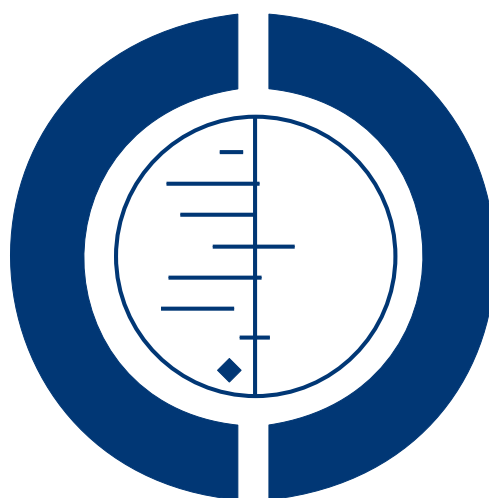# Corticosteroids for the management of cancer-related pain in adults (Protocol)

Hardy JR, Jenkins-Marsh S, Pinkerton E, Rickett K, Good P

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TABLE OF CONTENTS

Corticosteroids for the management of cancer-related pain in adults

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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 analgesic effects of corticosteroids for the management of cancer-related pain in adults.

BACKGROUND

to optimise pain control. Corticosteroids (steroids) are commonly used in this context.

Description of the condition

Cancer remains the leading cause of death worldwide. Over 12 million new cases are diagnosed each year (Foley 2011). The disease carries significant morbidity. Pain resulting directly or indirectly from the abnormal growth of malignant cells in normal tissue is the most common and most feared symptom associated with cancer (Van den Beuken-van Everdingen 2007). It is estimated that one third of cancer patients in active therapy, and two thirds of those with advanced disease, experience pain that requires treatment with analgesic drugs (Foley 2011). Of concern, there is also considerable evidence that cancer pain is often undertreated (Foley 2011). While opioids remain the mainstay of treatment for cancer pain, co-analgesics or adjuvants are often used concurrently

Description of the intervention

Steroids are essential for maintaining homeostasis and regulating a wide variety of physiological processes in the human body (Busillo 2013). Therapeutically they are widely prescribed for the treatment of inflammation, auto-immune disorders and malignancies (Busillo 2013). They are commonly used in the management of cancer pain.

How the intervention might work

The exact mechanism of action of steroids in relieving pain in cancer is unknown, but it is probably related to their potent anti-

inflammatory effect that occurs via a complex interplay between glucocorticoid receptor-mediated transcriptional regulation and signal transduction within target tissues (Baschant 2012). Pro-inflammatory cytokines have been implicated in a number of different pain states. Steroids may act as anti-inflammatory agents through the inhibition of these cytokines (Paulsen 2013).

Why it is important to do this review

Corticosteroids are used commonly in palliative care practice, especially for patients with advanced malignant disease, for a variety of symptom control indications including pain, nausea, mood elevation, anorexia and fatigue (Farr 1990; Hardy 2001; Riechelmann 2007). This is despite the fact that steroids are associated with significant side effects, especially following long-term use (Hanks 2009). There is little objective evidence in the literature to support the use of corticosteroids for symptom control, and concerns have been raised about the 'uncontrolled' use of steroids in cancer patients (Gannon 2002). Patients who are started on steroids in the palliative care setting are often not closely monitored, allowing for the development of debilitating side effects, often in the context of limited clinical benefit. Some of these side effects include: proximal myopathy, oral candidiasis, the development of osteoporosis, symptomatic hyperglycaemia, psychological disturbances, gastrointestinal irritation and increased susceptibility to infections. For example, although steroids are frequently administered to assist with mood elevation, some studies have shown that corticosteroid therapy may result in more disturbing side effects such as insomnia, delirium, depression, anxiety, and psychosis (Vyvey 2010). There is a relevant gap in the body of knowledge, in that most patients with cancer will be prescribed steroids at some stage during their disease course.

O B J E C T I V E S

To assess the analgesic effects of corticosteroids for the management of cancer-related pain in adults.

M E T H O D S

Criteria for considering studies for this review

Types of studies

Any randomised controlled or prospective controlled trials. If no randomised controlled trials are found, prospective controlled studies will be examined.

Types of participants

Participants with cancer-related pain, aged 18 years and above.

Types of interventions

Any corticosteroid used to treat cancer-related pain.
All routes of drug administration will be considered.
Comparisons:
- placebo,
- no intervention,
- usual treatment or supportive care, or
- alternative non-pharmacological treatment for pain.

Types of outcome measures

Primary outcomes

Patient-reported pain intensity and pain relief using validated scales (Visual Analogue Scale (VAS), Verbal Rating Scale (VRS), Numerical Rating Scale (NRS)).

Secondary outcomes

- Adverse events.
- Quality of life scores.
- Patient satisfaction.
- Other relevant outcome measure e.g., cost-effectiveness data.

Search methods for identification of studies

We will not apply language, date or publication status (published in full, published as abstract, unpublished) restrictions to the search.

Electronic searches

We will search the following databases:
1. The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*)
2. MEDLINE (OVID) (1966 to present)
3. EMBASE (OVID) (1970 to present)
4. CINAHL (1982 to present)
5. Science Citation Index (Web of Science) (1899 to present)
6. Conference Proceedings Citation Index - Science (Web of Science) (1990 to present).
The search strategy for MEDLINE (OVID) can be seen in Appendix 1.

Searching other resources

We will check the bibliographic references of relevant identified studies in order to find additional trials not identified by the electronic searches. We will also search www.Clinicaltrials.gov, the metaRegister of Controlled Trials (mRCT www.controlled-trials.com/mrct/), and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials. We will contact authors of the included studies to ask if they know of any other relevant studies. We will contact investigators/researchers, pharmaceutical companies, and international funding agencies interested in this field to identify any further studies. We will search the Internet using the Google scholar search engine (www.googlescholar.com) with selected terms from the above strategy, for any further unpublished or grey literature.

Data collection and analysis

Selection of studies

One of the authors (KR) will run the searches and collate the search results. Two of the review authors will independently assess the titles and abstracts of all the studies identified by the search for potential inclusion. We will independently consider the full records of all potentially-relevant studies for inclusion by applying the selection criteria outlined in the 'Criteria for considering studies for this review' section. We will resolve potential disagreements by discussion. If we cannot reach agreement, we will seek the opinion of a third review author for a final judgment.

We plan to include a PRISMA study flow diagram in the full review (Liberati 2009) to document the screening process, as recommended in Part 2, Section 11.2.1 of the *Cochrane Handbook* (Higgins 2011).

Data extraction and management

Two review authors will independently extract data from the studies, using a piloted data extraction form. Data extracted will include information about the year of study, study design, number of participants treated, participant demographic details, type of cancer, drug and dosing regimen, study design (placebo or active control) and methods, study duration and follow-up, outcome measures (measurement of pain, pain scale), withdrawals and adverse events. We will resolve potential disagreements by discussion. If there are studies for which only a subgroup of the participants meet the inclusion criteria for the current review, we will only extract data on this subgroup provided randomisation will not be broken. If there are any missing data, we will attempt to contact the authors of the original studies for clarification.

Assessment of risk of bias in included studies

Two of the authors will independently assess the risk of bias of each of the included studies by using the 'Risk of bias' assessment method outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For each study we will assess the risk of bias for the following domains:

1. Selection bias (random sequence generation, allocation concealment)
2. Performance bias (blinding of patients, blinding of treating personnel)
3. Detection bias (blinding of outcome assessment)
4. Attrition bias (incomplete outcome data)
5. Selective reporting (reporting bias due to selective outcome reporting)
6. Other sources of bias (bias due to problems not covered elsewhere).

Measures of treatment effect

For dichotomous outcomes between groups, we will estimate and compare the risk ratio (RR) using a 95% confidence interval (CI). For continuous outcomes between groups, we will measure arithmetic means and standard deviation (SD) and report the mean difference (MD) with 95% CI. When an outcome was derived with different instruments measuring the same construct, we will use standardized mean difference (SMD) with 95% CIs.

For unwanted effects, we will calculate the numbers needed to treat to harm (NNH) using dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CI). We will use the following terms to describe adverse outcomes in terms of harm or prevention of harm:

- When significantly fewer adverse outcomes occur with corticosteroids than with control (placebo or active) we will use the term 'number needed to treat to prevent one event' (NNTp).

- When significantly more adverse outcomes occur with corticosteroids compared with control (placebo or active) we will use the term 'number needed to harm or cause one event' (NNH).

Unit of analysis issues

We will only include studies in which randomisation is by the individual patient; this may include cross-over or n = 1 studies.

Dealing with missing data

In cases where data are missing, we will contact the authors to request the missing data. Intention-to-treat (ITT) analysis will be used. If there are missing participants or information, they will be assigned to a zero improvement category where possible. The method of assessing data processed from withdrawals will be ascertained where possible. Where there are substantial numbers

(> 10%) of participants missing from analyses, we will comment, and plan to perform sensitivity analyses.

Assessment of heterogeneity

There may be an effect of differences between patients, environment (inpatient vs. outpatient) and outcome measures. We will assess heterogeneity by using the I^2 statistic. We will consider I^2 values above 50% to represent substantial heterogeneity in line with Higgins 2011 and we will assess potential sources of heterogeneity through subgroup analyses.

Assessment of reporting biases

We will interpret the results of tests in the light of visual inspection of the funnel plot. If there is evidence of small study effects, we will consider publication bias as only one of a number of possible explanations (Higgins 2011).

Data synthesis

We will enter the data extracted from the included studies into Review Manager (RevMan 2012) which will be used for data synthesis. Where appropriate, we will pool data for each dichotomous outcome and calculate risk ratios with 95% confidence intervals (CI) using the fixed-effect model, together with numbers needed to treat to benefit (NNTs) with 95% CIs and, for adverse events, numbers needed to treat to harm (NNHs) with 95% CIs .

Subgroup analysis and investigation of heterogeneity

Different aspects of the trials are likely to contribute heterogeneity to the proposed main analyses. If there are sufficient data, we will therefore perform subgroup analyses based on: type of corticosteroid, doses, route of administration, types of cancer, type of pain (nociceptive, neuropathic, cancer-related, treatment-related), and length of the trials.

Sensitivity analysis

If sufficient data are available, we will examine the robustness of the meta-analyses by conducting sensitivity analyses using different components of the 'Risk of bias' assessment, particularly those relating to whether allocation concealment and patient/assessor blinding were adequate. We will conduct further sensitivity analyses to examine the impact of missing data on the results if a large proportion of the studies are at an 'unknown' or 'high risk' of attrition bias, and finally, sensitivity analyses will examine whether publication status and trial size influence the results.

Summary of findings table

A Summary of findings table will be included as outlined in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) (including a grade of the quality of evidence).

R E F E R E N C E S

Additional references

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Busillo 2013
Busillo JM, Cidlowski JA. The five Rs of glucocorticoid action during inflammation: ready, reinforce, repress, resolve, and restore. *Trends in Endocrinology and Metabolism* 2013;**24**(3):109–19.

Farr 1990
Farr WC. The use of corticosteroids for symptom management in terminally ill patients. *American Journal of Hospice and Palliative Care* 1990;**7**:41.

Foley 2011
Floey MK. How well is cancer pain treated?. *Palliative Medicine* 2011;**25**(5):398–401.

Gannon 2002
Gannon C, McNamara P. A retrospective observation of corticosteroid use at the end of life in a hospice. *Journal of Pain and Symptom Management* 2002;**24**(3):328–34.

Hanks 2009
Hanks G, Cherny N, Christakis N, Fallon M, Kaasa S, Portenoy R (Editors). *Oxford Textbook of Palliative Care*. 4th Edition. Oxford Press, 2009.

Hardy 2001
Hardy J, Rees E, Ling J, Stone P, Burman R, Feuer D, et al.A prospective survey of the use of dexamethasone on a palliative care unit. *Palliative Medicine* 2001;**15**:3–8.

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Higgins JPT, Altman DG (editors). Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. The Cochrane Collaboration, Updated March 2011.

Liberati 2009
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al.The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of Internal Medicine* 2009;**151**(4):W65–W94. [DOI: 10.7326/0003-4819-151-4-200908180-00136]

Paulsen 2013

Paulsen O, Aass N, Kaasa S, Dale O. Do corticosteroids provide analgesic effects in cancer patients? A systematic review. *Journal of Pain and Symptom Management* 2013;**46**: 96–105.

RevMan 2012

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Riechelmann 2007

Riechelmann RP, Krzyanowska MK, O'Carroll A, Zimmermann C. Symptom and medication profiles among cancer patients attending a palliative care clinic. *Supportive Care in Cancer* 2007;**15**(12):1407–12.

Van den Beuken-van Everdingen 2007

Van den Beuken-van Everdingen MHJ, De Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Annals of Oncology* 2007;**18**:1437–49.

Vyvey 2010

Vyvey M. Steroids as pain relief adjuvants. *Canadian Family Physician* 2010;**56**(12):1295–7.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Adrenal Cortex Hormones/
2. (corticoid* or corticosteroid* or glucocorticoid*).tw.
3. (adrenal adj2 hormone*).tw.
4. Betamethasone/
5. betamethasone.tw.
6. Fludrocortisone/
7. fludrocortisone.tw.
8. Cortisone/
9. (cortisone acetate or cortisone).tw.
10. deflazacort.tw.
11. Dexamethasone/
12. dexamethasone.tw.
13. Hydrocortisone/
14. hydrocortisone.tw.
15. Methylprednisolone/
16. methylprednisolone.tw.
17. Prednisolone/
18. prednisolone.tw.
19. Triamcinolone/
20. triamcinolone.tw.
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. exp Pain/
23. pain.tw.
24. Pain Measurement/
25. exp Analgesics/
26. exp Analgesia/
27. "analges*".tw.
28. (quality adj2 life).tw.
29. quality of life/
30. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. malignant.tw.
32. malignancy.tw.

33. "tumor*".tw.
34. "tumour*".tw.
35. "cancer*".tw.
36. "carcinoma*".tw.
37. exp Neoplasms/
38. 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 21 and 30 and 38
40. randomized controlled trial.pt.
41. controlled clinical trial.pt.
42. randomized.ab.
43. randomised.ab.
44. placebo.ab.
45. drug therapy.fs.
46. randomly.ab.
47. trial.ab.
48. groups.ab.
49. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
50. exp animals/ not humans.sh.
51. 49 not 50
52. 39 and 51

CONTRIBUTIONS OF AUTHORS

All authors initiated and designed the study and drafted the protocol. All authors will extract the data and conduct 'Risk of bias' assessment.

PG will supervise the statistical analysis, comment on and revise the review and will check the data extraction and arbitrate in the event of disagreement between other authors.

DECLARATIONS OF INTEREST

None known.