Notes	

Haedersdal

Trial name or title	Treatment of recalcitrant hand and foot warts with intense pulsed light -a randomised controlled trial
Methods	
Participants	Adults with refractory warts
Interventions	IPL and paring versus paring alone
Outcomes	
Starting date	November 2005

Haedersdal (*Continued*)

Contact information	
Notes	

Hutchinson

Trial name or title	A randomised, open label study of imiquimod versus standard cryotherapy
Methods	
Participants	
Interventions	Imiquimod and cryotherapy
Outcomes	
Starting date	August 2000
Contact information	
Notes	

Pearson

Trial name or title	Treatment of plantar warts with topical photodynamic therapy
Methods	
Participants	
Interventions	Not clear: possibly not RCT
Outcomes	
Starting date	March 2001
Contact information	
Notes	

Spigt

Trial name or title	The efficacy of duct tape versus placebo in the treatment of common warts
Methods	
Participants	Primary school children

Spigt (*Continued*)

Interventions	Duct tape and placebo corn ring around warts
Outcomes	
Starting date	October 2005
Contact information	
Notes	

DATA AND ANALYSES

Comparison 1. Trials of topicals containing salicylic acid +/- lactic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional data			Other data	No numeric data

Comparison 2. Trials of cryotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional data			Other data	No numeric data

Comparison 3. Trials of intralesional bleomycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional data			Other data	No numeric data

Comparison 4. Trials of 5-fluorouracil

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional data			Other data	No numeric data

Comparison 5. Trials of intralesional interferons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional data			Other data	No numeric data

Comparison 6. Trials of dinitrochlorobenzene (DNCB)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional data			Other data	No numeric data

Comparison 7. Trials of photodynamic therapy (PDT)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional data			Other data	No numeric data

Comparison 8. Trials of pulsed dye laser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional data			Other data	No numeric data

Comparison 9. Topical SA/LA vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	5	322	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.16, 2.23]

Comparison 10. Cryotherapy vs placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	69	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.26, 2.95]

Comparison 11. Cryotherapy vs SA/LA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	320	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.88, 1.22]
1.1 hands alone	2	272	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.85, 1.20]
1.2 feet alone	1	48	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.77, 2.57]

Comparison 12. Cryotherapy at 2 vs 3 weekly intervals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	3	313	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.77, 1.37]

Comparison 13. Cryotherapy at 3 vs 4 weekly intervals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	161	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.76, 2.63]

Comparison 14. Cryotherapy at 2 vs 4 weekly intervals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	167	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.70, 2.38]

Comparison 15. Aggressive vs gentle cryotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	4	592	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.15, 3.15]

Comparison 16. Cryotherapy + SA/LA vs SA/LA alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	318	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.07, 1.43]
1.1 Hands alone	2	271	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.02, 1.53]
1.2 Feet alone	1	47	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.74, 2.52]

Comparison 17. Cryotherapy + SA/LA vs cryotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	328	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.99, 1.45]
1.1 Hands alone	2	277	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.99, 1.57]
1.2 Feet alone	1	51	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.60, 1.57]

Comparison 18. Intralesional bleomycin vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	1	31	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.92, 1.78]

Comparison 19. Intralesional interferons vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	3	150	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.56, 1.33]
1.1 Alpha interferons	3	150	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.56, 1.33]

Comparison 20. Topical DNCB vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	2	80	Risk Ratio (M-H, Random, 95% CI)	2.12 [1.38, 3.26]

Comparison 21. Photodynamic therapy vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	1	67	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.22, 3.08]

Comparison 22. Duct tape vs cryotherapy (ITT)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 cure rate	1	61	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.99, 2.31]

Comparison 23. Duct tape vs cryotherapy (per protocol)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure rate	1	57	Risk Ratio (M-H, Random, 95% CI)	1.75 [1.17, 2.61]

Comparison 24. Miscellaneous trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Additional data			Other data	No numeric data

Analysis 1.1. Comparison 1 Trials of topicals containing salicylic acid +/- lactic acid, Outcome 1 Additional data.

Additional data

Abou-Auda 1987	15% SA patch vs placebo patch	SA better than placebo	'Successful treatment' in 27/31 (87%) vs 11/23 (48%) at 12w	Low
Auken 1975	SA/LA vs 'conventional treatment' (anything else or no treatment)	No advantage of either approach	cure in 43/84 (51%) vs 54/101 (54%) at 3m	Low
Bart 1989	SA vs placebo	SA better than placebo	cure in 19/28 (68%) vs 7/25 (28%) at 12w	Low
Bunney 1971	SA vs collodion alone vs callusolve vs 50% podophyllin	No significant difference between any of the treatments. Lower cure rates for mosaic as opposed to simple plantar warts.	cure in 64/76 (84%) vs 50/76 (66%) vs 47/70 (67%) vs 60/74 (81%) at 12w	Low
Bunney 1976c	SA vs SA + polyoxyethylene	no difference	cure in 55/71(77%) vs 50/67 (75%) at 12w	Low
Bunney 1976d	10% glutaraldehyde vs SA	no difference	cure in 18/38 (47%) vs 19/43 (44%) at 12w	Low
Bunney 1976e	40% SA vs ordinary SA/LA	no significant difference	cure in 15/50 (30%) vs 17/43 (40%) at 12w	Low
Felt 1998	relaxation imagery vs SA vs no treatment	relaxation imagery no better than SA	total cure in 7/14 (50%) vs 10/17 (59%) vs 5/20 (25%) at 6 - 18m	Low
Flindt-Hansen 198	anthralin vs SA/LA	anthralin significantly better than conventional SA/LA	cure in 15/27 (56%) vs 8/31 (26%) at 2m	Low
Parton 1994	abrasion vs SA	faster cure with abrasion	Mean time to cure of 2.1w (2-4) vs 18.2w (8-38). Itching in 93% of abrasion group.	Medium

Additional data (*Continued*)

			(100% cure rate with both treatments implied by text)	
Spanos 1990	hypnosis vs SA vs placebo vs no treatment	Hypnosis significantly better than all the other 3 groups	'loss of warts' in 6/10 (60%) vs 0/10 (0%) vs 1/10 (10%) vs 3/10 (30%) at 6w	Medium
Steele 1988ii	MCAA+SA vs placebo	MCAA/SA more effective than placebo	cure in 19/29 (66%) vs 5/28 (18%) at 6w cure in 24/29 (83%) vs 15/28 (54%) at 6m	High
Veien 1991	SA/LA with vs without occlusion	No difference between 2 groups. No advantage of occlusion.	cure in 48% and 47% at 17w	Low

Analysis 2.1. Comparison 2 Trials of cryotherapy, Outcome 1 Additional data.

Additional data

Berth-Jones 1992a	Cryo + SA/LA with vs without paring	Paring improves cure rate in plantar warts only. Chance of cure inversely related to duration of warts. Low cure rate compared to Bunney's work in the 1970s may reflect higher proportion of refractory warts in secondary care.	cure in 46% vs 50% of hands and 75 vs 39% of feet at 3m
Berth-Jones 1992b	Cryo continued after 3m for refractory warts vs discontinuing	No significant increase in cure rate by prolonging treatment.	cure in 43% and 38% after a further 3m
Berth-Jones 1994	Cryo + SA/LA: double vs single freeze	Results suggest that a double freeze impoves cure rate for plantar warts only. No comments on side effects.	cure in 46/103 (45%) vs 41/100 (41%) hands and 33/66 (50%) vs 16/55 (29%) feet at 3m
Bourke 1995	Cryo + SA/LA: weekly vs 2 weekly vs 3 weekly	Faster cure with more frequent treatments but no significant difference in long term cure rate. Pain and blistering seen more frequently with short treatment intervals	43%, 48% and 44% cured after 12 treatments. Faster cure in more frequent treatments Blistering in 29%, 7% and 0%
Bunney 1976a	Cryo: 2 vs 3 vs 4 weekly	70-80% cure rate achievable within 12 weeks as long as treatment interval is not longer than 3 weeks. Cure unlikely with less than 3 treatments.	87%, 78% and 64% cured after 6 treatments. Cure in 18/34 (53%) vs 18/31 (58%) vs 10/35 (29%) at 12w

Additional data (*Continued*)

		No comments on side effects.	(with ITT)
Bunney 1976b	Cryo vs SA/LA vs both	Topical SA/LA as good as cryo for effecting cure at 12 weeks. Addition of topicals to cryo may improve the cure rate.	cure in 68/99 (69%), 64/95 (67%) and 78/100 (78%) at 12w
Connolly 1999	Aggressive vs gentle cryo	Significantly higher cure rate with aggressive cryo but also higher rate of pain and blistering	cure in 42/71 (59%) vs 25/75 (33%) at 8w Pain/blistering in 64 (64%) vs 44 (44%)
Erkens 1992	Cryo vs 2 weekly histofreezer	Significantly higher cure rate with cryo. More severe pain during treatment reported in cryo group.	cure in 25/43 (58%) vs 14/50 (28%) at 2.5m
Focht 2002	Cryo vs duct tape occlusion	Duct tape more effective with fewer side effects	cure in 22/26 (85%) vs 15/25 (60%) at 2 months
Gibson 1984	Topical aciclovir vs placebo vs cryo/gluterol	No statistically significant difference between any of the 3 treatments. Trend suggests the creams were superior to cryo.	cure in 7/18 (39%), 5/18 (28%) and 1/11 (9%) at 8w
Hansen 1986	Cryoprobe: 2 mins vs 15s	Significantly higher cure rate in 2 mins group but higher rate of pain and blistering	cure in 24/33 (73%) and 7/27 (26%) at 9w. Pain in 19% of 2 mins group
Larsen 1996	Cryo: 2 vs 3 vs 4 weekly	No significant difference between the 3 groups after 6m. No comment on side effects.	cure in 31/49 (63%), 32/46 (70%) and 31/49 (63%) index warts at 6m
Marroquin 1997	Jatropha sap vs cryo (X1 only) vs placebo	100% cure rate with jatropha sap	100%, 85% and 0% of warts cured at 30d
Martinez 1996	dimethyl ether propane cryo vs liquid nitrogen cryo	no significant difference between the two treatments	cure in 65/68 (96%) vs 80/86 (93%) 15d after last treatment
Sonnex 1988	Aggressive vs gentle cryo for refractory warts	Only aggressive cryo was effective. No comment on side effects.	cure in 11/16 (69%) vs 0/16 (0%) hands and 3/15 (20%) vs 0/15 (0%) feet at 4w
Steele 1988i	Cryo vs SA/LA vs both	Both treatments together significantly better than either alone for hand warts. No significant difference for plantar warts.	cure in 24/40 (60%), 23/38 (61%) and 33/38 (87%) hands and 15/26 (58%), 9/22 (41%) and 14/25 (56%) feet at 6m

Analysis 3.1. Comparison 3 Trials of intralesional bleomycin, Outcome 1 Additional data.

Additional data

Bunney 1984	Bleomycin vs placebo	Higher cure rate with bleomycin.	cure in 34/59 (58%) vs 6/59 (10%) warts at 6w. One withdrawal with pain	Medium
Hayes 1986	3 different doses of bleomycin used (0.25, 0.5 & 1.0 IU-	No significant difference between treatments. Trend towards higher concentrations being more effective.	cure in 11/15 (73%) vs 21/24 (88%) vs 9/10 (90%) warts at 3m. Most patients experienced pain irrespective of dose.	Low
Munkvad 1983	Bleomycin vs placebo	No difference between treatments (Infact significantly higher cure rates with placebo). Bleomycin not recommended.	cure in 4/22 (18%) vs 5/36 (14%) vs 8/19 (42%) vs 10/22 (45%) warts at 3m. 'Adverse events' in 19/62 (31%) patients.	Low
Perez 1992	Bleomycin vs placebo	No significant difference between treatments. Saline cheaper and as effective a treatment.	cure in 15/16 (94%) and 11/15 (73%) patients at 30d	Low
Rossi 1981	Bleomycin vs placebo	Bleomycin significantly better	cure in 31/38 (82%) vs 16/46 (35%) warts at 1m	Low

Analysis 4.1. Comparison 4 Trials of 5-fluorouracil, Outcome 1 Additional data.

Additional data

Artese 1994	5FU+SA vs cautery	5FU better than cautery	cure in 127/150 (85%) vs 99/150 (66%) at 75d	Low
Bunney 1973	2% 5-FU vs 5% 5-FU vs SA/LA vs Idoxuridine	No significant difference between any of these	cure in 13/28 (46%), 8/15 (53%), 8/16 (50%) and 9/36 (25%) at 12w	Low
Hursthouse 1975	5FU vs placebo	5FU significantly better	cure in 29/64 (45%) vs 8/64 (13%%) at 4w	Medium
Schmidt 1981	5FU/SA vs placebo	5FU/SA significantly better	cure in 13/28 (46%) vs 5/27 (19%) at 6w	Low
Wolff 1980	5FU/SA vs placebo	5FU/SA significantly better	Success in 12/21 (57%) vs 9/21 (43%)	Low

Analysis 5.1. Comparison 5 Trials of intralesional interferons, Outcome 1 Additional data.

Additional data

Berman 1986	IFN alpha vs placebo	Results suggest that IFN alpha is an effective treatment	cure in 2/4 (50%) vs 1/4 (25%) at 8w	Low
Lee 1990	IFN gamma: high dose vs low dose vs placebo	Significantly higher response rate with higher dose interferon but also a higher rate of systemic side effects	cure in 20/36 (56%) vs 16/53 (30%) vs 6/36 (17%) at 4w Fever in 71% and 26% of high dose and low dose groups	Low
Niimura 1990	IFN beta vs placebo	IFN beta significantly better than placebo No adverse effects	cure in 42/64 (66%) vs 7/64 (11%) at 10w	Low
Pazin 1982	IFN alpha vs placebo	IFN alpha significantly better than placebo	cure in 5/12 (42%) vs 0/4 (0%) warts at 15.5w	Low
Vance 1986	IFN alpha: high dose vs low dose vs placebo	No significant difference between any of the groups	cure in 4/30 (13%) vs 7/32 (22%) vs 8/38 (21%) at 12w	Medium
Varnavides 1997	IFN alpha vs placebo	no significant difference	cure in 12/23 (52%) vs 12/19 (63%) at 24w	Medium

Analysis 6.1. Comparison 6 Trials of dinitrochlorobenzene (DNCB), Outcome 1 Additional data.

Additional data

Cancino 1989	DNCB vs placebo	Significantly higher cure rate with DNCB	cure in 16/20 (80%) and 7/20 (35%).	Low
Wilson 1983	DNCB vs cryo vs placebo	DNCB more effective than conventional cryotherapy	cure in 16/20 (80%), 10/20 (50%) and 8/20 (40%) at 4m	Low

Analysis 7.1. Comparison 7 Trials of photodynamic therapy (PDT), Outcome 1 Additional data.

Additional data

Fabbrocini 2001	ALA PDT vs placebo PDT	ALA PDT can be an alternative treatment	Cure of 48/65 (75%) vs 13/57 (22.8%) warts at 2m	High
Stahl 1979	PDT with methylene blue/DMSO X8 vs SA/creosote	Neither treatment very effective	cure in 5/65 (8%) vs 8/56 (15%) at 8w	Low

Additional data (*Continued*)

Stender 1999	ALA-PDT with white light X1 vs white X3 vs red X3 vs blue light X3 vs cryotherapy (X4)	White light superior to blue or red for ALA-PDT	cure in 73%, 71%, 42%, 28% and 20% of warts at 4 - 6w	Medium
Stender 2000	ALA-PDT vs placebo PDT with a red light source (X3-6)	ALA-PDT a safe and effective treatment	cure in 64/114 (56%) vs 47/113 (42%) of warts at 18w	High
Veien 1977	PDT with proflavine or neutral red (both in DMSO) vs placebo PDT with picric acid or color rubor (both in DMSO)	PDT moderately effective. Simultaneous clearing of the placebo-treated half could be due to part of the placebo treatment having a therapeutic effect -possibly DMSO	cure in 10/27 (37%) proflavine vs 10/23 (43%) neutral red at 8w	Medium

Analysis 8.1. Comparison 8 Trials of pulsed dye laser, Outcome 1 Additional data.

Additional data

Robson 2000	Pulsed dye laser (585 nm) vs conventional treatment	Pulsed dye laser as effective as conventional treatment	complete response in 70% vs 66% of warts at approximately 16w	Low

Analysis 9.1. Comparison 9 Topical SA/LA vs placebo, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 9 Topical SA/LA vs placebo

Outcome: 1 Cure rate

Study or subgroup	SA n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bart 1989	19/28	7/28		15.5 %	2.71 [1.36, 5.41]
Bunney 1971	64/76	50/76		42.6 %	1.28 [1.06, 1.55]
Felt 1998	10/17	5/20		11.3 %	2.35 [1.00, 5.54]
Spanos 1990	0/10	1/10		1.1 %	0.33 [0.02, 7.32]
Steele 1988ii	24/29	15/28		29.6 %	1.54 [1.05, 2.27]
Total (95% CI)	**160**	**162**		**100.0 %**	**1.60 [1.16, 2.23]**

Total events: 117 (SA), 78 (Placebo)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 7.59$, df = 4 (P = 0.11); $I^2 = 47\%$

Test for overall effect: Z = 2.83 (P = 0.0047)

Analysis 10.1. Comparison 10 Cryotherapy vs placebo/no treatment, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 10 Cryotherapy vs placebo/no treatment

Outcome: 1 Cure rate

Study or subgroup	Cryotherapy n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Gibson 1984	1/11	5/18		26.4 %	0.33 [0.04, 2.45]
Wilson 1983	10/20	8/20		73.6 %	1.25 [0.63, 2.50]
Total (95% CI)	**31**	**38**		**100.0 %**	**0.88 [0.26, 2.95]**

Total events: 11 (Cryotherapy), 13 (Placebo)

Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 1.67$, df = 1 (P = 0.20); $I^2 = 40\%$

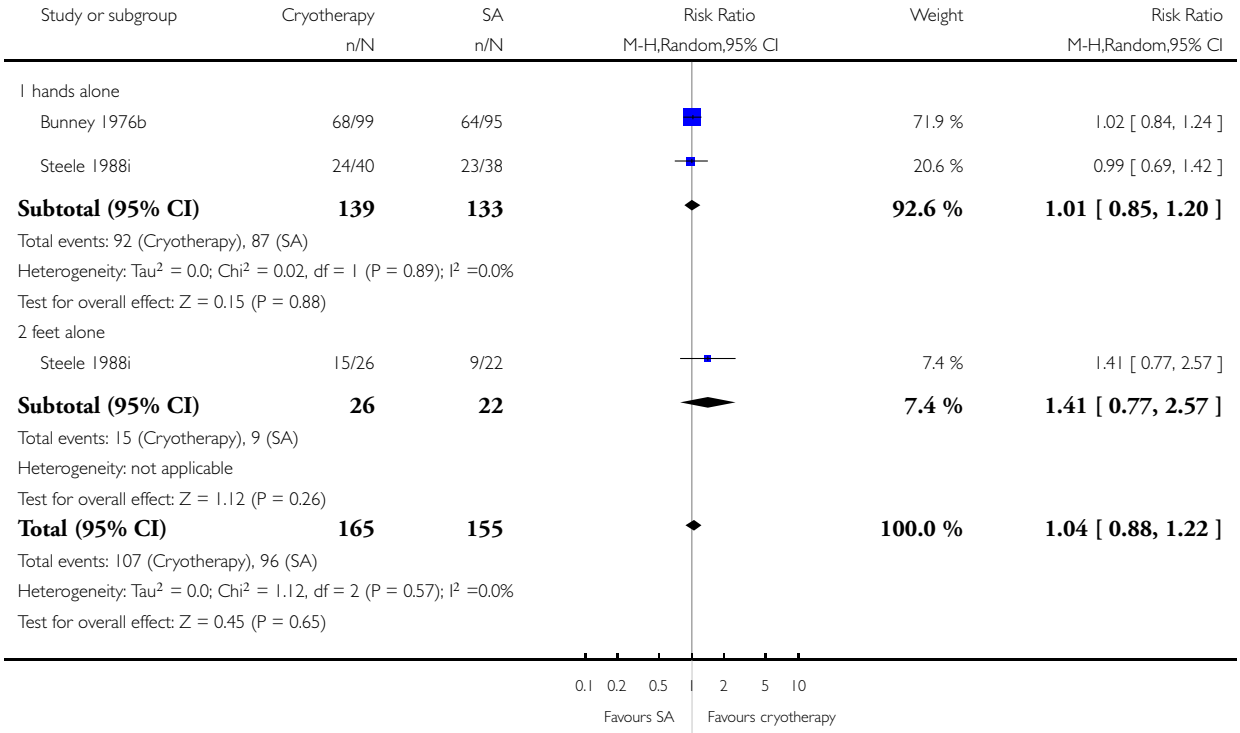
Test for overall effect: Z = 0.21 (P = 0.83)

Analysis 11.1. Comparison 11 Cryotherapy vs SA/LA, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 11 Cryotherapy vs SA/LA

Outcome: 1 Cure rate



Analysis 12.1. Comparison 12 Cryotherapy at 2 vs 3 weekly intervals, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 12 Cryotherapy at 2 vs 3 weekly intervals

Outcome: 1 Cure rate

Study or subgroup	2 w interval n/N	3 w interval n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bourke 1995	28/75	20/78		25.3 %	1.46 [0.90, 2.35]
Bunney 1976a	18/34	18/31		28.7 %	0.91 [0.59, 1.41]
Larsen 1996	31/49	32/46		46.0 %	0.91 [0.68, 1.21]
Total (95% CI)	**158**	**155**		**100.0 %**	**1.03 [0.77, 1.37]**

Total events: 77 (2 w interval), 70 (3 w interval)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.25$, df = 2 (P = 0.20); $I^2 = 38\%$

Test for overall effect: Z = 0.17 (P = 0.87)

Analysis 13.1. Comparison 13 Cryotherapy at 3 vs 4 weekly intervals, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 13 Cryotherapy at 3 vs 4 weekly intervals

Outcome: 1 Cure rate

Study or subgroup	3 w interval n/N	4 week interval n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bunney 1976a	18/31	10/35		41.1 %	2.03 [1.11, 3.71]
Larsen 1996	32/46	31/49		58.9 %	1.10 [0.83, 1.46]
Total (95% CI)	**77**	**84**		**100.0 %**	**1.42 [0.76, 2.63]**

Total events: 50 (3 w interval), 41 (4 week interval)

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 3.54$, df = 1 (P = 0.06); $I^2 = 72\%$

Test for overall effect: Z = 1.10 (P = 0.27)

Analysis 14.1. Comparison 14 Cryotherapy at 2 vs 4 weekly intervals, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 14 Cryotherapy at 2 vs 4 weekly intervals

Outcome: 1 Cure rate

Study or subgroup	2 w interval n/N	4 w interval n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bunney 1976a	18/34	10/35		41.0 %	1.85 [1.00, 3.42]
Larsen 1996	31/49	31/49		59.0 %	1.00 [0.74, 1.35]
Total (95% CI)	**83**	**84**		**100.0 %**	**1.29 [0.70, 2.38]**

Total events: 49 (2 w interval), 41 (4 w interval)

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 3.37$, df = 1 (P = 0.07); $I^2 = 70\%$

Test for overall effect: Z = 0.80 (P = 0.42)

Analysis 15.1. Comparison 15 Aggressive vs gentle cryotherapy, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 15 Aggressive vs gentle cryotherapy

Outcome: 1 Cure rate

Study or subgroup	aggressive cryo n/N	'gentle' cryo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Berth-Jones 1994	79/169	57/155		38.2 %	1.27 [0.98, 1.65]
Connolly 1999	42/71	25/75		34.5 %	1.77 [1.22, 2.58]
Hansen 1986	24/33	7/27		24.3 %	2.81 [1.43, 5.49]
Sonnex 1988	14/31	0/31		3.1 %	29.00 [1.81, 465.72]
Total (95% CI)	**304**	**288**		**100.0 %**	**1.90 [1.15, 3.15]**

Total events: 159 (aggressive cryo), 89 ('gentle' cryo)

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 10.76$, df = 3 (P = 0.01); $I^2 = 72\%$

Test for overall effect: Z = 2.50 (P = 0.013)

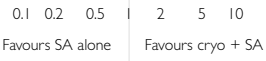
Analysis 16.1. Comparison 16 Cryotherapy + SA/LA vs SA/LA alone, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 16 Cryotherapy + SA/LA vs SA/LA alone

Outcome: 1 Cure rate

Study or subgroup	Cryo + SA n/N	SA alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Hands alone					
Bunney 1976b	78/100	64/95		68.7 %	1.16 [0.97, 1.38]
Steele 1988i	33/38	23/38		25.7 %	1.43 [1.08, 1.91]
Subtotal (95% CI)	**138**	**133**		**94.4 %**	**1.25 [1.02, 1.53]**
Total events: 111 (Cryo + SA), 87 (SA alone)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.58$, df = 1 (P = 0.21); $I^2 = 37\%$					
Test for overall effect: Z = 2.17 (P = 0.030)					
2 Feet alone					
Steele 1988i	14/25	9/22		5.6 %	1.37 [0.74, 2.52]
Subtotal (95% CI)	**25**	**22**		**5.6 %**	**1.37 [0.74, 2.52]**
Total events: 14 (Cryo + SA), 9 (SA alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
Total (95% CI)	**163**	**155**		**100.0 %**	**1.24 [1.07, 1.43]**
Total events: 125 (Cryo + SA), 96 (SA alone)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.71$, df = 2 (P = 0.43); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.86 (P = 0.0042)					



Analysis 17.1. Comparison 17 Cryotherapy + SA/LA vs cryotherapy alone, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 17 Cryotherapy + SA/LA vs cryotherapy alone

Outcome: 1 Cure rate

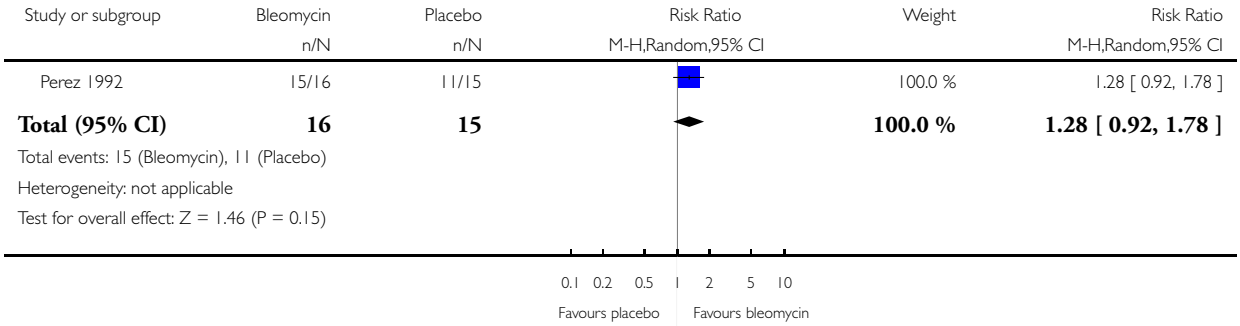
Study or subgroup	Cryo + SA n/N	Cryo alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Hands alone					
Bunney 1976b	78/100	68/99		55.8 %	1.14 [0.96, 1.34]
Steele 1988i	33/38	24/40		30.9 %	1.45 [1.09, 1.92]
Subtotal (95% CI)	**138**	**139**		**86.7 %**	**1.25 [0.99, 1.57]**
Total events: 111 (Cryo + SA), 92 (Cryo alone)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 2.10, df = 1 (P = 0.15); I^2 =52%					
Test for overall effect: Z = 1.87 (P = 0.061)					
2 Feet alone					
Steele 1988i	14/25	15/26		13.3 %	0.97 [0.60, 1.57]
Subtotal (95% CI)	**25**	**26**		**13.3 %**	**0.97 [0.60, 1.57]**
Total events: 14 (Cryo + SA), 15 (Cryo alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.90)					
Total (95% CI)	**163**	**165**		**100.0 %**	**1.20 [0.99, 1.45]**
Total events: 125 (Cryo + SA), 107 (Cryo alone)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 2.85, df = 2 (P = 0.24); I^2 =30%					
Test for overall effect: Z = 1.90 (P = 0.058)					

Analysis 18.1. Comparison 18 Intralesional bleomycin vs placebo, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 18 Intralesional bleomycin vs placebo

Outcome: 1 Cure rate

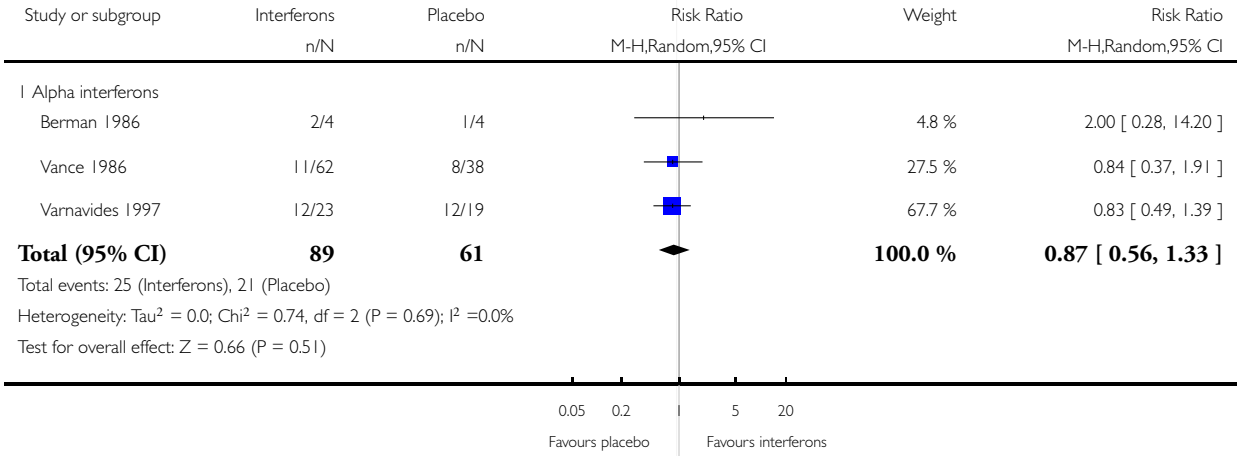


Analysis 19.1. Comparison 19 Intralesional interferons vs placebo, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 19 Intralesional interferons vs placebo

Outcome: 1 Cure rate



Analysis 20.1. Comparison 20 Topical DNCB vs placebo, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 20 Topical DNCB vs placebo

Outcome: 1 Cure rate

Study or subgroup	DNCB n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Cancino 1989	16/20	7/20		45.4 %	2.29 [1.21, 4.32]
Wilson 1983	16/20	8/20		54.6 %	2.00 [1.12, 3.57]
Total (95% CI)	**40**	**40**		**100.0 %**	**2.12 [1.38, 3.26]**

Total events: 32 (DNCB), 15 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 3.45 (P = 0.00057)

Analysis 21.1. Comparison 21 Photodynamic therapy vs placebo, Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 21 Photodynamic therapy vs placebo

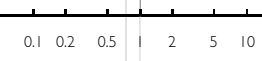
Outcome: 1 Cure rate

Study or subgroup	PDT n/N	Placebo PDT n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Fabbrocini 2001	26/34	13/33		100.0 %	1.94 [1.22, 3.08]
Total (95% CI)	**34**	**33**		**100.0 %**	**1.94 [1.22, 3.08]**

Total events: 26 (PDT), 13 (Placebo PDT)

Heterogeneity: not applicable

Test for overall effect: Z = 2.81 (P = 0.0049)

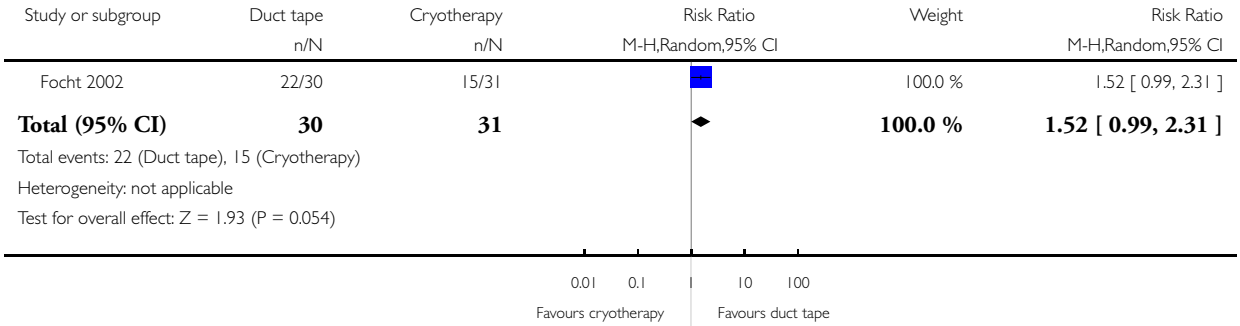


Analysis 22.1. Comparison 22 Duct tape vs cryotherapy (ITT), Outcome 1 cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 22 Duct tape vs cryotherapy (ITT)

Outcome: 1 cure rate

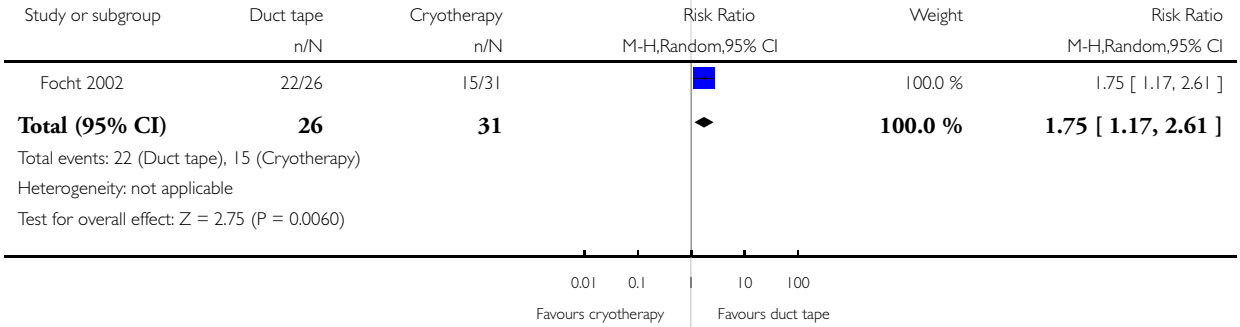


Analysis 23.1. Comparison 23 Duct tape vs cryotherapy (per protocol), Outcome 1 Cure rate.

Review: Topical treatments for cutaneous warts

Comparison: 23 Duct tape vs cryotherapy (per protocol)

Outcome: 1 Cure rate



Analysis 24.1. Comparison 24 Miscellaneous trials, Outcome 1 Additional data.

Additional data

Gustafsson 2004	alpha-lactalbumin-oleic acid (ALOA) vs saline	ALOA has a beneficial and lasting effect	9/20 (45%) vs 3/20 (15%) with at least one wart resolved	Medium

Additional data (*Continued*)

Horn 2005	intralesional skin test antigen vs antigen+IFN vs IFN vs saline	intralesional immunotherapy is an effective treatment for warts	57/95 (60%) antigen vs 25/106 (24%), saline or IFN had resolution of at least one wart	Low
Iscimen 2004	intralesional 5FU/lidocaine/epinephrine vs saline	5FU +LE mixture is safe and effective	118/169 (70%) vs 43/146 (29%) warts showed complete response	Low
Khan 1999	Topical Thuja vs placebo	Efficacy of Thuja demonstrated	12/15 (80%) vs 5/15 (33%) showed resolution	Low
Khan 2000	Hexane vs chloroform vs ethyl acetate fractions of Thuja	Chloroform fraction superior	0/10 vs 10/10 vs 4/10 cases respectively resolved	Low
Wang 2002	Chinese herbal medicine + 0.1% retinoic acid vs retinoic acid alone	Chinese herbal medicine + retinoic acid has a relatively good efficacy	cure in 57/70 (81%) vs29/56 (52%)	Low
Zhang 1999	Chinese herbal medicine decoction vs electrocautery knife	chinese herbal medicine is more effective than electrocautery	Recovery in 58/89 (65%) vs 7/18 (39%)	Low

APPENDICES

Appendix 1. Cochrane Skin group Specialised Register (March 2005) Search Strategy

A search was made on 21/1/05 using the search strategy below:
((PLANTAR AND WART*) OR VERRUCA* OR (VERRUCA* AND VULGARIS) OR (PAPILLOMAVIRUS AND HUMAN) OR (HPV) OR (MOSAIC AND WART*) OR (PLANE AND WART*) OR (COMMON AND WART*) OR (FOOT AND DERMATOS*) OR (HAND AND DERMATOS*) OR (SKIN AND DISEASE* AND VIRAL) OR (PAPOVAVIRIDAE AND INFECTION*)) AND NOT (genital and (ulcer* or wart*))

Appendix 2. The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 2005) Search Strategy

A search was made using the following terms:
#1 ((plantar or plane or common or mosaic or cutaneous or resistant or recalcitrant) near wart*) or verruca* or (papilloma near vir* near human) in All Fields, from 1800 to 2005 in all products
#2 (skin near disease* near vir*) in All Fields, from 1800 to 2005 in all products
#3 (papovaviridae near infection*) in All Fields, from 1800 to 2005 in all products
#4 MeSH descriptor Epidermodysplasia Verruciformis explode all trees in MeSH products
#5 MeSH descriptor Warts, this term only in MeSH products
#6 (#1 OR #2 OR #3 OR #4 OR #5)

#7 (genital* or vagina* or anogenital or cervical or condylomata) in Record Title, from 1800 to 2005 in all products
#8 (#6 AND NOT #7)

Appendix 3. MEDLINE (OVID) (March 2005)

(i) Search strategy to locate RCTs:
MEDLINE (OVID) was searched using the search strategy to locate RCTs search terms lines 1-29, as given in the Cochrane Reviewer's Handbook (Alderson 2004) App 5b.2

(ii) Search strategy to locate disease terms:
30. warts.mp. or exp WARTS/
31. (plant$ adj5 wart$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32. (mosaic adj5 wart$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
33. (common adj5 wart$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
34. (cutaneous adj5 wart$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
35. verruca$.mp.
36. (papilloma adj5 vir$ adj5 human).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
37. (papovaviridae adj5 infect$ adj5 human).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
38. *Papillomavirus, Human/
39. *Papovaviridae Infections/
40. (hand or foot or feet or skin).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41. 36 or 37 or 38 or 39
42. 41 and 40
43. 30 or 31 or 32 or 33 or 34 or 35 or 42
44. 29 and 43
45. limit 44 to yr=2003 - 2005
The results from the searches (i) and (ii) were combined using the Boolean operator AND.

Appendix 4. EMBASE (OVID) (March 2005)

EMBASE (OVID) was searched on 2/3/05 using the following search strategy:
1. random$.mp.
2. factorial$.mp.
3. crossover$.mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
7. assign$.mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. warts.mp. or exp Verruca Vulgaris/
15. (plant$ adj5 wart$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
16. (mosaic adj5 wart$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]

17. (common adj5 wart$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
18. (cutaneous adj5 wart$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
19. verruca$.mp.
20. (papilloma adj5 vir$ adj5 human).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
21. (papovaviridae adj5 infect$ adj5 human).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
22. exp papilloma virus/
23. exp papovavirus/
24. (hand or foot or feet or skin).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
25. 20 or 21 or 22 or 23
26. 24 and 25
27. 14 or 15 or 16 or 17 or 18 or 19 or 26
28. 13 and 27
29. limit 28 to yr=2003 - 2005

F E E D B A C K

Personal story received 3 December 2002

Summary

Verruca history
I suffered from verrucas for 5 years, having picked them up in a swimming pool abroad when I was forty and ignored them until I moved back to England the following year. I finally went for treatment about a year after I had contracted them. On the doctor's advice, I filed my warts down with a foot file every night and tried all the wart paints on the market, both over-the-counter and on prescription, to no avail. I had the warts frozen with liquid nitrogen every fortnight at a wart clinic, which was painful and had no result - they quickly grew back. Finally, after a year's unsuccessful treatment, the doctor gave up and recommended me to the local hospital, where I saw a dermatologist after about a year's wait.
While I was waiting to see the specialist, the doctor suggested that I try homeopathy, since although it might not work, it should do me no harm. I duly went along to a homeopath, who (on payment of £25) listened to me sympathetically, drew pictures of my verruca-covered feet, and made notes about everything else that had recently happened in my life. He then gave me a few pills to take over a week, with the instruction to report back on any changes. There were no changes for either better or worse, so he made me some more pills for another £25, and then another batch for a further £25...eventually, after sampling quite a number of these tailor-made remedies, I was no better off and, indeed, somewhat poorer. I had no adverse side-effects, but my verrucas had not improved at all. The homeopath agreed that homeopathic treatment did not work for everyone, and gave up.
By this time, both feet, and the backs of my heels, were completely covered in verrucas. As I was starting to think about being involved in an Evidence-Based Education project, I looked up the Cochrane report on the web to discover what evidence there was for any treatment being effective, and found that the evidence was inconclusive. I mentioned this to the dermatologist at the hospital, and he agreed with me, but thought he could try and laser one or two of my warts (both underneath my big toe). When he did this, my foot bled quite a lot, since the roots of one large verruca went down further than he had expected. It was also initially extremely painful, since the local anaesthetic had not worked properly and I could feel that I was being burnt. (I was given more anaesthetic at this point, so at the end I could just smell the burning flesh but not actually feel it). The wound was dressed by a nurse at the hospital and I was told to come back to the hospital for it to be redressed in a few days.
However, the next night, when I had a shower with my foot encased in a plastic bag to avoid getting the wound wet, water unfortunately got into the bag which I'd tied rather inexpertly round my leg, and the wound started bleeding and wouldn't stop. So I hobbled to the phone and phoned the NHS Helpline and a nurse eventually rang me back about 45 minutes later and suggested that if it was still

bleeding (which it was) I should tie a tea towel around it, which I did, and it eventually stopped. The next day I went to see a nurse at my GP's practice, but although she redressed the wound for me, she didn't want to use the special blue pack filled with water which I'd been told by the hospital to put onto the wound directly before dressing it, because she was unfamiliar with this material (as indeed I was). I should have insisted, but I didn't and put it back in my bag. When I went back to the hospital a few days later, the dressing had stuck inside the rather cavernous hole in my foot, and had to be soaked out. I then learnt how to dress the wound properly myself, so at least I learnt something from the experience.

After this, I did not want to have any more warts lasered, and at the time I suspected that my foot would be scarred for life (although this was not the case). On the advice of the dermatologist, I tried one more remedy - soaking my heel in a formaldehyde solution - another unpleasant procedure, which caused oedema, and left me with the problem of disposing of the toxic solution (I poured it outside on the flowerbed and it killed a primula). I finally decided that since there wasn't any evidence that anything worked, I would stop treating my verrucas and indeed, ignore them.

I did this for a couple of months and then, by chance, saw that the verrucas were disappearing from my foot - a wave of clear skin was appearing. The doctor was astonished on my next visit, and thought that perhaps the wound from my laser treatment had meant the virus had got into my blood stream and caused my immune system to finally kick back. At the time, I thought that it could also mean that doing nothing was just as effective as doing anything, since treatment does not necessarily work. However, I now think he was right. Wounding my foot seemed a rather drastic treatment at the time, but perhaps that was what was needed.

Anyway, the laser wound has now completely healed and I only have one (rather large and painful) wart on the sole of my foot instead of having both feet completely covered with warts. (I also still have 2 warts on my right hand, but at one time I had a lot more). So it is not a complete success story, and at forty-five I still have some warts, but at least my feet don't hurt all the time, as they used to even when I was lying in bed.

From my own experience, I would agree with the Cochrane report that there is not much evidence for anything being a foolproof way of curing warts - the one good thing about reading the evidence meant that I had information which was previously only accessible to doctors, and if there had been any treatment which had been proved to be effective, I would have found out about it. It also put me in a better position when discussing my problem with them. It is only a pity that no evidence has been found of an effective treatment, but perhaps if more people report their experiences, more comparative tests can be carried out in the future to see if what works for one person will work for others.

Reply

We have decided to use the comments and criticism facility, occasionally, to publish personal experiences, relevant to particular reviews, and will withhold the senders name if requested.

Contributors

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WHAT'S NEW

Last assessed as up-to-date: 23 May 2006.

16 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 2, 2001

24 May 2006	New citation required and conclusions have changed	Substantive amendment
27 April 2006	Amended	Minor update.
1 September 2005	New search has been performed	Major changes as at September 2005 update 1) new searches included 2) 8 additional trials included 3) text and tables adjusted viz new data from newly included trials 4) Abu-Auda trial removed from SA vs placebo (comparison 09) meta-analysis (end point 'improvement' rather than cure) 5) Abstract shortened to <400 words 6) statistical measure of treatment effect changed from Odds Ratio to Risk Ratio (Relative Risk).
1 March 2005	New search has been performed	New studies found and included or excluded.
30 April 2003	New search has been performed	3 major changes as at May 2003 update: 1) 3 new trials: Robson, Fabbrocini and Focht. 2) Table of excluded studies now complete 3) More comprehensive details of adverse effects.
13 March 2003	Feedback has been incorporated	Response to feedback
13 March 2003	Feedback has been incorporated	Feedback added.

CONTRIBUTIONS OF AUTHORS

Ian Harvey: Reviewing of trials

Sam Gibbs: Reviewing of trials and overall management and writing of the review

Jane Sterling and Rosie Stark were involved in the original version of this review much of which still remains

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Norfolk Health Authority, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Topical; Bleomycin [administration & dosage]; Cryotherapy; Dermatologic Agents [therapeutic use]; Dinitrochlorobenzene [administration & dosage]; Fluorouracil [administration & dosage]; Interferons [administration & dosage]; Photochemotherapy; Randomized Controlled Trials as Topic; Salicylic Acids [administration & dosage]; Warts [drug therapy; *therapy]

MeSH check words

Humans