Long-term topical corticosteroid use and risk of skin cancer: A systematic review protocol

Sonia Ratib[1]

Esther Burden-Teh[1]

Jo Leonardi-Bee[2]

Catherine Harwood[3]

Fiona Bath-Hextall[4]

1 Centre of Evidence Based Dermatology, University of Nottingham, UK

2 Division of Epidemiology and Public Health, University of Nottingham, UK

3 Department of Dermatology, Royal London Hospital, Whitechapel, UK

4 Centre for Evidence Based Health Care, School of Health Sciences, University of Nottingham: a Collaborating Centre of the Joanna Briggs Institute

Corresponding author: Sonia Ratib
Sonia.ratib@nottingham.ac.uk

Background

Topical corticosteroids (TCS) are used to reduce inflammation and are one of the most commonly prescribed medicines in dermatology. They were first used successfully by Sulzberger and Witten in 1952 and their success marked a cornerstone in the history of dermatology.[1] Topical corticosteroids are the mainstay of atopic dermatitis treatment and used for other skin conditions such as psoriasis, where they are often required for months or years to control the disease and ultimately restore patients' quality of life. Numerous TCS are now available in different preparations, concentrations and potencies; however, when used appropriately TCS efficacy and safety are well established.[2-6]

The beneficial anti-inflammatory effects of TCS are complex, being largely mediated via the cytoplasmic steroid receptor and involving actions on circulating cellular and cytokine mediators of inflammation as well as on the peripheral vasculture.[7] The use of TCS is tempered by consideration of local and less frequently encountered systemic side effects. Known local side effects include skin atrophy, contact allergy, acne, mild hypopigmentation and hypertrichosis. Rarely absorption through the skin can cause adrenal suppression. The risk of developing side effects is related to the potency, preparation, frequency and duration of use and the age of the patient. In clinical practice these side effects are uncommon when TCS are used within their guidance.

There are two types of skin cancers: melanoma and non-melanoma (keratinocyte). Around 97% of skin cancers are non-melanoma (NMSC), comprising mainly of basal cell carcinomas (BCCs) or cutaneous cell carcinomas (cSCCs). The incidence of NMSC is increasing worldwide,[8-12] with an estimated 2-3 million new cases of NMSC recorded each year.[13] With respect to cutaneous malignant melanoma (CMM), this is the most serious form of skin cancer and has been increasing steadily in incidence over the past 30 years.[14] Mortality due to CMM is much higher than that of NMSC.[15]

There are several observational studies that have looked at the relative risk of developing skin cancer due to oral corticosteroid exposure.[16-17] These studies have provided conflicting results as to whether corticosteroids are associated with an increased risk of skin cancer.Karagas et al.[16] conducted a case-control study on over 800 non-transplant SSC and BCC patients. The authors found that oral glucocorticoids may increase the risk of non-melanoma skin cancers, whereas Baibergenova et al. found no association between non-melanoma skin cancers and oral corticosteroids in a follow-up study of a chemotherapy trial with 1051 study participants.[17] These studies highlight the clinical equipoise that exists around the impact oral corticosteroids have on the risk of skin cancer.

There have been several epidemiological studies that have explored the risk of cancer specifically amongst atopic dermatitis patients. Hagwstromer et al. conducted a hospital-based study on 15 666 patients with atopic dermatitis in Sweden between 1965 and 1999. [18]The authors reported men faced a 50% increased risk of non-melanoma skin cancer during the first 10 years of follow-up, but this did not reach statistical significance.[18] Wang et al. conducted a review of atopic dermatitis studies published before 2004 and found no consistent associations were observed for skin cancers.[19] This review did not look at the effect of TCS use on the risk of skin cancer. At present, we don't know in particular what impact TCS have on the risk of skin cancer in the atopic dermatitis population.

With regards the organ transplant population, it is well established that immunosuppression increases the risk of skin malignancy.[20,21] This occurs when systemic corticosteroids are used, although most studies include patients treated with a combination of immunosuppressants including azathioprine and calcineurin inhibitors.[22,23] Corticosteroids are known to have an immunosuppressive effect, and TCS may have a local immunosuppressive effect. It is not known whether TCS may increase the risk of skin cancer through this mechanism.

On the other hand, it is possible that treating skin inflammation with TCS may reduce the risk of skin cancer. Several systematic reviews and meta-analyses report the benefits of anti-inflammatory drugs in reducing the risk of cancer, including skin cancers.[24,25] The management of certain types of inflammatory skin diseases includes the rationale that reducing inflammation reduces the risk of SCC

development in vulval and penile lichen sclerosus as well as hypertrophic lichen planus. It is also known that chronic inflammation is a risk for the development of SCC, such as in chronic ulceration and the development Marjolin's ulcer.[26,27] This mainly holds true for SCC but less is known about BCC and melanoma. .Therefore, overall TCS may decrease the risk of skin cancer in patients where TCS are used to treat inflammatory skin disease.

To date, no published systematic review or meta-analysis have been performed to collate evidence on long-term TCS use on the risk of skin cancer. We checked MEDLINE and EMBASE, Immunosuppression induced by TCS, either local or systemic, may allow these cancers to emerge from reduced innate immunosurveillance. However, TCS may also reduce the risk of skin cancer in patients where TCS are used to treat inflammatory skin disease. With TCS use being one of the most commonly prescribed drugs in the clinical field of dermatology and the increasing incidence of skin cancer there is a need to review all current evidence about the possible association.

Review question

The objective of this systematic review is to synthesize the best available research evidence to determine the risk of skin cancer in patients on long-term use of topical corticosteroids.

In people using long-term (regular use over 1 month) topical corticosteroids what is the risk of developing skin cancer (clinically or histologically confirmed basal cell carcinoma, squamous cell carcinoma or melanoma)?

Keywords

Basal cell carcinoma; melanoma; keratinocyte; non-melanoma; squamous cell carcinoma; topical corticosteroids; systematic review; meta-analysis.

Methods

Inclusion criteria

Participants

This review will consider studies that include people, of all ages, genders and ethnicities.

Participants with HIV, transplant participants or participants with genetic diseases (for example Gorlin-Goltz syndrome) will be included.

Exposure of interest

This review will consider studies that evaluate long-term use of topical corticosteroids. Our definition of 'long-term' consists of more than once a week for a month or longer.

Outcome or response

This review will consider studies that include the following outcome measures:

Non-melanoma skin cancer, cutaneous squamous cell carcinoma (SSC), basal cell carcinoma (BCC) or melanoma skin cancer. These outcomes will be measured by a clinical diagnosis and where available histological confirmation. Pre-cursors such as Bowen's disease will be secondary outcomes.

Study types

This review will include analytical comparative observational studies including prospective and retrospective cohort studies, case-control studies and cross-sectional studies.

Search strategy

The search strategy will aim to identify both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and EMBASE was undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using identified key words and index terms has been used to develop a comprehensive search strategy. The search strategy for MEDLINE is detailed in Appendix 1. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published in all languages will be included. There will be no date exclusion.

Information Sources

The electronic databases to be searched include:

MEDLINE, EMBASE and LILACS all from inception to current date.

The search for unpublished studies will include:

Skin cancer experts who have been identified from the included studies will be contacted. We will also search EThOS at the British library (http://ethos.bl.uk) to identify other unpublished work.

Study selection

Following the search, all identified citations will be collated and uploaded EndNote and duplicates removed. Titles and abstracts will then be screened by two independent reviewers (SR and EBT) for assessment against the inclusion criteria for the review. Studies that appear to meet the inclusion

criteria will be retrieved in full and their details imported into SUMARI. The full text of selected citations will be retrieved and assessed independently by two reviewers (SR and EBT) in detail against the inclusion criteria. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (FBH).

Critical appraisal

Included studies will be critically appraised by two independent reviewers (SR and EBT) at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for cohort, cross-sectional surveys and/or case-control study designs (Appendices 2 and 3). The instrument will be amended for our needs. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (FBH). The results of critical appraisal will be reported in narrative form and in a table.

Data extraction

Data will be extracted from papers included in the review using the standardized data extraction tool for cohort, cross-sectional surveys and/or case control studies in JBI SUMARI (Appendices 2 and 3) by two independent reviewers (SR and EBT). We will tailor the extraction form to our needs. The data extracted will include specific details about the exposure of interest including different exposure categories if applicable, populations, study methods and relevant outcomes measures. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (FBH). Authors of papers will be contacted to request missing or additional data where required.

Data synthesis

Papers will, where possible be pooled using random effect meta-analysis methods in RevMan 5.3. Effect sizes will be expressed as relative risks (odds ratios or risk ratios) together with their 95% confidence intervals. If we can assume the outcome of interest is rare (i.e. <5-10%), then the odds ratio will be very similar to the risk ratio. Effect measures adjusted for confounders will be used in preference to crude effect measures. Where effect estimates and measures of precision (for example, standard errors, 95% CI) cannot be directly extracted from the included study, we will estimate them from data presented in the paper.

Heterogeneity will be quantified using I^2 and τ^2. Subgroup analyses will be conducted to explore reasons for heterogeneity in the meta-analysis models based on study quality, adjusted versus crude measures of effect, dose of TCS (low versus high), non-melanoma/melanoma and type of patient population (HIV/transplant participants/participants with syndromes versus those without those conditions) . Where there is insufficient data to allow for meta-analysis, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

We will conduct a sensitivity analysis excluding keratinised epithelium in special sites (e.g. vulvar and penile skin) to determine if there is a difference compared to the overall result. A funnel plot will be generated using RevMan 5.3 to assess publication bias if there are 10 or more studies included in a meta-analysis. he GRADE approach for assessing confidence in the quality of evidence will be used for this review, with the results presented in a summary of findings table created using GRADEPro.

Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Search Strategy for Medline using OVID

1. Epidemiologic studies/
2. Exp Case-control studies/
3. Exp Cohort studies/
4. Epidemiologic$ stud$.mp.
5. Case control stud$.mp.
6. Cohort stud$.mp.
7. Cohort analy$.mp.
8. Follow up stud$.mp.
9. Observational stud$.mp.
10. Longitudinal.mp.
11. Retrospective.mp.
12. Cross sectional stud$.mp.
13. Cross Sectional Studies/
14. Exp Observational Study/
15. Or/1-14
16. Carcinoma, Basal Cell/
17. Neoplasms, Basal Cell/
18. Basal Cell Nevus Syndrome/
19. Basal cell carcinoma$.mp.
20. Basal cell cancer$.mp.
21. Basal cell neoplasm$.mp.
22. Nodular BCC.mp.
23. Naevoid BCC.mp.
24. Gorlin syndrome.mp.
25. Basal cell Epithelioma$.mp.
26. Basalioma$.mp.
27. BCC.mp.
28. Rodent ulcer$.mp.
29. Or/16-28
30. Exp Neoplasms, Squamous cell/
31. Exp Carcinoma Squamous Cell/
32. Squamous cell carcinoma$.mp.
33. Squamous cell cancer$.mp.
34. Squamous cell neoplasm$.mp.
35. Bowen's disease.mp.
36. Planocellular carcinoma$.mp.
37. SCC.mp.
38. Or/30-37
39. Skin neoplasms/
40. NMSC.mp.
41. Non melanoma skin cancer$.mp.
42. Skin cancer$.mp.
43. Skin tumo$.mp
44. Skin neoplasm$

45. Exp Keratinocytes/
46. Keratinocytes.mp.
47. Or/38-46
48. Melanoma/
49. Melanoma.mp.
50. Or/48-49

51. topical corticosteroid$.mp.
52. steroid$.mp.
53. corticosteroid$.mp.
54. exp Glucocorticoids/
55. alclometasone.mp.
56. alclomethasone.mp.
57. amcinonide.mp.
58. beclometasone.mp.
59. beclomethasone.mp.
60. exp Beclomethasone/
61. betametasone.mp.
62. betamethasone.mp.
63. exp Betamethasone/
64. clobetasol.mp.
65. exp Clobetasol/
66. clobetasone.mp.
67. desonide.mp.
68. exp Desonide/
69. desoximetasone.mp.
70. exp Desoximetasone/
71. diflorasone.mp.
72. diflucortolone.mp.
73. exp Diflucortolone/
74. fludroxycortide.mp.
75. flumetasone.mp.
76. flumethasone.mp.
77. exp Flumethasone/
78. fluocinolone.mp.
79. exp Fluocinolone Acetonide/
80. fluocinonide.mp.
81. exp Fluocinonide/
82. fluocortolone.mp.
83. exp Fluocortolone/
84. flurandrenolide.mp.
85. flurandrenolone.mp.
86. exp Flurandrenolone/
87. fluticasone.mp.
88. halcinonide.mp.
89. exp Halcinonide/
90. halobetasol.mp.

91. halometasone.mp.
92. hydrocortisone.mp.
93. exp Hydrocortisone/
94. methylprednisolone.mp.
95. exp methylprednisolone/
96. mometasone.mp.
97. triamcinolone.mp.
98. exp Triamcinolone/
99. Or/ 51-98
100. 15 AND (29 OR 38 OR 47 OR 50) AND 99

Appendix 2: Appraisal instruments

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix 3: Data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

_____

Intervention B _____

_____

Authors Conclusions:

_____

_____

_____

Reviewers Conclusions:

_____

_____

_____

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number