Local treatments for cutaneous warts: systematic review

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Abstract

Objective To assess the evidence for the efficacy of local treatments for cutaneous warts.
Methods Systematic review of randomised controlled trials.
Main outcomes measures Total clearance of warts and adverse effects such as irritation, pain, and blistering.
Study selection Randomised controlled trials of any local treatment for uncomplicated cutaneous warts. All published and unpublished material was considered, with no restriction on date or language.
Results 50 included trials provided generally weak evidence because of poor methods and reporting. The best evidence was for topical treatments containing salicylic acid. Data pooled from six placebo controlled trials showed a cure rate of 75% (144 of 191) in cases compared with 48% (89 of 185) in controls (odds ratio 3.91, 95% confidence interval 2.40 to 6.36). Some evidence for the efficacy of contact immunotherapy was provided by two small trials comparing dinitrochlorobenzene with placebo. Evidence for the efficacy of cryotherapy was limited. No consistent evidence was found for the efficacy of intralesional bleomycin, and only limited evidence was found for the efficacy of topical fluorouracil, intralesional interferons, photodynamic therapy, and pulsed dye laser.
Conclusions Reviewed trials of local treatments for cutaneous warts were highly variable in methods and quality, and there was a paucity of evidence from randomised, placebo controlled trials on which to base the rational use of the treatments. There is good evidence that topical treatments containing salicylic acid have a therapeutic effect and some evidence for the efficacy of dinitrochlorobenzene. Less evidence was found for the efficacy of all the other treatments reviewed, including cryotherapy.

Introduction

Viral warts are common, benign, and usually self limiting skin lesions that occur usually on the hands and feet.[1] Extragenital warts in people who are immunocompetant are harmless and usually resolve spontaneously within months or years owing to natural immunity. In view of this, a policy of not treating them is often advised. However there is considerable social stigma associated with warts on the face and hands, and they can be painful on the soles of the feet and near the nails. Many patients request treatment for their warts.

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

Methods

We conducted computer searches with standardised search strategies.[2] We searched Medline (from 1966 to May 2000), Embase (from 1980 to August 2000), and the Cochrane controlled trials register (March 1999). We manually searched cited references from identified trials and recent review articles. We contacted pharmaceutical companies and experts in the specialty. We included non-English papers, which we had translated.

Two reviewers (SG and IH) independently examined the full text of all studies identified as possible randomised controlled trials. All studies in which participants were randomised to different interventions were included.

The reviewers assessed the quality of the methods from concealment of allocation, blinding of outcome assessment and handling of withdrawals, and dropouts.[3] They also considered the adequacy of sample size, comparability of treatment groups at baseline, overall quality of reporting, and handling of data. Trial quality was classified subjectively and then by consensus as high, medium, or low quality. Trials clearly showing adequate concealment, blinding, and intention to treat analysis were classified as high quality.

The trials were then examined in detail and a descriptive synthesis drawn up, with pooling of dichotomous data when trials had a similar design, methods, and outcome. The main outcome examined was the complete clearance of warts. Data were pooled with the Cochrane Collaboration's review manager software. Because of the overall heterogeneity of the trials we used odds ratios with 95% confidence intervals as the main measure of effect with a random effects model.

Results

Fifty trials were identified from 45 papers (table).[4–48] Further details of included and excluded trials are available in the Cochrane Library.[49] Evidence from

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bmj.com 2002;325:461

Details of included trials

Reference	Setting, design*	No of participants randomised (dropouts or withdrawals), age, type† and site of warts	Interventions	Outcomes	Notes	Quality
Salicylic acid						
Abou-Auda et al 1987[4]	Primary care, multicentre, blind	?100 (46) (54 analysed), adults and children, ordinary, hands and feet	15% salicylic acid patch *v* placebo patch	Successful treatment in 27/31 (87%) *v* 11/23 (48%) at 12 weeks	Successful treatment rather than cure as end point. Number of withdrawals and dropouts not clear	Low
Auken et al 1975[6]	?Secondary care, multicentre, blind	240 (55), adults and children, not stated, hands and feet	Lactic acid and salicylic acid *v* "conventional" (anything else or no treatment)	Cure in 43/84 (51%) *v* 54/101 (54%) at 3 months		Low
Bart et al 1989[7]	Secondary care, blind	61 (8), adults, ordinary hands only	Salicylic acid patch *v* placebo patch	Cure in 19/28 (68%) *v* 7/25 (28%) at 12 weeks		Low
Bunney et al 1971[14]	Secondary care, blind	382 (86), adults and children, not stated, feet only	Salicylic acid and lactic acid *v* collodion *v* callusolve‡ *v* 50% podophyllin	Cure in 64/76 (84%), 50/76 (66%), 47/70 (67%), and 60/74 (81%) at 12 weeks	Lower cure rates for mosaic plantar *v* simple plantar warts with all treatments, 58% *v* 75%	Low
Bunney et al 1976[13]	Secondary care, blind	156 (18), adults and children, not stated, feet (simple plantar)	Salicylic acid and lactic acid *v* salicylic acid and lactic acid plus polyoxyethylene	Cure in 55/71 (77%) *v* 50/67 (75%) at 12 weeks		Low
Bunney et al 1976[13]	Secondary care, blind	94 (13), adults and children, not stated, feet (mosaic plantar)	10% glutaraldehyde *v* salicylic acid and lactic acid	Cure in 18/38 (47%) *v* 19/43 (44%) at 12 weeks		Low
Bunney et al 1976[13]	Secondary care, blind	110 (17), adults and children, not stated, feet (mosaic plantar)	40% salicylic acid *v* salicylic acid and lactic acid	Cure in 15/50 (30%) *v* 17/43 (40%) at 12 weeks		Low
Felt et al 1998[18]	Secondary care, open	61 (10), children, ordinary, anywhere	Relaxation imagery *v* salicylic acid *v* no treatment	Cure in 7/14 (50%), 10/17 (59%), and 5/20 (25%) at 6-18 months	Only one index wart treated in each child	Low
Flindt-Hansen et al 1984[19]	Secondary care, open	72 (14), adults and children, not stated, hands and feet	Anthralin *v* lactic acid and salicylic acid	Cure in 15/27 (56%) *v* 8/31 (26%) at 2 months		Low
Parton and Sommerville 1994[30]	Primary care, open	49 (0), children, ordinary, feet	Abrasion *v* salicylic acid	Mean time to cure of 2.1 weeks (2-4) *v* 18.2 weeks (8-38). Itching in 93% of abrasion group	Brief report. 100% cure rate implied by text	Medium
Spanos et al 1990[38]	Secondary care, blind	40 (0), adults, not stated, hands and feet	Hypnosis *v* salicylic acid *v* placebo *v* nil	"Loss of warts" in 6/10 (60%), 0/10 (0%), 1/10 (10%), and 3/10 (30%) at 6 weeks		Medium
Steele et al 1988[41]	Primary care, blind	57 (0), adults and children, ordinary, feet (simple plantar)	Monochloroacetic acid crystals and 60% salicylic acid *v* placebo	Cure in 19/29 (66%) *v* 5/28 (18%) at 6 weeks, cure in 24/29 (83%) *v* 15/28 (54%) at 6 months		High
Viein et al 1991[47]	Secondary care, open, intention to treat analysis	250 (80), adults and children, not stated, feet (simple plantar)	Salicylic acid and lactic acid with occlusion *v* salicylic acid and lactic acid	Cure in 48% and 47% at 17 weeks	Results expressed as percentages only, higher cure rates in children noted	Low
Cryotherapy						
Berth-Jones and Hutchinson 1992[10]	Secondary care, open	400 (77), adults and children, mixed, hands and feet	3 weekly cotton wool bud cryotherapy plus salicylic acid and lactic acid with paring *v* without paring	Cure in 46% *v* 50% of hands and 75% *v* 39% of feet at 3 months	Cure rate expressed as percentages only	Low
Berth-Jones et al 1992[10]	Secondary care, open	155 (40), adults and children, refractory, hands and feet	3 weekly cotton wool bud cryotherapy plus salicylic acid and lactic acid *v* no further treatment	Cure in 43% and 38% after a further 3 months	Second part of study above. Oral inosine pranobex also used for some patients, with no apparent benefit	Low
Berth-Jones et al 1994[9]	Secondary care, open, intention to treat analysis	300 (93), adults and children, mixed, hands and feet	3 weekly cotton wool bud cryotherapy plus salicylic acid and lactic acid: double *v* single freeze	Cure in 46/103 (45%) *v* 41/100 (41%) hands and 33/66 (50%) *v* 16/55 (29%) feet at 3 months		Low
Bourke et al 1995[11]	Secondary care, open, intention to treat analysis	245 (143), adults and children, mixed, hands and feet	Cotton wool bud cryotherapy plus salicylic acid and lactic acid: 1 *v* 2 *v* 3 weekly intervals between freezes	43%, 48%, and 44% cured after 12 treatments. Faster cure with more frequent treatments	High attrition rate and cure rates only given as percentages	Low
Bunney et al 1976[13]	Secondary care, open	100 (28), adults and children, not stated, hands only	Cotton wool bud cryotherapy: 2 *v* 3 *v* 4 weekly intervals between freezes	Cure in 18/34 (53%), 18/31 (58%), and 10/35 (29%) at 12 weeks (with intention to treat analysis). 87%, 78%, and 64% cured after 6 treatments		Low
Bunney et al 1976[13]	Secondary care, open	389 (95), adults and children, not stated, hands only	3 weekly cotton wool bud cryotherapy *v* salicylic acid and lactic acid *v* both	Cure in 68/99 (69%), 64/95 (67%), and 78/100 (78%) at 12 weeks		Low
Connolly et al 2001[16]	Secondary care, open	200 (54), adults and children, not stated, hands and feet	Cryogun or cryospray: 10 second freeze *v* "gentle" freeze	Cure in 42/71 (59%) *v* 25/75 (33%) at 8 weeks		Low

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Details of included trials—*continued*

Reference	Setting, design*	No of participants randomised (dropouts or withdrawals), age, type† and site of warts	Interventions	Outcomes	Notes	Quality
Erkens et al 1992[17]	Primary care, open, intention to treat analysis	93 (18), adults and children, ordinary, hands only	Monthly cotton wool bud cryotherapy *v* bimonthly histofreezer	Cure in 25/43 (58%) *v* 14/50 (28%) at 2.5 months		Medium
Gibson et al 1984[20]	Secondary care, blind (creams)	52 (5), adults and children, not stated, feet only	Topical aciclovir *v* placebo cream *v* 2 weekly cryogun or cryospray plus glutarol	Cure in 7/18 (39%), 5/18 (28%),and 1/11 (9%) at 8 weeks		Low
Hansen and Schmidt 1986[21]	Primary care, open, intention to treat analsysis	77 (17), adults and children, ordinary, feet only	Cryoprobe: 2 minutes *v* 15 seconds	Cure in 24/33 (73%) *v* 7/27 (26%) at 9 weeks		Low
Larsen and Laurberg 1996[24]	Secondary care, multicentre, open, intention to treat analysis	185 (41), adults and children, ordinary hands only	Cotton wool bud cryotherapy: 2 *v* 3 *v* 4 weekly intervals between freezes	Cure in 31/49 (63%), 32/46 (70%), and 31/49 (63%) at 6 months	Study done on one index wart per patient only	Low
Marroquin et al 1997[26]	Primary care, open, within patient study	30 (?), adults and children, not stated, hands and feet	Jatropha sap *v* cryotherapy (×1 only) *v* petrolatum	100%, 84.7%, and 0% of warts cured at 30 days	Warts used as unit of analysis; only three warts treated per patient	Low
Martinez et al 1996[27]	Primary care, open	124 (3), adults and children, ordinary, anywhere	Dimethyl ether propane *v* cotton wool bud cryotherapy	Cure in 65/68 (96%) *v* 80/86 (93%) 15 days after last treatment	Warts used as unit of analysis	Low
Sonnex and Camp 1988[37]	Secondary care, open	31 (0), adults, refractory, hands and feet	Cryogun or cryospray: aggressive (with local anaesthetic) *v* standard cryotherapy	Cure in 11/16 (69%) *v* 0/16 (0%) hands and 3/15 (20%) *v* 0/15 (0%) feet at 4 weeks	Published as abstract only	Low
Steele and Irwin 1988[40]	Primary care, open	207 (18), adults and children, ordinary, hands and feet	Weekly cotton wool bud cryotherapy *v* salicylic acid and lactic acid *v* both	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 6 months	Multiple and mosaic warts excluded	Low
Intralesional bleomycin						
Bunney et al 1984[12]	Secondary care, blind, left and right comparison study	24 (0), adults, refractory, hands only	0.1% bleomycin *v* saline ×2 if necessary	Cure in 34/59 (58%) *v* 6/59 (10%) of warts at 6 weeks	Warts used as unit of analysis. Patients switched to active treatment after 6 weeks	Medium
Hayes and O'Keefe 1986[22]	Secondary care, blind	26 (?), adults, refractory, hands only	Bleomycin: 0.25 *v* 0.5 *v* 1.0 U per wart up to 3× at 3 weekly intervals	Cure in 11/15 (73%), 21/24 (88%), and 9/10 (90%) of warts at 3 months	Warts used as unit of analysis. Number of dropouts not clear	Low
Munkvad et al 1983[28]	Secondary care, blind	62 (?), adults, not stated, hands and feet	1% bleomycin in saline *v* in oil *v* saline alone *v* oil alone using dermajet	Cure in 4/22 (18%), 5/36 (14%), 8/19 (42%), and 10/22 (45%) of warts at 3 months	Warts used as unit of analysis	Low
Perez et al 1992[32]	Secondary care, blind	37 (6), adults and children, not stated, hands and feet	0.1% bleomycin *v* saline ×2 if necessary	Cure in 15/16 (94%) *v* 11/15 (73%) at 30 days		Low
Rossi et al 1981[35]	Secondary care, blind	16 (0), adults and children, refractory, anywhere	Bleomycin 0.1% *v* saline placebo ×1	Cure in 31/38 (82%) *v* 16/46 (35%) of warts at 1 month	Warts used as unit of analysis	Low
Fluorouracil						
Artese et al 1994[5]	Secondary care, open, intention to treat analysis	300 (6), adults and children, ordinary, hands and feet	Fluorouracil plus salicylic acid and lactic acid *v* cautery	Cure in 127/150 (85%) *v* 99/150 (66%) at 75 days		Low
Bunney 1973[15]	Secondary care, blinding unclear	95 analysed, not stated, not stated, feet (mosaic)	2% fluorouracil *v* 5% fluorouracil *v* salicylic acid and lactic acid *v* 5% idoxuridine	Cure in 13/28 (46%), 8/15 (53%), 8/16 (50%), and 9/36 (25%) at 12 weeks		Low
Hursthouse 1975[23]	Secondary care, blind, left and right comparison study	66 (2), adults and children, not stated, hands and feet	5% fluorouracil cream *v* placebo	Cure in 29/64 (45%) *v* 8/64 (13%) at 4 weeks		Medium
Schmidt and Jacobsen 1981[36]	Secondary care, blind	60 (5), adults, not stated, hands and feet	Fluorouracil and salicylic acid *v* vehicle alone	Cure in 13/28 (46%) *v* 5/27 (19%)		Low
Intralesional interferons						
Berman et al 1986[8]	Secondary care, blind	8 (0), adults, refractory, not stated	Interferon alfa (0.1 ml of 1 million U/ml) *v* placebo	Cure in 2/4 (50%) *v* 1/4 (25%) at 8 weeks		Low
Lee et al 1990[25]	Secondary care, blind, left and right comparison study	74 (?), adults and children, refractory, hands and feet	Interferon gamma: high dose (5 million U/ml) *v* low dose (1 million U/ml) *v* placebo	Cure in 20/36 (56%) *v* 16/53 (30%) *v* 3/36 (17%) at 4 weeks		Low
Niimura 1990[29]	Secondary care, blind, left and right comparison study	80 (16), adults and children, not stated, hands and feet	Interferon beta (0.1 ml of 1 million U/ml weekly) *v* placebo	Cure in 42/64 (66%) *v* 7/64 (11%) at 10 weeks		Low
Pazin et al 1982[31]	Secondary care, blind	1 (0), adult, refractory, hands and feet	Interferon alfa *v* placebo (various regimens and doses)	Cure in 5/12 (42%) *v* 0/4 (0%) of warts at 15.5 weeks		Low
Vance et al 1986[44]	Secondary care, multicentre, blind	111 (11), adults, not stated, feet only	Interferon alfa: high dose (10 million U/ml) *v* low dose (1 million U/ml) *v* placebo	Cure in 4/30 (30%) *v* 7/32 (22%) *v* 8/38 (21%) at 12 weeks		Medium

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Details of included trials—*continued*

Reference	Setting, design*	No of participants randomised (dropouts or withdrawals), age, type† and site of warts	Interventions	Outcomes	Notes	Quality
Varnavides et al 1997[45]	Secondary care, blind	51 (9), adults, refractory, hands and feet	Interferon alfa (10 IU/ml weekly ×12) *v* placebo	Cure in 12/23 (52%) *v* 12/19 (63%) at 24 weeks		Medium
Dinitrochlorobenzene						
Rosado-Cancino et al 1989[34]	Secondary care, open	40 (0), children, refractory, anywhere	Dinitrochlorobenzene *v* placebo	Cure in 16/20 (80%) *v* 7/20 (35%)	Duration of trial unclear	Low
Wilson 1983[48]	Secondary care, open	60 (0), adults, ordinary, hands only	Dinitrochlorobenzene *v* cryotherapy *v* no treatment	Cure in 16/20 (80%), 10/20 (50%), and 8/20 (40%) at 4 months	Published as abstract only	Low
Photodynamic therapy						
Stahl et al 1979[39]	Secondary care, open	149 (29), adults and children, ordinary, hands and feet	Methylene blue and dimethyl sulphoxide *v* salicylic acid and creosote	Cure in 5/65 (8%) *v* 8/56 (15%) at 8 weeks		Low
Stender et al 1999[42]	Secondary care, blind, intention to treat analysis, within patient	30 (2), adults, refractory, hands and feet	White (×3 and ×1), red (×3), and blue (×3) light *v* cryotherapy (×4)	Cure in 73%, 71%, 42%, 28%, and 20% of warts at 4-6 weeks	Warts used as unit of analysis, results in % only, no placebo groups, and salicylic acid used in all groups	Medium
Stender et al 2000[43]	Secondary care, blind, intention to treat analysis, within patient	45 (5), adults, refractory, hands and feet	20% aminolaevulinic acid and red light *v* placebo photodynamic therapy	Cure in 64/114 (56%) *v* 47/113 (42%) of warts at 18 weeks		High
Viein et al 1977[46]	Secondary care, blind, left and right comparison study	56 (6), adults and children, refractory, hands and feet	Proflavine and dimethyl sulphoxide or neutral red and dimethyl sulphoxide *v* placebo photodynamic therapy (×8)	Cure in 10/27 (37%) proflavine *v* 10/23 (43%) neutral red at 8 weeks	Placebo half cured in all responders and no placebo response in all non-responders	Medium
Pulsed dye laser						
Robson et al 2000[33]	Secondary care, open	40 (5), adults, not stated, any site	Monthly pulsed dye laser (up to ×4) *v* "conventional" treatment	Cure in 66% *v* 70% of warts	Warts used as unit of analysis and cure rates expressed as percentages only	Low

All studies except left and right comparison studies and within patient design were parallel group randomised controlled trials. ?=not clear. Cryotherapy is with liquid nitrogen.
*Blinding refers to assessment of outcome only and not blinding of participants
†Refractory broadly defined as warts that did not respond to previous treatments.
‡Callusolve contains a quarternary ammonium germicide.

these studies was generally weak largely because of a lack of high quality trials. Overall, 41 (82%) trials were classified as low quality and seven as intermediate quality. Only two were classified as high quality.[41 43] Moreover, the heterogeneity of the methods, particularly the unit of analysis used, hindered the pooling of data for many treatments. Despite this, some useful pooling of data was possible.

Placebo

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

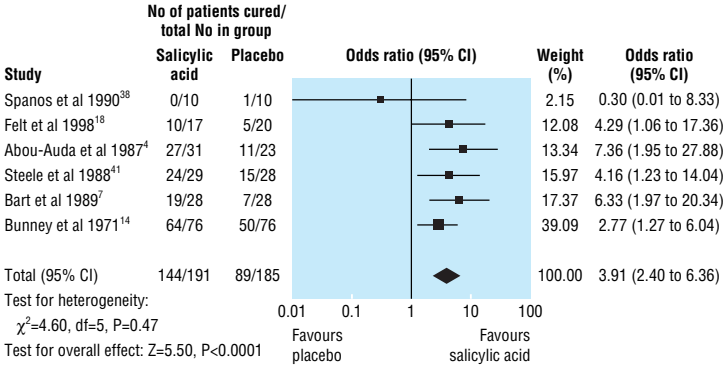

Fig 1 Cure rates in trials comparing topical salicylic acid with placebo for treatment of cutaneous warts

Salicylic acid

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

Data pooled from six placebo controlled trials showed a cure rate of 75% (144 of 191) in cases compared with 48% (89 of 185) in controls (odds ratio 3.91, 95% confidence interval 2.40 to 6.36; fig 1).

In one placebo controlled trial one of 29 patients treated with a mixture of monochloroacetic acid and 60% salicylic acid developed cellulitis.[41] Minor skin irritation was reported occasionally in some of the other trials, but generally there were no major harmful effects of topical salicylic acid.

Cryotherapy

Sixteen trials assessed cryotherapy. Most of these studied different regimens rather than comparing cryotherapy with other treatments or placebo. Pooled data from two small trials including cryotherapy and placebo or no treatment showed no significant difference in cure rates (fig 2). In two other larger trials no significant difference in efficacy was found between cryotherapy and salicylic acid (fig 3).

Pooling of data from four trials showed "aggressive" cryotherapy (various definitions) to be significantly more effective than "gentle" cryotherapy, with cure rates of 52% (159 of 304) and 31% (89 of 288), respectively (3.69, 1.45 to 9.41).[9 16 21 37] Reporting of side effects was less complete, but pain and blistering seemed to be more common with aggressive

cryotherapy. Pain or blistering was noted in 64 of 100 (64%) participants treated with an aggressive (10 second) regimen compared with 44 of 100 (44%) treated with a gentle (brief freeze) regimen (2.26, 1.28 to 3.99).[16] Five participants withdrew from the aggressive group and one from the gentle group because of pain and blistering.

Three trials examined the optimum treatment interval.[11 13 24] No significant difference was found in long term cure rates between treatment at 2, 3, and 4 weekly intervals. In one trial pain or blistering was reported in 29%, 7%, and 0% of those treated at 1, 2, and 3 weekly intervals, respectively.[11] The higher rate of adverse effects with a shorter interval between treatments might have been a reporting artefact due to participants being seen soon after each treatment.

Only one trial examined the optimum number of treatments.[10] This trial showed no significant benefit of prolonging 3 weekly cryotherapy beyond 3 months (about four freezes) in participants with warts on the hands and feet.

Topical immunotherapy with dinitrochlorobenzene

Two small trials comparing the potent contact sensitiser dinitrochlorobenzene with placebo showed some evidence for the efficacy of the active treatment.[34 48] Pooled data showed cure rates of 80% (32 of 40) and 38% (15 of 40), respectively (6.67, 2.44 to 18.23; fig 4).

No precise data were found on adverse effects in either of these trials. One trial found that six of 20 participants treated with 2% dinitrochlorobenzene became sensitised only after a second application.[34] All of them subsequently experienced major local irritation with or without blistering when they were treated with 1% dinitrochlorobenzene. None withdrew from the study.

Intralesional bleomycin

No consistent evidence was found for the effectiveness of intralesional bleomycin in five trials.[12 22 28 32 35] Four of the trials, with widely varying results, used warts rather than individuals as the unit of analysis and could not be meaningfully pooled.[12 22 28 35] Cure rates in all five studies ranged from 16% to 94%. Two trials showed higher cure rates with bleomycin than with placebo, one showed no significant difference between bleomycin and placebo, and one showed higher cure rates with placebo than with bleomycin.

None of these trials provided precise data on adverse affects. One trial reported adverse events in 19 of 62 (31%) participants but did not specify what the adverse events were or their distribution between the active treatment and placebo groups.[28] Three of the other four trials reported pain in most participants.[12 22 35] In two of the five trials, local anaesthetic was used routinely before the injection of bleomycin. One trial reported pain in most participants irrespective of dose.[22] In another trial, two of 24 participants receiving bleomycin withdrew either because of the pain of the injections or because of pain after the injections.[12]

Fluorouracil and intralesional interferons

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

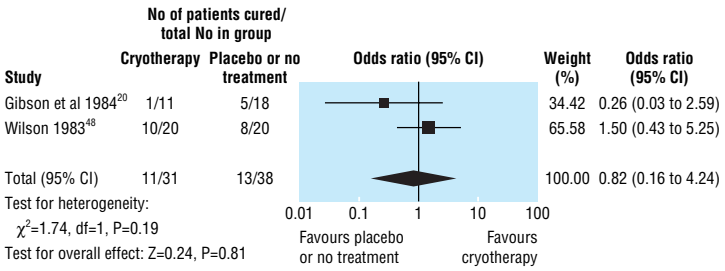

Fig 2 Cure rates in trials with cryotherapy and placebo or no treatment for treatment of cutaneous warts

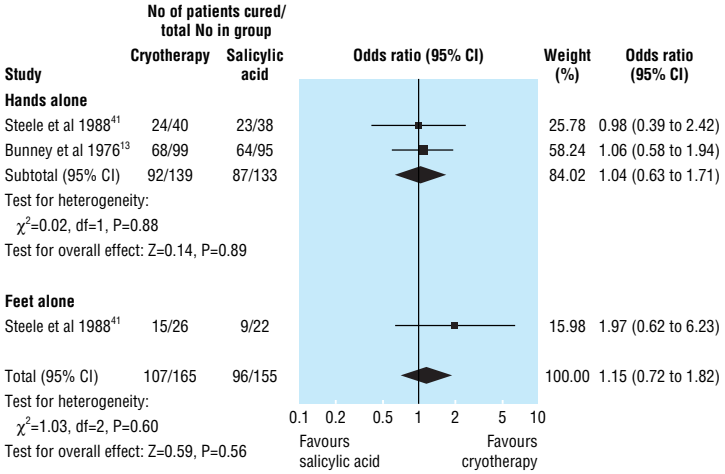

Fig 3 Cure rates in trials comparing cryotherapy with salicylic acid for treatment of cutaneous warts

Photodynamic therapy

Four trials reported varying success with different types of photodynamic therapy.[39 42 43 46] The heterogeneity in methods and variations in trial quality made it impossible to draw firm conclusions. One well designed trial in 40 adults reported cure in 56% of warts treated with aminolaevulinic acid photodynamic therapy compared with 42% treated by placebo photodynamic therapy.[43] Topical salicylic acid was also used for all participants.

Two trials provided no data on adverse effects. In one trial, burning and itching during treatment and

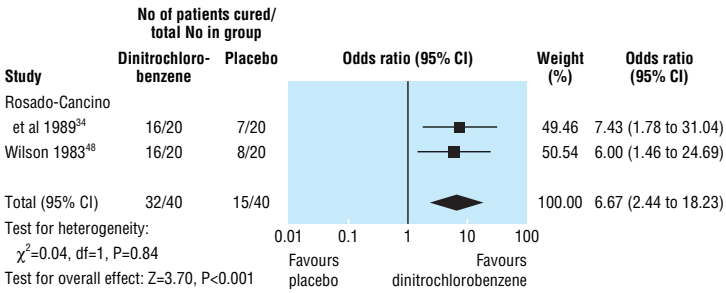

Fig 4 Cure rates in trials comparing topical dinitrochlorobenzene with placebo for treatment of cutaneous warts

mild discomfort afterwards was reported universally with aminolaevulinic acid photodynamic therapy.[42] All participants with plantar warts were able to walk after treatment. In another study severe or unbearable pain during treatment was reported in about 17% of warts with active treatment and about 4% of with placebo photodynamic therapy.[43]

Other treatments

One trial of 40 patients treated by pulsed dye laser showed no significant difference in cure rates between four treatments at monthly intervals and "conventional" treatment with either cryotherapy or cantharidin, a potent irritant.[33]

Six trials of more obscure local treatments (two trials of ultrasonography, one of silver nitrate, one of topical thuja, one of 0.05% tretinoin cream, and one of heat) were not included in the review.[49]

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

Discussion

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

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

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

Factors contributing to heterogeneity of wart trials

Factors related to participants

Age: 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

Type of lesion: mosaic plantar warts differ in response to treatment from simple plantar warts as do plane warts from common warts

Length of history and previous treatment: longstanding warts that have not cleared with previous treatments are likely to be the result of a suboptimal immune response to human papillomavirus

Trial populations: trials conducted in hospital clinics dealing with warts are likely to have had very different proportions of incident and refractory warts depending on referral patterns at the time of the trial

Factors related to treatment

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 giving cryotherapy

Intralesional treatments: different concentrations, vehicles, intervals between treatments, and numbers of injections

Follow up period: different periods of treatment and different periods before assessment of outcome

What is already known on this topic

A wide range of local treatments is available for treating warts

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

What this study adds

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

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

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

Implications for practice

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

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

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

Contributors: RS performed the electronic searches. JS was responsible for the scientific aspects of human papillomavirus infection, searched for unpublished studies, and edited the manuscript. IH supervised SG and reviewed the trials. SG coordinated the searches, reviewed the trials, and was responsible for the overall management and writing of the review; he will act as guarantor for the paper.

Funding: Norfolk Health Authority provided funding for the translation of some trials.

Competing interests: None declared.

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(Accepted 20 February 2002)

Commentary: Systematic reviewers face challenges from varied study designs

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

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

Several design options exist. Firstly, each patient could simply be randomised to a single treatment and each patient's outcome summarised across all of his or her warts. (A variation would be to treat just one wart per patient.) Secondly, individual warts could be randomised, if possible ensuring that each patient has at least one wart in each treatment group. The analysis should take account of the clustering.[5] Thirdly, treatment could be restricted to two warts for each patient, randomly allocating these to the two treatment arms. A simple paired analysis can then be done, making this design an attractive option.

It would seem preferable to take advantage of the multiple lesions to compare treatments within patients.

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

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

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