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[Intervention Review]

Interventions for actinic keratoses

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ABSTRACT

Background

Actinic keratoses are a skin disease caused by long-term sun exposure, and their lesions have the potential to develop into squamous cell carcinoma. Treatments for actinic keratoses are sought for cosmetic reasons, for the relief of associated symptoms, or for the prevention of skin cancer development. Detectable lesions are often associated with alteration of the surrounding skin (field) where subclinical lesions might be present. The interventions available for the treatment of actinic keratoses include individual lesion-based (e.g. cryotherapy) or field-directed (e.g. topical) treatments. These might vary in terms of efficacy, safety, and cosmetic outcomes.

Objectives

To assess the effects of topical, oral, mechanical, and chemical interventions for actinic keratosis.

Search methods

We searched the following databases up to March 2011: the Cochrane Skin Group Specialised Register, CENTRAL in *The Cochrane Library*, MEDLINE (from 2005), EMBASE (from 2010), and LILACS (from 1982). We also searched trials registers, conference proceedings, and grey literature sources.

Selection criteria

Randomised controlled trials (RCTs) comparing the treatment of actinic keratoses with either placebo, vehicle, or another active therapy.

Data collection and analysis

At least two authors independently abstracted data, which included adverse events, and assessed the quality of evidence. We performed meta-analysis to calculate a weighted treatment effect across trials, and we expressed the results as risk ratios (RR) and 95% confidence intervals (CI) for dichotomous outcomes (e.g. participant complete clearance rates), and mean difference (MD) and 95% CI for continuous outcomes (e.g. mean reduction in lesion counts).

Main results

We included 83 RCTs in this review, with a total of 10,036 participants. The RCTs covered 18 topical treatments, 1 oral treatment, 2 mechanical interventions, and 3 chemical interventions, including photodynamic therapy (PDT). Most of the studies lacked descriptions of some methodological details, such as the generation of the randomisation sequence or allocation concealment, and half of the studies had a high risk of reporting bias. Study comparison was difficult because of the multiple parameters used to report efficacy and safety outcomes, as well as statistical limitations. We found no data on the possible reduction of squamous cell carcinoma.

The primary outcome 'participant complete clearance' significantly favoured four field-directed treatments compared to vehicle or placebo: 3% diclofenac in 2.5% hyaluronic acid (RR 2.46, 95% CI 1.66 to 3.66; 3 studies with 420 participants), 0.5% 5-fluorouracil (RR 8.86, 95% CI: 3.67 to 21.44; 3 studies with 522 participants), 5% imiquimod (RR 7.70, 95% CI 4.63 to 12.79; 9 studies with1871 participants), and 0.025% to 0.05% ingenol mebutate (RR 4.50, 95% CI 2.61 to 7.74; 2 studies with 456 participants).

It also significantly favoured the treatment of individual lesions with photodynamic therapy (PDT) compared to placebo-PDT with the following photosensitisers: aminolevulinic acid (ALA) (blue light: RR 6.22, 95% CI 2.88 to 13.43; 1 study with 243 participants, aminolevulinic acid (ALA) (red light: RR 5.94, 95% CI 3.35 to 10.54; 3 studies with 422 participants), and methyl aminolevulinate (MAL) (red light: RR 4.46, 95% CI 3.17 to 6.28; 5 studies with 482 participants). ALA-PDT was also significantly favoured compared to cryotherapy (RR 1.31, 95% CI 1.05 to 1.64).

The corresponding comparative risks in terms of number of participants completely cleared per 1000 were as follows: 313 with 3% diclofenac compared to 127 with 2.5% hyaluronic acid; 136 with 0.5% 5-fluorouracil compared to 15 with placebo; 371 with 5% imiquimod compared to 48 with placebo; 331 with ingenol mebutate compared to 73 with vehicle; 527 to 656 with ALA/MAL-PDT treatment compared to 89 to 147 for placebo-PDT; and 580 with ALA-PDT compared to 443 with cryotherapy.

5% 5-fluorouracil efficacy was not compared to placebo, but it was comparable to 5% imiquimod (RR 1.85, 95% Cl 0.41 to 8.33).

A significant number of participants withdrew because of adverse events with 144 participants affected out of 1000 taking 3% diclofenac in 2.5% hyaluronic acid, compared to 40 participants affected out of 1000 taking 2.5% hyaluronic acid alone, and 56 participants affected out of 1000 taking 5% imiquimod compared to 21 participants affected out of 1000 taking placebo.

Based on investigator and participant evaluation, imiquimod treatment and photodynamic therapy resulted in better cosmetic outcomes than cryotherapy and 5-fluorouracil.

Authors' conclusions

For individual lesions, photodynamic therapy appears more effective and has a better cosmetic outcome than cryotherapy. For field-directed treatments, diclofenac, 5-fluorouracil, imiquimod, and ingenol mebutate had similar efficacy, but their associated adverse events and cosmetic outcomes are different. More direct comparisons between these treatments are needed to determine the best therapeutic approach.

PLAIN LANGUAGE SUMMARY

Interventions for actinic keratoses

Actinic keratoses are a skin disease caused by long-term sun exposure. Damaged skin shows small, red, rough, scaly, flat spots called actinic keratoses or lesions, which feel like patches of dry skin. Symptoms such as bleeding and pain can be associated with actinic keratoses. Moreover, actinic keratoses have the potential to develop into skin cancer if left untreated. The reasons for treatment may include cosmetic appearance, relief of symptoms, or prevention of skin cancer. Treatment can be directed either at individual lesions or to larger areas of the skin where several visible and less visible lesions occur (field-directed treatment).

This systematic review included results from 83 randomised controlled clinical trials evaluating 24 treatments, with a total of 10,036 participants diagnosed with actinic keratosis. We included 18 topical creams or gels applied to a skin area by the participants: adapalene gel, aretinoid methyl sulfone (Ro 14-9706), betulin-based oleogel, calcipotriol (vitamin D), colchicine, diclofenac, 2-(difluoromethyl)-dl-ornithine (DFMO), 5-fluorouracil, ß-1,3-D-glucan, imiquimod, ingenol mebutate (PEP005), isotretinoin, masoprocol, nicotinamide, resiquimod, sunscreen, DL-α-tocopherol (vitamin E), and tretinoin. One treatment, etretinate, was taken orally. Clinical staff administered two mechanical treatments (carbon dioxide and Er:YAG laser resurfacing) on a skin area, and they administered three chemical treatments: cryotherapy on individual lesions, photodynamic therapy on individual lesions or a skin area, and trichloroacetic acid peel on a skin area.

The clinical effects resulting from the treatment of actinic keratoses were reported differently from one study to another. In spite of this inconsistency, it can be concluded that several good treatment options exist for the treatment of actinic keratoses. Actinic keratoses were successfully treated with cryotherapy, diclofenac, 5-fluorouracil, imiquimod, ingenol mebutate, photodynamic therapy, resurfacing, and trichloroacetic acid peel. These different treatments were generally comparably effective. Skin irritation was associated with some of these treatments, such as diclofenac and 5-fluorouracil, but other side-effects were uncommon. The final cosmetic appearance varies from one treatment to another. Imiquimod treatment and photodynamic therapy resulted in better cosmetic appearance than treatment with cryotherapy and 5-fluorouracil.

Treatment with photodynamic therapy gives better therapeutic and cosmetic results than cryotherapy for individual lesions. For field-directed treatments, diclofenac, 5-fluorouracil, imiquimod, and ingenol mebutate are good options associated with different side-effects and cosmetic results. Thus, the choice of treatment option for actinic keratosis depends on the number of lesions, the individual's desired results, and tolerance to the treatments.