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[Intervention Protocol]

Intramuscular versus oral corticosteroids to reduce relapses following discharge from the emergency department for acute asthma

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To examine the effectiveness and safety of intramuscular (IM) versus oral corticosteroids in the treatment of acute asthma after discharge from a hospital emergency department (ED) or equivalent acute care setting.

BACKGROUND

Description of the condition

Asthma is a chronic inflammatory disease of the lungs that affects both children and adults. The worldwide prevalence of asthma is estimated to be 300 million people (Croisant 2014). In the United States, the prevalence of asthma has increased from 7.3% to 8.2% from 2001 to 2009 (Croisant 2014). Acute asthma, characterised by worsening cough, wheezing, shortness of breath, or chest tightness, is a common cause of presentation to the hospital emergency department (ED) or acute care centres. While most patients can be safely managed and discharged from the ED (Rowe 2009), approximately 10% to 18% (Emerman 1999; Emerman 2001; Rowe 2015; Topal 2014), and up to 31% (Ducharme 1993), of patients will relapse within the following four weeks. It is estimated that 27,000 adults will miss work due to asthma, while 36,000 children will miss school (Croisant 2014). Identifying effective treatment options to help patients manage their symptoms after discharge from acute care and reducing the risk of relapse are important management issues designed to improve health outcomes for patients with asthma.

Description of the intervention

Systemic corticosteroids are potent general anti-inflammatory agents for the treatment of asthma (Alangari 2014). When given in the ED, systemic corticosteroids can reduce the risk for hospitalisation and improve lung function in patients with acute asthma (Rowe 2001). A Cochrane Review reported significant decreases

in symptom scores following discharge from the ED with systemic corticosteroids, but heterogeneity in outcome reporting prohibited meaningful pooling (Rowe 2007). Treatment with systemic corticosteroids at discharge has also been shown to prevent relapse (Rowe 2007). Current guidelines recommend that discharge management of patients with all but the mildest presentations of acute asthma from the ED include systemic corticosteroids to prevent relapse (GINA 2016). While systemic corticosteroids can effectively prevent asthma relapses, the optimal route of administration is less clear.

How the intervention might work

At discharge from the ED or acute care setting, systemic corticosteroids maybe provided via intramuscular (IM) or oral routes of administration. A single dose of IM corticosteroids has long-acting pharmacokinetic properties, with fewer side effects associated with nausea/vomiting, but pain and swelling around the injection site can occur (Lahn 2004). Oral corticosteroids have short-acting properties, and patients are typically provided with a short-course of oral corticosteroids for five to seven days (GINA 2016). While no injection is needed, side effects associated with oral corticosteroids often include nausea and vomiting, and adherence/compliance with oral corticosteroid regimens is often suboptimal (Ducharme 2011). While it seems that IM corticosteroids could be alternative treatment option for patients with palatability or adherence/compliance issues with oral corticosteroids, it is unclear whether IM corticosteroids are as effective as oral corticosteroids in mitigating relapse.

Why it is important to do this review

While the effectiveness of systemic corticosteroids is known (Rowe 2007), and widely accepted by clinicians, whether patients benefit more from IM or oral corticosteroids is less clear. A previous umbrella review reported no differences in relapse events in adults after treatment with IM or oral corticosteroids for acute asthma (Krishnan 2009); however, this review was limited to English-language studies. Since Krishnan 2009 was published, no systematic reviews have been conducted that have used an extensive literature search to synthesize all of the available evidence from studies that have compared IM to oral corticosteroids.

OBJECTIVES

To examine the effectiveness and safety of intramuscular (IM) versus oral corticosteroids in the treatment of acute asthma after discharge from a hospital emergency department (ED) or equivalent acute care setting.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials. We will include studies reported in full text, those published as an abstract only, and unpublished data.

Types of participants

We will consider studies that include children or adults presenting to a hospital emergency department (ED) or other equivalent acute care setting with an uncomplicated exacerbation of asthma for inclusion in the overview. The asthma diagnosis must be made either using international/national clinical or spirometric criteria, or both. We will exclude studies that focus on corticosteroid treatment in hospitalised patients from this review. We will include studies that recruit patients who are discharged from the ED or acute care setting. Also, we will only include studies that assess patients who present to the ED or other urgent care/acute care setting with acute asthma. For studies that include patients with both chronic obstructive pulmonary disease (COPD) or asthma, we will only include these if the studies if they provide results of the asthma patients separately from the COPD patients, or if the total study population consisted of less than 20% COPD patients.

Types of interventions

We will include studies that compare a single dose of intramuscular (IM) corticosteroids prior to discharge versus a short course (one to 14 days) of oral corticosteroids. There will be no restrictions on the IM or oral corticosteroids used, or the dosage. We will not set any restrictions on the type of co-interventions patients may receive (e.g. beta$_2$-agonists, corticosteroids, anticholinergics, theophylline compounds, or antihistamines) during their stay in the ED or equivalent acute care setting.

Types of outcome measures

Primary outcomes

The primary dichotomous outcome will be relapse to additional care defined as an unscheduled visit to a health practitioner for worsening symptoms. We will accept the occurrence of relapse at any point as well as whether the occurrence of relapse was reported via self-report or verification via health records.

Secondary outcomes

1. The occurrence of serious adverse events (e.g. hospitalisation; intensive care unit (ICU) admission; death; relapse for visits other than worsening symptoms of asthma).
2. Adverse events (e.g. pain, cellulitis/abscess, gastrointestinal bleeding, vomiting, behavioural/mental health exacerbations, abdominal pain, insomnia, hyperphagia/weight gain, skin eruptions, etc.).
3. Continuous data from pulmonary function testing (including peak expiratory flow (PEF), percent change from baseline PEF, and percent predicted PEF, percent change of forced expiratory volume in one second (FEV_1), and percent predicted FEV_1).
4. Continuous data from symptom scores, measured via validated scales.
5. Duration of symptoms (days).
6. Descriptive analysis of compliance/adherence with oral corticosteroid treatment.
7. Quality of life measures measured via validated scale.
8. The number of $beta_2$-agonists doses taken by patients within a 24-hour period of discharge.

Reporting one or more of the outcomes listed here in the study is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Trials Register (CATR), which is maintained by the Information Specialist for the Cochrane Airways Group. The CATR contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (http://crso.cochrane.org/).
2. Weekly searches of MEDLINE Ovid SP.
3. Weekly searches of Embase Ovid SP.
4. Monthly searches of PsycINFO Ovid SP.
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature).
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine).
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the CATR are identified through search strategies based on the scope of the Cochrane Airways Group. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

In addition, an expert medical librarian (SC) will conduct a supplemental search of nine electronic databases including MEDLINE, Embase, EBM reviews, Global Health, International Pharmaceutical abstracts, CINAHL, ProQuest Dissertation Abstracts, SCOPUS, and LILACS using controlled vocabulary and key words.

We will also conduct an extensive search of the grey literature including: ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), Google Scholar, bibliographies of included studies and relevant reviews, SCOPUS forward search of a sentinel paper, and a handsearch of medical conference abstracts from 2008 to 2016 including the Canadian Journal of Emergency Medicine, Academic Emergency Medicine, and Annals of Emergency Medicine.

We will conduct all searches without any restrictions on language of publication.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for study information.

We will search for errata or retractions from included studies published in full text on PubMed and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (SWK and EC) will screen the titles and abstracts of the search results independently and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies and two review authors (SWK and EC) will independently screen them for inclusion and will record the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (CVR or BHR). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which we will have piloted on at least one included study in the review. Two review authors (SWK, EC) will independently extract the following study characteristics from the included studies.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of study authors.

Two review authors (SWK and EC) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if an included study did not report outcome data in a usable way. We will resolve disagreements by consensus or by involving a third review author (CVR or BHR). One review author (SWK) will transfer data into the Review Manager 5 (RevMan 5) file (RevMan 2014). We will double-check that SWK has entered data correctly by comparing the data presented in the systematic review with the study reports. A second review author (EC) will spot-check the study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (SWK and EC) will assess risk of bias independently for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving a third review author (CVR or BHR). We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will judge each potential source of bias as either high, low, or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a author, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as relative risk (RR) values and continuous data as mean difference (MD) or standardised mean difference (SMD) values. If we combine data from rating scales in a meta-analysis, we will ensure we enter them with a consistent direction of effect (e.g. lower scores always indicate improvement).

We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.

We will describe skewed data qualitatively (e.g. as medians and interquartile ranges for each group).

Where multiple study arms are reported in a single study, we will include only the relevant study arms. If we combine two comparisons (e.g. IM corticosteroids versus different regimens of oral corticosteroids) in the same meta-analysis, we will either combine the active study arms or halve the control group to avoid double-counting.

If a study reports outcomes at multiple time points, we will use the last time point measured.

We will conduct an 'as reported' and intention-to-treat (ITT) analysis of the primary outcome. We will assess the secondary outcomes using an 'as reported' analysis.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital rather than number of admissions per child).

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when we identify a study as an abstract only). Where this is not possible and we believe that the missing data may introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity we will report it and explore the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We will use a random-effects model and perform a sensitivity analysis with a fixed-effect model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes including: relapse, relapse within 10 days postdischarge, relapse after 10 days postdischarge, adverse events, peak expiratory flow, symptom scores, and beta$_2$-agonist use in a 24-hour period. We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and will use GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We will examine potential sources of heterogeneity in the following subgroup analyses.

1. Children (zero to 18 years of age) versus adults (18 years of age and older) to examine any potential age specific treatment effects of IM or oral corticosteroids.
2. Relapse occurring within 10 days and over 10 days postdischarge.
3. Low versus moderate versus high exacerbation severity based on the pulmonary function taken at the time of the patients presentation to the ED, prior to treatment with a bronchodilator;
4. Co-interventions received (inhaled corticosteroids versus inhaled corticosteroids/long-acting beta$_2$-agonists).

We will use the formal test for subgroup interactions in RevMan 5 (RevMan 2014). We will restrict subgroup analysis to relapse.

Sensitivity analysis

We plan to carry out the following sensitivity analyses, by removing the following types of studies from the primary outcome analyses.

1. Studies that we consider to be at high risk of bias based the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
2. Studies in which the duration of oral corticosteroid treatment was less than five days.

We will compare the results from a fixed-effect model with the random-effects model.

ACKNOWLEDGEMENTS

Chris Cates was the Editor for this protocol and commented critically on the protocol.

The Background and Methods sections of this protocol are based on a standard template used by the Cochrane Airways Group.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group's Specialised Register (CAGR)

Electronic searches: core databases

Database	Search frequency
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify studies for the CAGR

Condition search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15
17. exp Aspergillosis, Allergic Bronchopulmonary/
18. lung diseases, fungal/
19. aspergillosis/
20. 18 and 19
21. (bronchopulmonar$ adj3 aspergillosis).mp.
22. 17 or 20 or 21
23. 16 or 22
24. Lung Diseases, Obstructive/
25. exp Pulmonary Disease, Chronic Obstructive/
26. emphysema$.mp.
27. (chronic$ adj3 bronchiti$).mp.
28. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
29. COPD.mp.
30. COAD.mp.
31. COBD.mp.
32. AECB.mp.
33. or/24-32
34. exp Bronchiectasis/
35. bronchiect$.mp.
36. bronchoect$.mp.
37. kartagener$.mp.
38. (ciliary adj3 dyskinesia).mp.
39. (bronchial$ adj3 dilat$).mp.
40. or/34-39
41. exp Sleep Apnea Syndromes/
42. (sleep$ adj3 (apnea$ or apnoea$)).mp.
43. (hypopnoea$ or hypopnoea$).mp.
44. OSA.mp.
45. SHS.mp.
46. OSAHS.mp.
47. or/41-46
48. Lung Diseases, Interstitial/
49. Pulmonary Fibrosis/
50. Sarcoidosis, Pulmonary/
51. (interstitial$ adj3 (lung$ or disease$ or pneumon$)).mp.

52. ((pulmonary$ or lung$ or alveoli$) adj3 (fibros$ or fibrot$)).mp.
53. ((pulmonary$ or lung$) adj3 (sarcoid$ or granulom$)).mp.
54. or/48-53
55. 23 or 33 or 40 or 47 or 54

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify studies in other electronic databases

Appendix 2. Search strategy to identify relevant studies from the CAGR

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 prednis*
#6 methylprednis*
#7 dexamethasone
#8 cortisone
#9 hydrocortisone*
#10 medrol
#11 solumedrol
#12 solu-medrol
#13 betamethasone
#14 triamcinolone
#15 steroid* or corticosteroid* or glucocorticoid*
#16 MeSH DESCRIPTOR Dexamethasone
#17 MeSH DESCRIPTOR Prednisolone Explode All
#18 MeSH DESCRIPTOR Prednisone
#19 MeSH DESCRIPTOR Cortisone
#20 MeSH DESCRIPTOR Injections, Intramuscular
#21 intramuscular* OR intra* NEXT muscular*
#22 IM:ti,ab
#23 injection*
#24 #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
#25 #20 or #21 or #22 or #23
#26 #4 AND #24 AND #25

[Note: in search line #1, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, asthma]

CONTRIBUTIONS OF AUTHORS

Scott W Kirkland (SWK) contributed to the development of the protocol.

Elfriede Cross (EC) contributed to the development of the protocol.

Sandra Campbell (SC) edited the protocol.

Cristina Villa-Roel (CVR) edited the protocol.

Brian H Rowe (BHR) contributed to the development of the protocol.

DECLARATIONS OF INTEREST

SWK is supported by the Partnerships in Research Innovation in Health Services (PRIHS) Choosing Wisely Project Health. SWK has no known conflicts of interest.

EC is supported by the Department of Emergency Medicine, University of Alberta. EC has no known conflicts of interest.

SC has no known conflicts of interest.

CVR is supported by the Emergency Medicine Research Group (EMeRG). CVR has no known conflicts of interest.

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