Interventions for cutaneous molluscum contagiosum (Review)

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ABSTRACT

Background

Molluscum contagiosum is a common skin infection, caused by a virus, which will usually resolve within months in people with a normal immune system. Many treatments have been promoted for molluscum contagiosum but a clear evidence base supporting them is lacking.

Objectives

To assess the effects of management strategies (including waiting for natural resolution) for cutaneous, non-genital molluscum contagiosum in healthy people.

Search strategy

We searched the Skin Group Specialised Register (March 2004), the Cochrane Central Register of Controlled Trials (2004, Issue 2), MEDLINE (from 1966 to March 2004), EMBASE (from 1980 to March 2004) and LILACS (from 1982 to March 2004) databases. We also searched reference lists and contacted pharmaceutical companies and experts in the field.

Selection criteria

Randomised controlled trials for treatment of molluscum contagiosum were investigated. Trials on sexually transmitted molluscum contagiosum and in people with lowered immunity (including those with HIV infection) were excluded.

Data collection and analysis

Study selection and assessment of methodological quality were carried out by two independent authors. As similar comparisons between two interventions were not made in more than one study, statistical pooling was not performed.

Main results

Five studies, with a total number of 137 participants, examined the effects of topical (three studies), systemic and homoeopathic interventions (one study each). Limited evidence was found for sodium nitrite co-applied with salicylic acid compared to salicylic acid alone (risk ratio (RR) 3.50, 95% confidence interval (CI) 1.23 to 9.92). No statistically significant differences were found for topical povidone iodine plus salicylic acid compared to povidone iodine alone (RR of cure 1.67, 95% CI 0.81 to 3.41) or compared to salicylic acid alone. Also no statistically significant differences were found for potassium hydroxide compared to placebo; systemic treatment with cimetidine versus placebo or systemic treatment with calcarea carbonic a, a homoeopathic drug, versus placebo (RR 5.57, 95% CI 0.93 to 33.54).

Study limitations included no blinding (two studies), many dropouts (three studies) and no intention-to-treat analysis (two studies); small study sizes may have led to important differences being missed. None of the evaluated treatment options were associated with serious adverse effects.

Authors' conclusions

No single intervention has been shown to be convincingly effective in treating molluscum contagiosum.

PLAIN LANGUAGE SUMMARY

There is not enough evidence to show that any particular treatment is effective for treating molluscum infection.

Molluscum contagiosum, in healthy people, is a self-limiting, relatively harmless viral skin infection. It affects mainly children and adolescents. People may seek treatment, however, for social and aesthetic reasons and because of concerns about spreading the disease to others. This review found that many common treatments for molluscum, such as physical destruction, have not been adequately evaluated. Since most lesions will resolve within months without leaving scars, molluscum contagiosum can be left to heal naturally until better evidence on treatment options emerges.

BACKGROUND

Description of the condition

Molluscum contagiosum is a viral skin infection most frequently encountered in children. The infection is caused by the molluscum contagiosum virus (MCV), which is classified within the family of poxviruses (*Poxviridae*). Infection follows contact with infected people or contaminated objects. Molluscum contagiosum usually presents as single or multiple (usually no more than 20) painless, spherical, shiny, pearly white papules (pimples) that classically have a central dimple. Their size may vary from tiny 1 mm papules to large nodules over 1 cm in diameter (Rogers 1998).

As well as the common form of benign skin tumours (mostly found in children), there is also a sexually transmitted variant of molluscum contagiosum which occurs on genital, perineal, pubic and surrounding skin. Molluscum contagiosum lesions may also appear in or around the mouth (Whitaker 1991). Molluscum contagiosum has also been observed with other diseases in people with a damaged immune system (Gottlieb 1994). People with HIV infection are particularly prone to molluscum contagiosum and prevalence in this population may be as high as 5 to 18% (Matis 1987; Hira 1988; Husak 1997). The focus of this review will be the common form of molluscum contagiosum only.

Epidemiology

Molluscum contagiosum occurs worldwide but is much more frequent in certain areas with warm climates, like Fiji, Congo and Papua New Guinea. Infection is rare under the age of one year, and typically occurs in the two to five year age group (Rogers 1998). The age of peak incidence is reported as being between two and three years in Fiji (Postlethwaite 1967), and between one and four years in the Congo (former Zaire) (Torfs 1959). In Papua New Guinea the annual attack rate for children under 10 years of age was 6% (Sturt 1971). For developed countries, population-based occurrence rates are scarce. In a large questionnaire study among parents of children attending kindergartens and elementary schools the reported prevalence of molluscum contagiosum was 5.6% and 7.4% respectively (Niizeki 1984). Much higher prevalence rates have been reported during outbreaks in closed communities (Overfield 1966).

In the United States, from 1990 to 1999 the estimated number of physician visits for molluscum contagiosum was 280,000 per year (Molino 2004). One out of six Dutch children aged 15 years have visited their doctor for molluscum contagiosum at least once (Koning 1994). There is generally no difference in incidence between males and females (Sturt 1971; Relyveld 1988; Koning 1994). However, an unequal sex ratio was found in studies from Japan (Niizeki 1984), Alaska (Overfield 1966) and Fiji (Hawley 1970), where boys were affected more often. This is probably due to habits associated with the spread of the infection, such as swimming (Postlethwaite 1967; Niizeki 1984). Outbreaks may occur among children who bathe or swim together. A history of eczema was found in 62% of children with molluscum contagiosum in Australia (Braue 2005). In the adolescent and adult age groups sexual transmission becomes important.

Natural history

The estimated incubation period varies from 14 days to 6 months. Lesions enlarge slowly and may reach a diameter of 5 to 10 mm in 6 to 12 weeks (Sterling 1998). After trauma (for example, scratching), or spontaneously after several months, inflammatory changes result in the production of pus, crusting and eventual destruction of the lesions. However, new lesions tend to appear as the old ones resolve as a consequence of the virus spreading to other areas of skin. The duration both of the individual lesion and of the entire episode is highly variable. Crops of molluscum may appear to come and go for several months, and although most cases are self limiting and resolve within six to nine months, some may persist for more than three or four years. Follow-up studies (Liveing 1878; Hawley 1970) confirm these figures and show that individual lesions are unlikely to persist for more than two months.

A Japanese study describes spontaneous resolution on average 6.5 months after infection in 205 out of 217 children (94.5%) affected by molluscum contagiosum (Takemura 1983). One month after the first consultation with the dermatologist, 23% of the children were cured.

Particularly in atopic people (who are prone to asthma, hay fever or eczema), there is a tendency for a patch of eczema (which is often particularly itchy) to develop around one or more of the lesions a month or more after their onset (De Oreo 1956; Beaulieu 2000). Erythema annulare centrifugum (a widespread rash of red inflammatory rings) has also been reported (Vasily 1978). Chronic conjunctivitis and superficial punctate keratitis may similarly complicate lesions on or near the eyelids (Haellmigk 1966; Redmond 2004). The eczema and conjunctivitis subside spontaneously when the molluscum lesion is removed.

Molluscum contagiosum behaves differently in HIV-infected individuals. As immunodeficiency progresses, molluscum contagiosum becomes more common and resistance to therapy increases. Frequently, multiple lesions in atypical areas such as the face and neck can be found. Only limited data are available on the course of the disease in this group of people.

Description of the intervention

Molluscum contagiosum is a self-limiting disease in people with an uncompromised immune system. Therapy is not necessary for recovery and awaiting spontaneous resolution is an important management strategy. Most lesions resolve within months without scarring in otherwise healthy people (Ordoukhanian 1997). Treatment is intended to accelerate this process. Destruction of the lesions and the production of an inflammatory response (Sterling 1998) are methods by which resolution of the lesions could be hastened.

Reasons to treat molluscum contagiosum include:

(a) alleviating discomfort, including itching;
(b) cosmetic reasons;
(c) social stigma associated with many visible lesions;
(d) limiting it's spread to other areas of the body and to other people;
(e) preventing scarring and secondary infection;
(f) preventing trauma and bleeding of lesions.

A large number of treatment options are used for molluscum contagiosum. These can be divided into three major categories:
(a) physical destruction of the lesions;
(b) topical agents (i.e. those applied directly to the lesions);
(c) systemic treatment (i.e. those affecting the whole body).

Physical destruction is recommended as the preferred method for treatment of molluscum contagiosum by most authors. Dermatology textbooks mention removal of the lesion with a sharp curette or the application of liquid nitrogen (cryotherapy) as being simple, painless and usually effective treatments (Sterling 1998; Lowy 1999). Gentle squeezing or pricking with a sterile needle (Berger 1996) are alternative recommended destructive therapies. Most of these therapies will have to be repeated at three to four weekly intervals. Treatment is often painful and may result in scarring (Friedman 1987). Squeezing of lesions may even lead to the formation of large abscesses due to the disruption of virus into the deeper layer of the skin (dermis) (Brandrup 1989).

Topical preparations such as podophyllotoxin, liquefied phenol, tretinoin, cantharidin or potassium hydroxide can be used to produce a local inflammatory response. In children, prior application of local anaesthetic cream may reduce the pain of treatment involving physical destruction or local inflammation (Rosdahl 1988; de Waard 1990). Other proposed topical treatments include immune response modifiers such as imiquimod and cidofivir.

Systemic treatment with cimetidine has been suggested as a possible treatment because of its systemic immunomodulatory effects; it increases lymphocyte proliferation and inhibits suppressor T-cell function (Orlow 1993; Sterling 1998).

Why it is important to do this review

Molluscum contagiosum is a common reason for consultation in family practice and dermatology. There are many treatment options available, some of which are painful and some may leave scars. A decision may be made in favour of active therapy to prevent further spread, relieve symptoms, prevent scarring and for cosmetic and social reasons. Indeed, many parents are concerned about the stigma associated with the lesions. Children with molluscum may be excluded from attending nursery and from participating in physical activities such as swimming. However, the scientific basis for treatment is unclear. Consequently, many practitioners find themselves in a dilemma as to whether or not to promote active treatment and, if they do decide on an active treatment strategy, are unclear as to the best option. We have carried out this systematic review to evaluate treatment options for molluscum contagiosum.

OBJECTIVES

To assess the effects of management strategies, including waiting for natural resolution, for cutaneous, non-genital molluscum contagiosum in healthy people.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) for treatment of molluscum contagiosum. Trials on sexually transmitted molluscum contagiosum and in people with lowered immunity (including those with HIV infection) were excluded.

Types of participants

People with a diagnosis of molluscum contagiosum, except for those with lowered immunity or sexually transmitted molluscum contagiosum.

In general, treatment is based on a clinical diagnosis only as molluscum contagiosum is an easy diagnosis to make and confusion is rare among clinicians. Therefore additional diagnostic criteria, such as histological examination and laboratory investigations, were considered unnecessary.

Types of interventions

All treatments aimed at eradicating molluscum contagiosum lesions, including:

- physical interventions;
- systemic treatments;
- topical agents;
- awaiting natural resolution.

Studies on other aspects of the treatment of molluscum contagiosum, for example on reducing pain in the studies that used analgesic EMLA cream (Juhlin 1980; de Waard 1990), were excluded.

Types of outcome measures

Primary outcomes

Short-term clinical cure

One month from last day of treatment, or in the case of different follow-up durations, the measurement point closest to one month (plus or minus one week).

Clinical cure was defined as complete disappearance of elevated molluscum contagiosum skin lesions, as assessed by a physician.

Secondary outcomes

(a) Medium and long-term clinical cure (after three months and six months, respectively)
(b) Medium and long-term improvement (after three months and six months, respectively)
(c) Time to cure

(d) Recurrences after 3, 6 and 12 months
(e) Adverse effects of treatment such as pain, blistering, sensitisation, scarring, erosion and pigmentary changes
(f) Spread to other people
(g) Disease-related quality of life

Measures (b) and (g) were not initially specified in the protocol, but were added afterwards since clinical cure at the end of the study was the most commonly reported outcome measure, and disease-related quality of life was considered to be a relevant additional measure.

Search methods for identification of studies

Electronic searches

Relevant trials were identified from:

(a) The Cochrane Skin Group Specialised Register (March 2004)

The following search term was used: 'Molluscum'.

(b) The Cochrane Central Register of Controlled Trials (CENTRAL) (2004, Issue 2)

The following search strategy was used: "Molluscum contagiosum/ OR molluscum contagiosum.ti, ab".
#1 molluscum contagiosum in All Fields in all products
#2 MeSH descriptor Molluscum Contagiosum explode all trees in MeSH products
#3 (#1 OR #2)

(c) MEDLINE (from 1980 to March 2004)

Search terms, as given in the Cochrane Handbook (Higgins 2005), appendix 5b.3. See Appendix 1.

(d) EMBASE (from 1980 to March 2004)

See Appendix 3.

(e) LILACS (Latin American and Caribbean Health Service Information database) (from 1982 to March 2004)

See Appendix 2.

Searching other resources

Ongoing trials

We searched the metaRegister of Current Controlled Trials on http://www.controlled-trials.com (March 2004).

References lists

Reference lists of each selected article or relevant review article were checked to identify additional studies.

Correspondence

Further relevant published and unpublished trials were obtained via correspondence with selected pharmaceutical companies and authors of recent publications.

Language

No language restrictions were imposed

Data collection and analysis

Selection of studies

Two authors (JCvdW, SG or JM) independently read all abstracts or titles of identified trials. If one of the authors considered the article potentially relevant, a full-text copy of the article was obtained for further consideration. Two authors (SK, LvSS) independently examined all full text copies to determine whether or not they met our inclusion criteria. Disagreements were resolved by discussion between the authors, with referral to a third author (JCvdW or JM) when necessary.
Trials on sexually transmitted molluscum contagiosum and in people with lowered immunity (including those with HIV infection) were excluded, in order to increase homogeneity of studies. If the full text of studies was not available published abstracts were considered for the review.
If an RCT included a variety of skin diseases, including molluscum contagiosum, the number of molluscum participants needed to be at least five in the active treatment and placebo groups. This criterion was added after the protocol was approved when a study was found which included 10 molluscum participants with a 9:1 distribution over the two treatment groups (Caballero 1996).

Data extraction and management

Two authors (MYB and SK) independently carried out data extraction using specially developed and piloted data extraction forms. Discrepancies were resolved by a third author (JCvdW). Missing data were obtained from authors where possible. One of two authors (JM or JCvdW) checked and entered the data.

Assessment of risk of bias in included studies

Two authors (MYB and JCvdW) independently assessed the methodological quality of the trials. The authors were not blinded to the names of authors, journals or institutions.
A third author (JM) acted as arbitrator when necessary. The quality assessment included an evaluation of the following components:
(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 / not blinded (participants, clinicians, outcome assessors);
(d) how many participants were lost to follow up in each arm (split into post-randomisation exclusions and later losses if possible), and whether participants were analysed in the groups to which they were originally randomised (intention-to-treat);
(e) additional 'review specific' quality criteria, such as unit of analysis in the case of multiple lesions.

Data synthesis

Trials relevant to the focus of this review were examined in greater detail. We provide a narrative synthesis of included trials, presenting the characteristics of trials and their results.

For studies with a similar type of intervention, meta-analyses were planned to calculate a weighted treatment effect across trials using a random-effects model (DerSimonian and Laird model). Similar comparisons between two interventions were not made in more than one study, therefore, we summarised data for each trial. For dichotomous outcomes, we expressed the results as risk ratios (RR) with 95% confidence intervals (CI); and as a number needed to treat (NNT), where appropriate.

For continuous outcomes, the results were to be expressed as weighted mean differences (WMD) with 95% CI. For time to cure as an outcome, the results were to be expressed as weighted hazard ratios with 95% CI. This was to be achieved by either combining the estimates from the log rank tests (O-E and V) using a modified version of Peto's method (Yusuf 1985) or by combining the log hazard ratio and variance from Cox proportional hazard models given in the publications using the generic inverse variance method. Where a mixture of these methods was used for the outcome the estimates from the log rank tests were to be converted to log hazard ratios and combined using the generic inverse variance method.

Heterogeneity between the studies was to be explored using I^2 and, if substantial heterogeneity (I^2 > 50%) existed between studies for the primary outcome, reasons for heterogeneity were to be explored, e.g., using sensitivity analyses to examine the effects of excluding studies with lower reported methodological quality.

Cross-over trials and within-participant designed trials were to be analysed using techniques appropriate for paired designs, with the help of a statistician.

Non-randomised controlled studies and excluded studies are listed but not discussed further. Studies relating to adverse effects of treatments are described qualitatively.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Seventeen abstracts were generated by searching the CENTRAL database: 131 abstracts from MEDLINE; 148 abstracts from EMBASE; and 45 from LILACS. From these 341 abstracts, some of which were duplicates, 18 studies were considered possibly to be RCTs and the full text was obtained. A further 17 studies were identified from the bibliographies of retrieved studies and the full text of these studies was also obtained. The papers discussed a variety of treatment options for molluscum contagiosum. (See for treatment options for molluscum contagiosum found in the literature.)

Most trials were reported in English. However, other languages included French, Chinese, Japanese and Spanish. Two of the Japanese papers and one Chinese study were translated. We read French and Spanish papers in their original language.

Included studies

Five studies were included in this review. The included studies involved a total of 137 molluscum participants, with numbers of participants in each study ranging from 20 to 38 (Antony 2001; Short 2002). Four of the five studies were obtained as full text articles. One study was available only as a published abstract (Antony 2001). Additional information was requested and obtained from the authors of three of the studies (Ohkuma 1990; Manchanda 1997b; Short 2002). One author did not reply to our request for additional information (Antony 2001). Three of the studies evaluated local therapies for molluscum contagiosum (Ohkuma 1990; Ormerod 1999; Short 2002). Two studies investigated systemic treatments (Manchanda 1997b; Antony 2001). The paper by Manchanda reported on two studies both making the same comparison but one in a cross-over design and one in a parallel design. We chose not to include the cross-over study because less than five participants were assigned to one of the treatment arms. All included studies were set in hospital outpatient or emergency departments. Only immunocompetent (non-HIV-participants) and non-genital molluscum contagiosum participants were included in the studies. Participants therefore consisted primarily of children and young adults (adolescents).

Topical therapy

Ohkuma 1990 assessed the effect of application of 10% povidone iodine solution combined with 50% salicylic acid plaster. Treatment was continued until resolution of the lesions. There were three intervention arms, 10% povidone iodine solution combined with 50% salicylic acid plaster (n = 20), povidone iodine alone (n = 5) and salicylic plaster alone (n = 10). Participants were aged between two and nine years.

Ormerod 1999 assessed the effect of 5% sodium nitrite co-applied daily with 5% salicylic acid, under occlusion (n = 16). A control group received an identical cream with 5% salicylic acid but without sodium nitrite (n = 14). Treatment was for three months or until participants were cured or dropped out, if sooner. Thirty participants with a median age of six years participated in this study.

Short 2002 assessed the application of a 10% potassium hydroxide solution (n = 10). The control group received saline (n = 10). The age of included participants ranged from 2 to 12 years. Assessment of the therapeutic response took place up to 90 days after start of treatment or one month after clearance, or both.

Systemic therapy

Antony 2001 assessed the effect of 35 mg/kg/day of cimetidine given once daily as an oral suspension for three months. Thirty-eight participants, aged 1 to 16 years, were enrolled in the trial, but assignment details are only given for the 19 participants who completed the study. Eight of these were randomised into the

treatment arm of the trial. The 11 participants in the control arm received a matched oral suspension. The follow-up period was four months from the start of treatment.

Manchanda 1997b evaluated different potencies of a homoeopathic drug called calcarea carbonica given daily for 15 days (n = 14). Six participants were randomised to receive plain sugar globules as a placebo.

Participants' ages ranged from 0 to 30 years. Follow-up duration was not reported.

Excluded studies

Thirty of the 35 studies did not fulfil our criteria. The most common reasons for exclusion were case series rather than RCTs, or because the participant groups were outside the focus of the review (see the Characteristics of excluded studies table).

Risk of bias in included studies

Table 1 gives the results of the quality assessment.

Table 1. Methodological quality of included studies

Quality item	Antony 2002	Manchanda 1997	Ohkuma 1990	Ormerod 1999	Short 2002
Method of generation of randomisation sequence	term 'randomized' mentioned, no details	randomisation not mentioned in paper, randomisation sequence generated manually (personal communication)	'randomised' (personal communication, not in paper)	term 'randomized' mentioned, group sequential design	term 'randomised' mentioned, no details
Method of allocation concealment	not mentioned	not mentioned	not mentioned	not mentioned	not mentioned
Blinding	term 'double-blind' mentioned, no details	term 'double-blind' mentioned, no details	term not mentioned, given treatments probably not blind	term 'double-blind' mentioned, no details	term 'double-blind' mentioned, no details
Loss to follow-up	50% dropouts, for whom no results	20% dropouts, not analysed	no loss reported, all patients in outcome table	30% dropouts after 1 month, analysis by intention to treat	10% dropouts after two weeks, intention to treat analysis

Method of generation of randomisation sequence

Three of the five studies were described in the text as randomised trials (Ormerod 1999; Antony 2001; Short 2002). Additional information was obtained from the authors of the other papers, who confirmed in writing that the participants were randomised into the different treatment groups (Ohkuma 1990; Manchanda 1997b). The way the randomisation sequence was generated was not described in any of the papers. In a personal communication, Manchanda informed us that in his study this was 'generated manually'.

Allocation

None of the papers described whether the investigators took any precautions to conceal the allocation schedule from those involved in entering participants into the study.

Blinding

Four of five studies were described as double-blind (Manchanda 1997b; Ormerod 1999; Antony 2001; Short 2002). However, none of them provided information about the visual similarity of treatments, nor whether blinding was maintained throughout follow up. Ormerod reported brown staining on the skin in six participants with active treatment, but none of the controls, which may have unblinded the assessment of outcomes (Ormerod 1999).

Follow up and exclusions

In two out of the five included studies (Ormerod 1999; Short 2002) all participants who underwent random allocation were analysed according to group assignment (intention-to-treat). In two studies this was not the case (Manchanda 1997b; Antony 2001). One study did not report any loss to follow up (Ohkuma 1990).

Effects of interventions

Primary outcome

The primary outcome for this review was complete disappearance of elevated molluscum contagiosum lesions after one month. None of the selected trials reported on the difference between treatment and control groups after one month of treatment.

Secondary outcomes

Three studies reported on medium term clinical cure (after three or four months) (Ormerod 1999; Antony 2001; Short 2002) and two on time to cure (Ohkuma 1990; Short 2002), but Short 2002 only reported this outcome for the group with active treatment. Three reported on adverse effects (Ohkuma 1990; Ormerod 1999; Short 2002).

As the same comparison between two interventions was not made in more than one study, testing for homogeneity between studies was not relevant, nor was a meta-analysis appropriate.

(1) Topical treatments (Analyses 1 to 5)

Application of 10% povidone iodine solution and 50% salicylic acid plaster (Ohkuma 1990) was effective in curing 20/20 participants (100%) compared with 3/5 (60%) who received povidone iodine alone (RR 1.67, 95% CI 0.81 to 3.41) (Analysis 1.1) and 7/10 (70%) who received salicylic plaster alone (RR 1.43, 95% CI 0.95 to 2.14) (Analysis 2.1). Thus, povidone iodine plus salicylic acid plaster resulted in more participants being completely cured than with salicylic plaster or povidone iodine alone, although this did not reach statistical significance. In addition, the mean time to cure was shorter for iodine plus salicylic acid plaster (mean time to cure of 26 days) than for either iodine alone (mean time to cure of 86 days) or salicylic plaster alone (mean time to cure of 47 days).

All participants developed local redness of the skin at the treatment site within three to seven days after the start of the treatment. Duration was variable for each individual. The more marked the inflammation, the earlier the participant was cured.

Treatment with 5% sodium nitrite co-applied daily with 5% salicylic acid under occlusion (Ormerod 1999) resulted in significantly more participants with complete resolution of the lesions after three months: 12/16 (75%) compared with 3/14 (21%) participants in the control group, treated with an identical cream but omitting sodium nitrite (RR 3.50, 95% CI 1.23 to 9.92) (Analysis 4.1). This resulted in a number needed to treat of less than two (i.e. for each cure achieved, two people need to be treated). The mean number of treatment days was 38 (standard deviation (SD) 20) in the treatment group and 49 (SD 25) in the control group. Brown staining was reported in 6 of the 16 participants using the active treatment. Four out of 16 participants (25%) stopped the active treatment because of irritation and lack of efficacy. Two additional participants, who were cured, complained of significant irritation.

Treatment with 10% potassium hydroxide solution was successful after three months in 6/10 participants (60%) compared with 2/10 (20%) in the placebo group (RR 3.00, 95% CI 0.79 to 11.44), which is not statistically significant (Analysis 5.1) (Short 2002). The average time to resolution in the potassium arm was 40 days; however, this was not reported for the control arm. Mild stinging was reported by most participants and two participants developed post-inflammatory pigmentary changes at the treatment site. In the treatment arm two participants withdrew from the study due to discomfort of the skin at the application site.

(2) Systemic treatments (Analyses 6 to 7)

Treatment with systemic cimetidine 35 mg/kg/day (Antony 2001) cleared lesions completely in 4/8 participants (50%) after four months of treatment, compared with 5/11 (46%) given placebo in the same period (Analysis 6.1); however, the difference for this effect was not statistically significant (RR 1.10, 95% CI 0.43 to 2.84). No data were reported for the 50% (19/38) of participants who withdrew from the study.

Treatment with calcarea carbonica (Manchanda 1997b) resulted in improvement of 13/14 participants in the treatment arm and 1/6 in the placebo arm of the trial (RR 5.57, 95% CI 0.93 to 33.54) (Analysis 7.1). However, study duration, time to resolution and adverse events were not reported and the study was not analysed by the intention-to-treat principle. The number of dropouts (20/104 for whole trial, including other skin conditions) is unclear for the molluscum participants.

DISCUSSION

The majority of the studies we identified evaluating treatments for molluscum contagiosum could not be included in this review because they were uncontrolled case series.

Only five RCTs were included. These studies examined the effects of five different interventions. Only one study (Ormerod 1999) found a statistically significant effect, comparing a combination of sodium nitrite with salicylic acid given under occlusion to an identical cream omitting sodium nitrite. The practical consequence of this finding is unclear as this study did not include a placebo treatment. Several of the studies suffered from major potential biases such as high drop out rates, no intention-to-treat analysis and unclear concealment of allocation making them very difficult to interpret. No treatment option was associated with serious adverse effects, although irritation was reported for some treatments.

All of the included studies were small in sample size with a median study size of 20 molluscum participants. Hence, all studies may have limited power, which was reflected in the wide confidence intervals around the risk ratios. In addition, many of the studies had large losses to follow up; the largest study had a 50% loss to follow up rate (Antony 2001). Furthermore, in two of the included studies the control used was not a placebo. In both of these studies, applying salicylic acid cream under occlusion, plaster alone and iodine alone, as the comparison treatment may have had some potential treatment effect. Therefore, it was difficult to compare the effect of interventions given the absence of a placebo group in most of the studies.

The lack of reported details on several methodological issues and follow up period, together with the small number of participants gives rise to doubts about the validity of the results of some of the studies.

We chose our primary outcome measure to be clinical cure after one month, calculated from the last day of treatment. However, this may not be the most appropriate outcome measure to cover the variety of treatments for molluscum. For example, when comparing a method of physical destruction (e.g. curettage) with a topical treatment that is applied during several days or weeks, our primary outcome measure would probably favour the first type of treatment. Although no clear-cut solution seems available, and so far no trials studied physical destruction, it is advisable to always consider multiple outcome measures and also to take the burden of treatment into account.

Several issues remain unclear due to lack of details in the published papers. For example, it is unclear whether duration of treatment, as used in Ormerod 1999, can be taken as a valid indicator for time to cure given dropouts and other possible reasons for stopping treatment. Although Antony 2001 did not report on adverse events, the 50% loss to follow up rate in the trial might have been caused by adverse effects of the treatment. It is unclear which dosing regimen was used in Manchanda 1997b when evaluating calcarea carbonica.

No evidence either for or against the most commonly used treatment options for molluscum contagiosum was found. For example, we did not find any study on curettage. Only one study on cryotherapy (Caballero 1996) and one on physical expression (squeezing) (Weller 1999) were identified. Neither of these studies could be included in this review. There is, therefore, an evidence gap regarding many commonly promoted and used treatment options for molluscum contagiosum. Furthermore, due to the small sample sizes of the studies that were included and which found no differences, clinically relevant differences might be found when treatments are evaluated in larger samples. The cure rates found by Weller for physical expression and for phenol ablation (75 and 77% of lesions respectively, after one month) (Weller 1999) compare favourably to the 23% of children found cured in the Japanese study on the natural history of the disease (Takemura 1983). This suggests a magnitude of effect for both therapies that would be worthy of proper testing in an RCT against placebo, although it should be noted that phenol ablation was found to show more scarring.

Several of the outcomes important to participants and clinicians were not used as outcome measures in the studies we found. These include recurrences, spread to other people, stigma and quality of life.

We were unable to perform meta-analyses in this review because none of the interventions were evaluated in more than one study. The evidence identified by this systematic review is, therefore, insufficient to propose any one intervention for molluscum contagiosum. Additional well-designed prospective blinded randomised controlled studies on common treatment options for molluscum contagiosum against a credible placebo or no intervention are needed to provide high quality evidence upon which to base clinical decision making.

We excluded studies on genital molluscum contagiosum and in participants with lowered immunity. Our conclusions do not apply to these participant groups as the need for treatment is probably higher.

AUTHORS' CONCLUSIONS

Implications for practice

No reliable evidence based recommendations can be given for the treatment of molluscum contagiosum at present. We were unable to locate any randomised controlled trials that addressed physical destruction of molluscum lesions. Until robust evidence emerges for effective and safe treatment, clinicians should consider expectant management, i.e. awaiting spontaneous resolution of the molluscum lesions.

Implications for research

(a) Additional well-designed prospective blinded randomised con-

trolled studies are needed to provide high quality clinical trial evidence upon which to base clinical decision-making. Future studies evaluating treatments for molluscum contagiosum should, as a priority, focus on commonly promoted and commonly used options for treatment (e.g. curettage and cryotherapy).

(b) Limited data on the natural history of molluscum contagiosum is available. Additional studies into the rate of resolution without active interventions are therefore needed, preferably assessing this after various follow-up times (e.g. 1, 3, 6, and 12 months). This will help guide decisions concerning the use of active treatments.

(c) Outcome measures of future trials should preferably include recurrence rates, spread of the disease to other people and disease-related quality of life.

(d) A standardised outcome measure (e.g. time to resolution of the lesions or resolution after three months) would make studies easier to compare.

(e) Statistical power must be considered in conjunction with outcomes that are meaningful for people with molluscum contagiosum. For example, it is likely that a treatment that results in statistically fewer lesions may not be considered worthwhile because this reduction may not be sufficient to improve appearance or quality of life. People should be enabled to weigh costs and benefits, taking into account resolution of lesions, adverse effects and treatment burden.

(f) Molluscum contagiosum is a common disease in immunocompromised people (e.g. people living with HIV). There is also a sexually transmitted variant that affects immunocompetent sexually active people, which was excluded from this review. There is a need for reviews of studies of treatments for these important subgroups of people with molluscum contagiosum.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Antony 2001

Methods	Double-blind randomised placebo controlled trial. Method of generation of randomisation sequence is unclear, as is concealment of allocation. No intention-to-treat analysis.
Participants	Thirty-eight patients were enrolled, for 19 patients complete data were obtained, 8 of which had been randomised into the treatment arm. Nineteen patients withdrew from the study, no data on reasons for withdrawal.
Interventions	35 mg/kg/day cimetidine, given once daily as oral suspension versus a matching placebo.
Outcomes	Complete clearance after four months treatment. Reduction of lesions. Adverse events: not mentioned.
Notes	50% dropout rate. Published abstract only.

Risk of bias

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

Manchanda 1997b

Methods	Double-blind randomised controlled trial, addressing various types of warts (n = 124), including molluscum contagiosum (n = 20). Randomisation sequence was generated manually, identity of the drugs was kept secret in a sealed cover (personal communication Dr Manchanda). No intention-to-treat analysis.
Participants	Fourteen molluscum patients randomised into the treatment arm, six patients were randomised to receive plain sugar globules as a placebo (personal communication Dr Manchanda). Ten patients were aged below 10 years, 7 from 10 to 20 and 3 were from the age group 21 to 30 years (personal communication Dr Manchanda).
Interventions	Different potencies of a homeopathic drug called calcarea carbonica daily for 15 days (n = 14) versus sugar globules (placebo). Unclear which patients received what potency.
Outcomes	Improvement (not clear after what period)
Notes	Paper reports on (1) cross-over study (2) parallel study. The cross-over study was excluded, because less than five patients in one of the arms.

Risk of bias

Manchanda 1997b (*Continued*)

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

Ohkuma 1990

Methods	Randomised controlled trial (written correspondence Dr Ohkuma), the method of generation of randomisation sequence remained unclear, as was the concealment of allocation. It was also unclear if participants were analysed according to the group to which they were randomised (intention-to treat analysis) and how blinding was performed.
Participants	Thirty-five patients with molluscum contagiosum, aged between two and nine years. Japan.
Interventions	Three interventions were compared: 10% povidone iodine solution combined with 50% salicylic acid plaster (n = 20), iodine alone (n = 5) and salicylic plaster alone (n = 10).
Outcomes	Time to cure. Adverse events. Study duration unknown.
Notes	

Risk of bias

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

Ormerod 1999

Methods	Group sequential double blind randomised trial. All participants were analysed according to group assignment (intention to treat). Two patients did not complete the trial.
Participants	Thirty molluscum patients were enrolled, with 16 in the acidified nitrite group and 14 controls, with a median age of 6 years, 22 girls and 8 boys. Exclusion criteria were age below one year of age, pregnant of lactating women, and taking immunosuppressive drugs or known to have HIV infection.
Interventions	5% sodium nitrite co-applied daily with 5% salicylic acid under occlusion versus identical cream with 5% salicylic acid omitting sodium nitrite.
Outcomes	Time to complete resolution. Adverse events. Study duration three months.

Ormerod 1999 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Short 2002

Methods	Double-blind randomised placebo controlled trial. The method of generation of the randomization sequence is unclear as is concealment of allocation. All participants were analysed according to group assignment (intention-to treat analysis). 18/20 completed the study.
Participants	Twenty children from a paediatric dermatology clinic, age range 2 to 12 years. Exclusion criteria were known immunodeficiency and facial lesions.
Interventions	Application of 10% potassium hydroxide solution twice daily applied with a cotton swab, continued until the lesions showed signs of inflammation (n = 10). The control group received saline (n = 10).
Outcomes	Time to resolution. Adverse events. Study duration three months.
Notes	

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

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

Barba 2001	Uncontrolled case series (n = 13)
Barton 2002	HIV-infected patients (n = 40)
Bayerl 2003	Uncontrolled case series (n = 15)
Behl 1970	Uncontrolled case series (n = 33)

(*Continued*)

Braue 2005	Uncontrolled case series (n = 30)
Caballero 1996	RCT comparing two types of cryotherapy for cutaneous skin lesions: 124 patients, among which 10 molluscum patients, distributed 9:1 over two arms
Cope 1915	Uncontrolled case report (n = 1)
Cunningham 1998	Uncontrolled case series (n = 14)
Davies 1999	Uncontrolled case report (n = 1)
Davis 1896	Uncontrolled case report (n = 1)
de Waard 1990	Study on analgesic effect of lidocaine/prilocaine (EMLA) cream before physical therapy. Not a focus of this review. (n = 83)
Dohil 1996	Uncontrolled case series (n = 13)
Funt 1961	Uncontrolled case series (n = 12)
Gräfe 2000	Uncontrolled case series (n = 4)
Hammes 2001	Uncontrolled case series (n = 20)
He 2001	Large parallel controlled study (n = 1656), with four arms, no randomisation (personal communication with Dr He through Taixiang Wu)
Hengge 2000	20% of molluscum patients were HIV positive and 20% of lesions were in androgenital area (n = 15)
Hund 1975	Case report (n = 1)
Juhlin 1980	Study on analgesic effect of lidocaine/prilocaine (EMLA) cream before physical therapy. Not a focus of this review (n = 24)
Liota 2000	Uncontrolled case series (n = 13)
Manchanda 1997a	Cross-over study with different types of warts (n = 43), 10 molluscum patients. One of the treatment arms (placebo first?) had less than two patients
Markos 2001	Single case report (n = 1)
Niizeki 1999	Uncontrolled retrospective study (n = 389)
Quan 2000	Single case report (n = 1)

(*Continued*)

Romiti 1999	Uncontrolled case series (n = 35)
Romiti 2000	Uncontrolled case series (n = 20)
Rosendahl 1988	Study on analgesic effect of lidocaine/prilocaine (EMLA) cream before physical therapy. Not a focus of this review. (n = 55)
Ross 2004	Uncontrolled case series (n = 16)
Sharma 1998	Uncontrolled case series (n = 2)
Silverberg 2000	Uncontrolled retrospective study (n = 300)
Singh 1977	Uncontrolled case series (n = 4)
Skinner 2002	Uncontrolled case series (n = 3)
Syed 1994	RCT, n = 150, mainly genital lesions, which is not a focus of this review
Syed 1998	RCT, n = 100, mainly genital lesions, which is not a focus of this review
Teilla-Hamel 1996	Uncontrolled case series (n = 8)
Toro 2000	Uncontrolled case series (n = 2)
Weller 1999	Controlled trial (n = 16), comparing phenol ablation and physical expression. Lesions were unit of treatment and analysis. No randomisation
Wishart 1903	Uncontrolled case series (n = 5)
Yasher 1999	Uncontrolled case series (n = 2)
Zabawski 1999	Uncontrolled case series (n = 2)

DATA AND ANALYSES

Comparison 1. Topical: 10% povidone iodine and 50% salicylic plaster vs. 10% povidone iodine alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure at end of study (duration unknown)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 2. Topical: 10% povidone iodine and 50% salicylic acid plaster vs. 50% salicylic plaster alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure at end of study (duration unknown)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 3. Topical: 10% povidone iodine vs. 50% salicylic acid plaster

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure at end of study (duration unknown)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 4. Topical: 5% sodium nitrite in 5% salicylic acid vs. 5% salicylic acid alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure at medium term follow-up (3 months)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 5. Topical: 10% KOH vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure at medium-term follow-up (3 months)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 6. Systemic: cimetidine vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure at medium term follow-up (4 months)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 7. Systemic: calcarea carbonica vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement at end of study (duration unknown)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

WHAT'S NEW

Last assessed as up-to-date: 5 December 2005.

22 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 2, 2006

6 December 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordination of contributions from co-authors: JCvdW

Protocol: JCvdW, SG, with contributions from all

Searches: SG, JM, JCvdW

Screening abstracts: SG, JM, JCvdW

Obtaining copies of trials: SG, JCvdW

Assessing full papers for inclusion: SK, LvSS, MYB, JCvdW

Extracting data from trials: CB, MYB, SK, JCvdW

Assessing methodological quality: SG, SK, MB, JCvdW

Data entry: JM, JCvdW

Text of review: JM, JCvdW, with contributions from all

Consumer feedback on synopsis: MJAT

DECLARATIONS OF INTEREST

Anthony Ormerod who acted as a content expert for this review is also the author of one of the included trials. There has been no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Department of General Practice, Erasmus MC, Rotterdam, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title of the published protocol was inadvertently left as 'Interventions for molluscum contagiosum in children' although the decision had already been made not to restrict the review to children.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Infective Agents, Local [therapeutic use]; Cimetidine [therapeutic use]; Hydroxides [therapeutic use]; Molluscum Contagiosum [drug therapy; *therapy]; Potassium Compounds [therapeutic use]; Povidone-Iodine [therapeutic use]; Randomized Controlled Trials as Topic; Remission, Spontaneous; Salicylic Acid [therapeutic use]; Sodium Nitrite [therapeutic use]

MeSH check words

Humans