Interventions for Bowen's Disease (Protocol)

Bath-Hextall FJ, Askew DA, Wilkinson D, Leonardi-Bee J

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[Intervention Protocol]

Interventions for Bowen's Disease

Fiona J Bath-Hextall[1], Deborah A Askew[2], David Wilkinson[2], Jo Leonardi-Bee[3]

[1]School of Nursing, Faculty of Medicine and Health Science, The University of Nottingham, Nottingham, UK. [2]School of Medicine, University of Queensland, Brisbane, Australia. [3]Division of Epidemiology and Public Health, The University of Nottingham, Nottingham, UK

Contact address: Fiona J Bath-Hextall, School of Nursing, Faculty of Medicine and Health Science, The University of Nottingham, Room D83, Medical school, Queens medical centre, Nottingham, NG7 2UH, UK. fiona.bath-hextall@nottingham.ac.uk.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of therapeutic interventions for Bowen's disease.

BACKGROUND

Description of the condition

Bowen's disease was first described by John T Bowen in 1912. It is the clinical term for squamous cell carcinoma, a type of non-melanoma skin cancer (NMSC) that is confined to the outside layer of the skin - the epidermis (Arlette 2004). Typically, Bowen's Disease lesions are slow growing, non-pigmented reddish patches with irregular edges and a yellow or white crusting or scaling surface, although infrequently the lesions can be pigmented (Ragi 1988; Cox 1999; Arlette 2004). They are clearly demarcated from the surrounding, normal skin. They are generally asymptomatic, although larger lesions may itch (Arlette 2004). The lesions are usually solitary, but multiple lesions do occur in 10 to 20% of those affected (Eedy 1987; Thestrup-Ped 1988; Kovacs 1996). Their size varies considerably, from a few millimetres to several centimetres in diameter, with the size of the lesion being directly related to its duration (Arlette 2004). They are usually persistent and progressive, with a small potential for invasive malignancy (Cox 1999).

Incidence and demographics

Bowen's Disease can occur at any age in adults, although large population cohort studies suggest that it is commonly diagnosed in older people, between 60 and 90 years old (Eedy 1987; Thestrup-Ped 1988; Kossard 1992; Reizner 1994; Kovacs 1996; Jaeger 1999). These studies also reveal considerable worldwide variation in gender and body site distribution.
Generally, Bowen's Disease occurs more commonly in women, and varies from country to country as shown by the following figures: 57% of cases in an Australian study (Kossard 1992), 56% to 61% in two Danish studies respectively (Thestrup-Ped 1988; Jaeger 1999), 54% in a Japanese study (Kovacs 1996), 74% to 80% in two studies in the UK (Eedy 1987; Cox 1994), and 63% in a study from the USA (Reizner 1994). The exception to this predominance of Bowen's Disease in women was reported in a study of white people living in Hawaii where women only accounted

for 38% of the reported cases (Reizner 1994). Although few studies have calculated incidence rates, there is considerable variation between the rates reported in North America (15 per 100 000 in Minneapolis, USA (Chute 1991) and in Canada 28 per 100,000 for men, and 22 per 100,000 for women (Arlette 2004) compared to white people living in Hawaii (174 per 100,000 for men and 115 per 100,000 for women) (Reizner 1994).

In Australia, the most common sites of Bowen's Disease lesions are the head and neck (44%), followed by the lower limbs (30%) with 70% of lesions occurring below the knee. Australian men most commonly have lesions on their head and necks, while Australian women more commonly have Bowen's Disease lesions on their lower limbs (Kossard 1992). The head and neck regions were also the most common site for lesions in Denmark with 59% in one study (Thestrup-Ped 1988) and 40% in another (Jaeger 1999), and 66% in the USA (Reizner 1994). The UK has a very different pattern of distribution of lesions, with only 13% appearing on the head and neck and 67% occurring on the lower limbs (Eedy 1987). Generally, few Bowen's Disease lesions occur on the trunk, but a study in Japan (Kovacs 1996) and another on white people living in Hawaii (Reizner 1994) found a notably higher predominance of lesions on the trunk, 35% and 26% respectively.

Impact

In general, people with Bowen's Disease have an excellent prognosis because the disease is typically slow growing and responds favourably to treatment although, a significant number of lesions of Bowen's Disease are not treated due to its relatively benign nature and the demographics of the participants with the condition. The risk of progression of Bowen's Disease to invasive squamous cell carcinoma (SCC) is generally considered to be about 3%, of which approximately one third may metastasise (spread to other areas) (Cox 1999; Arlette 2004). These figures are high compared to what is actually seen in clinical practice and may reflect the inclusion of mucosal and anogenital Bowen's Disease where there is a higher risk of transformation and metastasis.

Bowen's Disease may represent a risk marker for other non-melanoma skin cancers. Studies that have investigated this association report about one third of people have another NMSC (most commonly basal cell carcinomas (BCC)) at the time of diagnosis (Thestrup-Ped 1988; Reizner 1994). There is also a 4.3 times increased risk of developing subsequent NMSC (Jaeger 1999).

There has been much discussion about an association between Bowen's Disease and internal malignancies, with several studies suggesting a significant relationship between the two (Cox 1999). However, a 1989 meta-analysis of 12 studies (10 cohort and 2 case-control studies) found no significant relationship between the 2 (Lycka 1989). This result was subsequently confirmed by two large population-based cohort studies, one in Denmark (Jaeger 1999) and the other in the USA. It is now generally accepted that there is no relationship between Bowen's Disease and internal malignancies, and therefore, routine investigation for internal malignancies is not justified (Cox 1999).

Causes

Bowen's Disease predominantly occurs in older age groups and on areas of the body subjected to chronic sun exposure (head and neck, and lower legs in women), suggesting a causal relationship between chronic exposure to ultraviolet light radiation and Bowen's Disease (Eedy 1987; Thestrup-Ped 1988; Kossard 1992; Cox 1994; Reizner 1994; Kovacs 1996). Exposure to arsenic through well water, older medications and occupational chemicals have been associated with the development of Bowen's Disease, with a typical time lag of more than ten years between exposure and development of lesions (Cox 1999; Arlette 2004). Viral causes include the human papillomavirus (HPV) and the human herpes virus type 8, although various studies report conflicting results about the frequency with which these agents are detected in Bowen's Disease lesions. Immunosuppression, either congenital, acquired or therapeutic, has also been associated with Bowen's Disease (Cox 1999). Although not the subject of this review, it is interesting to note that viral causes are involved in almost 100% of cases of mucosal and anogenital Bowen's Disease.

Description of the intervention

There are a range of treatment options for Bowen's disease, including:

- topical therapies such as 5-fluorouracil and imiquimod;
- surgical interventions such as excision, cryotherapy, curettage and cautery, and Mohs' surgery;
- light based therapies such as laser therapy and photodynamic therapy;
- radiotherapy.

How the intervention might work

Photodynamic therapy

Photodynamic therapy is a non-ionising radiation treatment using the interaction between visible light and tumour sensitising agents to generate cell death.

5-Fluorouracil

The primary mechanism of action of 5-fluorouracil is thought to be inhibition of DNA synthesis by competitive inhibition of thymidylate synthetase.

Imiquimod

Imiquimod is an immune response modifier that has been shown to induce cytokines that promote a TH1 lymphocyte or cell-mediated immune response.

Mohs' micrographic surgery

Mohs' micrographic surgery is a technique whereby 100% of the surgical margin is examined by mapping horizontal frozen sections from successive excision layers until clearance is achieved.

Radiotherapy

Radiotherapy works by destroying the cancer cells in the treated area using high energy X-rays.

Laser surgery

Laser surgery uses a highly focused beam of light that destroys only the cancer cells.

Cryotherapy

Cryotherapy uses liquid nitrogen to destroy tissue by freezing it to -196^{o}C.

Curettage and cautery

Electrodessication and curettage are generally known as 'scraping or burning-off of skin growths'. Curettage is performed under local anaesthesia. The curette is either an oval, semi sharp, spoon-shaped instrument or an open ring connected to a handle. The curette is designed to cut through abnormally soft or friable tissue with minimum force so that the diseased tissue can be selectively removed. Curettage should be combined with subsequent electrocautery which destroys additional tissue.

Why it is important to do this review

The relative effectiveness of the available treatments is not known for Bowen's disease. Treatment of Bowen's Disease needs to balance the burden of treatment against its benefit, particularly as the disease mainly affects the elderly and is predominantly slow growing in nature. Some Bowen's Disease lesions may deserve special consideration, for example, lesions of the lower limb and especially larger lesions, due to the potential for poor healing in the former and the high recurrence rates in the latter.

Given these issues, this review will attempt to address the following:

(1) What are the most effective treatments for Bowen's disease, with the fewest side effects?

(2) How do the various therapies compare in the following participant subgroups:

- participants with lower leg lesions (i.e. located below the knee)?
- participants with lesions > 2cm^2?
- patients with medical co-morbidities leading to poor wounding healing and/or age greater than 70 years?

OBJECTIVES

To assess the effects of therapeutic interventions for Bowen's disease.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) of any design

Types of participants

People with histologically proven Bowen's Disease. People with genodermatoses (genetic disorders of the skin), mucosal, or anogenital Bowen's Disease will be excluded.

Types of interventions

Any interventions for the treatment of Bowen's Disease, including:

Surgical

1. Surgical excision
2. Mohs' micrographic surgery

Destructive

1. Curettage and cautery/electrodesiccation
2. Cryosurgery - any number of cycles
3. Photodynamic therapy
4. Laser surgery
5. Radiotherapy

Other techniques

1. Topical therapy e.g. imiquimod, 5 fluorouracil

The comparators will be any other type of accepted and commonly used treatment modality, any interventions compared to control (placebo/no treatment), or different dosages/durations of the same interventions.

Types of outcome measures

Primary outcomes

(i) Complete clearance of the lesion

Ideally, clearance of the lesion will be determined by histology, but clinical clearance at follow-up will be accepted.
Since a number of treatments require more than one cycle of therapy we will look at:

- Number of patients with clearance after first treatment cycle;
- Recurrence at 12 months

Secondary outcomes

(i)Number of patients with clearance after each treatment cycle

(ii)Number of treatment cycles needed to achieve clearance

(iii)Recurrence at >12 months

(iv) Cosmetic outcome

This will be assessed using a recognised and validated instrument to measure cosmesis

(v) Consumer satisfaction with treatment modality and/or cosmesis and/or pain at site

We expect this to be recorded on a Likert or Likert-like scale.

(vi) Time to complete healing of lesion following treatment

This will be determined by clinical examination and / or by participant assessment through a diary or similar mechanism.

(vii) Quality of life

This will be determined by any validated quality of life instrument

(viii) Adverse outcomes

These will be categorised using the following system:
a) none;
b) mild: transient, requires no treatment, non interference with social/occupational function;
c) moderate: requires simple treatment, interferes with social/occupational function;
d) severe: requires vigorous treatment, hospitalisation, and interrupts social/occupational function.

(ix) Recurrence of Bowen's disease in same site

This will be determined by clinical examination

Search methods for identification of studies

Electronic searches

We shall search for relevant published trials in:

- the Cochrane Skin Group Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (last update);
- MEDLINE (from 2003) and EMBASE (from 2005);
- PsycInfo and LILACS (Latin American and Caribbean Health Science Information database) from inception
- CISCOM, ISI Science Citation Index (on BIDS) ISI web of science.

The UK Cochrane Centre has an ongoing project to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE to 2003 and in EMBASE to 2005. Further searching will be undertaken for this review by the Cochrane Skin Group to cover the years that have not been searched by the UKCC.
We have devised a draft search strategy for RCTs for MEDLINE (OVID) which is displayed in Appendix 1. This will be modified to include additional search terms where necessary and will be used as the basis for designing search strategies for the other databases listed.

Ongoing Trials

We shall search for ongoing trials in:

- The metaRegister of Controlled Trials on www.controlled-trials.com
- The U.S National Institutes of Health register on www.clinicaltrials.gov
- The Australian Clinical Trials Registry on www.anzctr.org.au
- The WHO portal on www.who.int/trialsearch/

- The Ongoing Skin Trials Register on www.nottingham.ac.uk/ongoingskintrials

Searching other resources

Grey Literature

We shall attempt to find unpublished studies through correspondence with key authors publishing in this area, and by contacting pharmaceutical companies who produce relevant products. The possible companies include:

- Valeant Pharmaceuticals Australasia Pty Ltd (5-fluorouracil, Efudex)
- ICN (5-fluorouracil, Efudex)
- Roche (5-fluorouracil, Efudix)
- Allergan (5-fluorouracil, Fluoroplex)
- Dermik (5-fluorouracil, Carac)
- 3M Pharmaceucticals and Graceway Pharmaceuticals (imiquimod, Aldara)
- Sigma (5-Aminolevulinic acid, 5-AlA)
- Biosynth (5-Aminolevulinic acid, 5-Ala, delta-Aminolevulinic acid)
- DUSA Pharmaceuticals (photodynamic therapy)
- Galderma (photodynamic therapy, Metvix-PDT)

Additional pharmaceutical companies who produce any further products identified during the process of undertaking this review will also be contacted.

Reference lists

We shall scan the bibliographies of published studies (both included and excluded studies) and reviews for possible references to RCTs.

Correspondence

We shall try to identify unpublished or on-going trials by correspondence with authors and pharmaceutical companies, as listed above under Grey Literature.

Adverse events

We will identify reports of adverse events in included and excluded studies, and through searching the web sites of the following adverse outcome reporting agencies:

- The European Medicines Agency http://emea.europa.eu
- The Therapeutic Goods Administration of Australia www.tga.gov.au
- The Medicines and Healthcare products regulatory Agency http://medicines.mhra.gov.uk
- The U.S. Food and Drug Administration www.fda.gov/medwatch

Language

We will impose no language restrictions and we shall seek translations where necessary.

Data collection and analysis

Selection of studies

Two authors (FB-H and JL-B) will review the titles and abstracts identified from the searches. Studies that are clearly not randomised controlled trials of treatments for Bowen's Disease will be excluded. The same two authors will independently assess the full text version of the remaining studies against the pre-defined selection criteria. We will resolve any differences of opinion through discussion with the third author (DW).

Data extraction and management

Two authors (FB-H and JL-B) will independently extract the data using a specially designed data extraction form. The third author (DW) will resolve any differences of opinion. One author will enter data into RevMan (FB-H).

Cosmetic outcome, consumer satisfaction with cosmesis, consumer pain ratings, and severity of adverse effects are all ordinal data outcomes. Where possible, we will translate these outcomes into dichotomous data and we will record both the original and translated results.

We will express all other outcomes as actual or percentage differences between treatment arms.

Assessment of risk of bias in included studies

The assessment of the methodological quality of included studies will include an evaluation of the following components of internal and external validity for each included study, since there is some evidence that these are associated with biased estimates of treatment effect (Juni 2001):

(a) the method of generation of the randomisation sequence

(b) the method of allocation concealment - we will consider it 'adequate' if the assignment could not be foreseen

(c) who was blinded and not blinded (participants, clinicians, outcome assessors), if appropriate

(d) the number of participants lost to follow-up in each treatment arm, and if the reasons for losses were adequately reported

(e) whether all participants were analysed according to the groups to which they were initially randomised (intention to treat principle)

In addition, we will assess the following:
(f) baseline comparability between treatment arms

Measures of treatment effect

We will express the results as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes; and we will use number needed to treat (NNT) to express the relative benefit (or otherwise) of the various treatment options where appropriate, for a range of plausible control event rates.
We shall use mean differences (MD) with 95% CI to express results for continuous outcomes where the same measurement scales have been used across trials, and we shall use standardised mean differences (SMD) to express results for continuous outcomes where different, but comparable, measurement scales have been used across trials.
We will analyise cross-over trials using techniques appropriate for paired designs, for appropriate outcome measures.
For time-to-event data, we will express the results as hazard ratios with 95% CI.
We will estimate the log hazard ratio and its variance with a Microsoft Excel spreadsheet authored by Matthew Sydes (Cancer Division) in collaboration with the Meta-analysis Group of the MRC Clinical Trials Unit, London, which is based on Parmar's methods (Parmar 1998). We will calculate the log hazard ratio and its variance either using directly extracted data or estimated from survival curves. Where ordinal data cannot be dichotomised, we will report a qualitative summary with presentation of the data in tables of figures as appropriate.
We shall translate ordinal outcomes (cosmetic outcome, consumer satisfaction with cosmesis, consumer pain ratings, and severity of adverse effects) into dichotomous data using established cut points, where possible.

Unit of analysis issues

We will analyse internally controlled trials using appropriate methods for paired designs and we will not pool these studies with studies of other designs. We will not include non-randomised controlled trials in the analysis, but we will comment on them in the discussion. If a trial contains multiple intervention groups, we shall make pairwise comparisons of interventions versus placebo or other interventions.

Dealing with missing data

We will deal with missing data due to participant drop-out through intention-to-treat analysis. In other words, we shall analyse all trial participants according to the group to which they were assigned and we will include all participants in the analysis irrespective of whether their outcomes were actually collected. For dichotomous outcomes we will assume that all the 'missings' had a poor outcome. For continuous outcomes, we will use the 'last recorded value taken forward' approach. We shall contact trial authors of studies less than 15 years old to provide information about participant drop-out and missing statistics such as standard deviations.

Assessment of heterogeneity

We will assess heterogeneity, or variability between studies visually and we will quantify using the I^2 statistic. I^2 describes the percentage of the variability in effect estimates that is due to variability among the studies rather than chance (Higgins 2008). If I^2 is >85% then we will not perform meta-analysis.

Assessment of reporting biases

We will use funnel plots to alert us to the potential of publication bias, although we are aware that factors other than publication bias can cause asymmetric funnel plots, and conversely, publication bias may be present with a symmetrical funnel plot.

Data synthesis

If the included studies have sufficient homogeneity, we will perform a meta-analysis to calculate a weighted treatment effect across trials. The degree of heterogeneity will determine if a fixed effect or random effects model is used. If it is not possible to perform a meta-analysis we shall summarise the data for each trial narratively.

Subgroup analysis and investigation of heterogeneity

If substantial heterogeneity exists (I^2 > 50%) between studies for the primary outcome we will explore heterogeneity by examining the effects of excluding study subgroups e.g. those studies with lower reported methodological quality (i.e. studies that did not clearly report randomisation, blinding and which do not have an intention-to-treat analysis), we shall also investigate potential causes of the heterogeneity, including dosage and duration of treatment, lesion characteristics (size, body site) and age groups of participants.
We shall conduct subgroup analyses where adequate information is available. The groups will include: body site of lesion (particularly lower leg lesions, i.e. located below the knee); size of lesion (particularly lesions > 2cm), age of the participants (particularly those over 70 years of age); and participants with medical co-morbidities (particularly those that could affect wound healing).

Sensitivity analysis

We plan to conduct sensitivity analyses to assess the robustness of the results of the review, relative to the key assumptions and decisions made during the progress of the review, as defined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008)

Adverse outcomes

We shall record the appropriateness and relevance of the methods used to detect adverse events, and the adequacy of the reporting. We shall summarise and describe the information qualitatively.

Other

In instances of uncertainty, clarification will be sought from trial authors or investigators. The consumer in our team (JD) will ensure the final review is relevant, readable and understandable.

ACKNOWLEDGEMENTS

We would like to acknowledge our debt to Seaver Soon, Tracy Bialy, Calvin McCall, Robyn Whyte, Aditya Gupta and Suephy Chen. They had previously published a protocol for a systematic review of interventions for Bowen's disease, but were unable to proceed to a full review. This current protocol has now been taken over by Fiona Bath-Hextall (lead reviewer) and Jo Leonardi-Bee. David Wilkinson and Deborah Askew have remained as co-authors. Jim Delitt has agreed to be the consumer for the review under the new team.

The editorial base would like to thank Stephen Schumack (external expert peer referee) and Kathie Godfrey (consumer referee).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. humans.sh.
10. 8 and 9
11. Bowen's disease.mp. or exp Bowen's Disease/
12. bowenoid papulosis.mp.
13. morbus bowen.mp.
14. exp Carcinoma, Squamous Cell/ or in situ squamous cell carcinoma.mp.
15. intraepidermal squamous cell carcinoma.mp.
16. 11 or 12 or 13 or 14 or 15
17. cryosurgery.mp. or exp Cryosurgery/
18. cryotherapy.mp. or exp Cryotherapy/
19. curettage.mp. or exp Curettage/
20. fluorouracil.mp. or exp Fluorouracil/
21. 5-fluorouracil.mp.
22. efudex.mp.
23. 5-FU.mp.
24. photochemotherapy.mp. or exp Photochemotherapy/
25. photodynamic therapy.mp.
26. exp Aminolevulinic Acid/ or aminolaevulinic acid.mp.
27. (ALA or ALA-PDT).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
28. imiquimod.mp.
29. aldara.mp.
30. liquid nitrogen.mp.
31. excision.mp.
32. mohs surgery.mp. or exp Mohs Surgery/
33. moh's surgery.mp.
34. laser surgery.mp. or exp Laser Surgery/
35. carbon dioxide laser.mp.
36. argon laser.mp.
37. Nd:YAG laser.mp.
38. lasers.mp. or exp Lasers/
39. radiotherapy.mp. or exp Radiotherapy/
40. recombinant interferon gamma.mp. or exp Interferon-gamma, Recombinant/
41. interferon type ii.mp. or exp Interferon Type II/
42. interferon gamma.mp.
43. interferons.mp. or exp Interferons/
44. interferon alfa-2b.mp. or exp Interferon Alfa-2b/
45. interferon alpha-2b.mp.
46. interferon.mp.
47. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48. 10 and 16 and 47

HISTORY

Protocol first published: Issue 3, 2008

CONTRIBUTIONS OF AUTHORS

Draft the protocol: FB-H, JL-B, DA, DW

Search for trials: FB-H, JL-B

Obtain copies of trials: FB-H, JL-B

Select which trials to include: FB-H, JL-B, arbitrator in case of disagreement: DW

Extract data from trials: FB-H, JL-B

Enter data into RevMan: FB-H

Conduct analysis: FB-H, JL-B

Interpret analysis: FB-H, JL-B, DA, DW

Draft final review: FB-H, JL-B

Update the review: FB-H, JL-B

DECLARATIONS OF INTEREST

None known

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Internal sources

- The University of Nottingham, UK.

External sources

- No sources of support supplied