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Corticosteroids for acute severe asthma in hospitalised patients (Review)

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TABLE OF CONTENTS

[Intervention Review]

Corticosteroids for acute severe asthma in hospitalised patients

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ABSTRACT

Background

Corticosteroids are currently used routinely in the management of acute severe asthma. The optimal dose and route of administration continues to be debated. Some investigators have reported a greater benefit of higher doses of corticosteroids in the management of severe asthma, while others have not.

Objectives

To determine whether higher doses of systemic corticosteroids (oral, intravenous or intramuscular) are more effective than lower doses in the management of patients with acute severe asthma requiring hospital admission.

Search methods

Randomised controlled trials were identified from the Cochrane Airways Group Asthma Register. In addition, primary authors and content experts were contacted to identify eligible studies. Bibliographies from included studies, known reviews and texts were also searched.

Selection criteria

Studies were selected for inclusion in the review if they met the following broad inclusion criteria: described as randomised controlled trials, included patients with acute severe asthma, compared different doses of corticosteroids (any route) in 2 or more treatment arms, and had a minimum period of follow up of 24 hours. Two reviewers independently assessed the studies for inclusion and disagreement was resolved by third party adjudication.

Data collection and analysis

Data were extracted independently by two reviewers if the authors were unable to verify the validity of information. Missing data were obtained from authors or calculated from other data presented in the paper. The data were analysed as weighted mean differences (WMD) for primary pulmonary function outcomes using a fixed effects model. For the purposes of the review, three broad categories of corticosteroid dose (equivalent dose of methylprednisolone in 24 hours) were defined in advance: low dose (< or = 80 mg), medium dose (> 80 mg and < or = 360 mg) and high dose (> 360 mg). There were thus 3 main comparison groups: low versus medium dose, medium versus high dose and low versus high dose.

Main results

Nine trials were included; a total of 344 adult patients have been studied (96 with low dose, 85 with medium dose and 163 with high dose corticosteroids). Only 6 trials provided sufficient data for the meta-analysis. There were no clinically or statistically significant differences detected in % predicted FEV1 among comparison groups after 24, 48 or 72 hours. At 48 hours, the weighted mean difference was -3.3% predicted (95% confidence interval -12.4 to + 5.8) for the low vs medium dose comparison, -1.9% predicted (95% CI -8.1 to + 4.3) for the

medium vs high dose comparison and + 0.5% predicted (95% CI - 7.8 to + 8.8) for the low vs high dose comparison. There appeared to be no significant differences in side effects or rates of respiratory failure among the varying doses of corticosteroids. A further search was conducted in September 2002. No new trials were identified.

Authors' conclusions

No differences were identified among the different doses of corticosteroids in acute asthma requiring hospital admission. Low dose corticosteroids (< or = 80 mg/day of methylprednisolone or < or = 400 mg/day of hydrocortisone) appear to be adequate in the initial management of these adult patients. Higher doses do not appear to offer a therapeutic advantage.

PLAIN LANGUAGE SUMMARY

Corticosteroids for acute severe asthma in hospitalised patients

In an asthma attack, the airways (passages to the lungs) narrow from muscle spasms and swelling (inflammation), which can cause breathing problems, wheezing and coughing. Attacks can be fatal. Drugs (by inhaler, taken by mouth, or through the veins) can be used to relieve the muscles. Steroids (corticosteroids) are anti-inflammatory drugs that can reduce the swelling. The review found that lower doses of corticosteroids work as well as higher doses to start with, when a person is hospitalised with an asthma attack.

BACKGROUND

Corticosteroids are currently used routinely in the management of acute severe asthma. The optimal dose and route of administration continues to be debated. Some investigators have reported a greater benefit of higher doses of corticosteroids in the management of severe asthma (Haskell 1983), while others have not (Bowler 1992). In general, studies which have examined the use and dosage of corticosteroids and other treatments in acute severe asthma have been small. This has often resulted in insufficient statistical power to detect a potentially clinically important difference between treatments (type II error) (Ward 1986).

While the benefit of corticosteroids is now widely accepted, there are a number of short term side effects that may occur in a dose dependent fashion. Studies which have examined acute psychiatric reactions have demonstrated a significant dose response relationship (BCDSP 1972). A similar relationship exists for steroid induced myopathy, usually with long term use (Bowyer 1985). However acute myopathy and rhabdomyolysis have also been associated with short term high dose corticosteroids. Fluid and electrolyte disturbance, hypertension, peptic ulcer disease and manifestation of latent diabetes may also be dependent on corticosteroid dosage. Moreover, differences in doses may be important from the perspective of treatment benefit and costs. Thus, determining the appropriate doses and route of delivery is an important issue in acute asthma care.

The mechanism of action of corticosteroids in asthma has been investigated most extensively in chronic and subacute asthma where inhaled corticosteroids have become the mainstay of modern asthma therapy (Barnes 1995a). Corticosteroids have been shown to improve asthma symptoms by reducing airway inflammation, airway reactivity and airway secretions and restoring the integrity of the airways (Barnes 1996). In contrast, research on the use and mechanisms of action of corticosteroids during an acute exacerbation of asthma has been limited. Objective improvements in airflow obstruction have usually not been demonstrated during the first 6 to 12 hours of treatment with corticosteroids in acute asthma (Stein 1990). The delayed onset of action is likely related to the way in which corticosteroids activate glucocorticoid receptors to directly or indirectly regulate transcription of certain target genes (Barnes 1998). Other aspects of steroid pharmacology might be important in the early phase of treatment including effects on the microvasculature with inhibition of plasma exudation and oedema formation in the airways (Persson 1986, McFadden 1992) and the reversal of beta-2 receptor subsensitivity (Svedmyr 1990).

Narrative reviews have previously examined the issue of corticosteroid dose in the management of acute asthma and have made broad recommendations, but have highlighted that clear dose response relationships have not been established (McFadden 1993, Engel 1991). A systematic review has also been conducted, this included both inpatient and outpatient studies and noted a trend toward improved outcome with high and moderate doses of corticosteroids which was not statistically significant, concluding that further research was needed to define the role of high dose regimens (Rowe 1992). Given the delayed onset of action of systemic corticosteroids in acute asthma and the different patterns of response to therapy in general in the emergency management of acute asthma (Strauss 1997), dose response characteristics may best be examined in the group of patients requiring hospitalisation and ongoing treatment.

OBJECTIVES

To determine whether higher doses of systemic corticosteroids (oral, intravenous or intramuscular) are more effective than lower doses in the management of patients with acute severe asthma requiring hospital admission.

Specifically this review examined three main comparisons:
(1) Low versus medium dose corticosteroids;
(2) Medium versus high dose corticosteroids;
(3) Low versus high dose corticosteroids.

METHODS

Criteria for considering studies for this review

Types of studies

Studies that were described as randomised controlled trials (RCT) were considered for inclusion in the review.

Types of participants

Adults (age 16 to 65) with acute severe asthma defined by history, doctor's diagnosis, response to initial treatment, spirometry or peak flow were considered. Only studies where patients were treated in an emergency or outpatient department and required hospital admission (but not mechanical ventilation) were included. Studies that included patients on pre-existing oral or inhaled corticosteroids were included and sub-group comparisons based on prior corticosteroid use were planned.

Types of interventions

Studies reporting results of patients randomised to receive oral, intravenous or intramuscular corticosteroids (including methylprednisolone, hydrocortisone, dexamethasone, prednisone, prednisolone, betamethasone or triamcinolone) at different doses were included.

To standardise the comparisons, all corticosteroid doses were converted to methylprednisolone equivalents based on known potencies (Zimet, 1986). Comparisons were made between the following groups defined in methylprednisolone (MP) equivalent doses (total daily dose). Hydrocortisone (HC) equivalent doses and prednisolone (P) equivalent doses are also provided (total daily dose) respectively below:

Low dose: less than or equal to 80 mg(MP) or 400 mg(HC) or 100 mg (P).

Medium dose: more than 80 mg(MP) or 400 mg(HC) or 100 mg (P) and less than or equal to 360 mg(MP) or 1800 mg(HC) or 450 mg (P).

High dose: more than 360 mg(MP) or 1800 mg(HC) or 450 mg (P).

These cut-points were chosen following review of the literature and reflect what previous researchers and authors had classified as low, medium or high dose. The reviewers also felt that these definitions were clinically appropriate. Nonetheless the terms low, medium and high are applied as descriptive labels only and do not represent a value judgement about the specific quantitative levels.

There were 3 main comparison categories, as follows: Low versus medium dose (L vs M); medium versus high dose (M vs H) and low versus high dose (L vs H).

Data on co-interventions was collected including information regarding additional therapy such as beta-agonists, anticholinergics, theophylline compounds, antibiotics, oxygen, etc.

Types of outcome measures

Primary outcomes

The primary outcome was continuous data from pulmonary function testing (peak expiratory flow rates (PEFR), forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and % predicted PEFR, FEV1 and FVC). To be included studies were required to have a minimum period of follow up of 24 hours.

Secondary outcomes

1. Clinical outcomes such as length of stay, need for intubation, non-invasive ventilation or death.
2. Symptom scores e.g. dyspnoea
3. Physiological measures such as vital signs, oxygen saturation or arterial blood gases.
4. Side effects of corticosteroid treatment (e.g. acute psychoses, myopathy, fluid retention, hyperglycaemia.)

Search methods for identification of studies

Electronic searches

The Cochrane Airways Review Group register was searched. The current overview includes register updates to January 1998. The search of this register was completed using the following terms:

Acute OR status OR exacerbation* AND Infusion OR multi-dose OR bolus OR intravenous OR administration OR dosage OR oral OR PO AND Prednisolone OR Prednisone OR methyl-prednisolone OR MP OR methylprednisolone OR corticosteroid OR hydrocortisone OR glucocorticoids OR solucortef OR solu-cortef OR solumedrol OR dexamethasone OR triamcinolone OR betamethasone.

Searching other resources

Current Contents (mid 1997 to November 1998) was also searched using the key words asthma and acute OR status OR exacerbation and corticosteroids (including the above list of alternative terms for corticosteroids). Authors of identified studies were contacted to determine whether they were aware of any related unpublished or published studies or work in progress. The bibliographies of identified studies and narrative reviews were searched for additional citations. Scientific advisors of the various pharmaceutical companies that manufacture corticosteroids were contacted for any unpublished or interim results on corticosteroid dosing research. An advanced search of the Cochrane Controlled Trials Register (CCTR) was conducted using the above search strategy. Finally, contact was made with colleagues, collaborators and other trialists working in the field of asthma to identify other potentially relevant studies.

Data collection and analysis

Selection of studies

Two independent reviewers (RM & MA) searched the titles and abstracts obtained from the initial computerised search for potentially relevant trials for full review. Initially studies were categorised into the following groups:
(1) Include: RCT meeting the described inclusion criteria and those where it was impossible to tell from the abstract, title, MESH headings or key words
(2) Exclude: Non RCT or paediatric age range, or treatment as an outpatient or for less than 24 hours.

The full texts of those studies in category one were then examined independently by both reviewers to determine whether the study met the inclusion criteria. Agreement was measured using simple agreement and kappa statistics. Disagreement was resolved by adjudication by a third reviewer (DR) or consensus.

Data extraction and management

Data was extracted by one of the reviewers (RM) and entered in the Cochrane Collaboration software (Review Manager). Authors of included studies were asked to confirm the data extracted and provide more data on individual patients if required. For some studies original data were not presented and results were extracted from graphs. A second reviewer (DR) also extracted data for the main study results.

Assessment of risk of bias in included studies

Two independent reviewers (RM & MA) assessed the quality of included studies as follows:
(1) Using the Cochrane approach to concealment of allocation, trials were scored and entered according to the grading listed below:
Grade A: Adequate concealment.
Grade B: Unclear concealment.
Grade C: Obviously not adequate concealment.

(2) Each study was assessed for validity using a 0-5 scale described by Jadad 1996:
(a) Was the study described as randomised? (1=Yes 0=No).
(b) Was the study described as being double blind? (1=Yes 0=No).
(c) Was there a description of withdrawals and dropouts? (1=Yes 0=No).
(d) Was the method of randomisation well described and appropriate? (1=Yes 0=No).
(e) Was the method of double blinding well described and appropriate? (1=Yes 0=No).
(f) Deduct one point if methods for randomisation or blinding were inappropriate.

Inter-reviewer reliability was measured using simple agreement, kappa and weighted kappa statistics. Disagreement was resolved by adjudication by a third reviewer (DR). The authors of included studies were asked to verify the assessments of study methodology.

Assessment of heterogeneity

Homogeneity of effect sizes among studies being pooled was tested using the Review manager with $P<0.05$ as the level for significance.

Data synthesis

Outcomes from included trials were combined using the Review Manager. Where appropriate, data were entered as negative values to conform to the Cochrane convention whereby effects that favour the treatment under review move to the left. For continuous outcomes the weighted mean difference (WMD) was used to estimate the individual and pooled effect sizes and 95% confidence intervals (95% CI). For dichotomous outcomes the Peto fixed effect model was used to estimate the individual and pooled odds ratio (OR) and 95% CI.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were planned:

(1) Dosage: Subgroup analysis was performed comparing the different dosing schedules based on the methylprednisolone equivalent scale described previously.
(2) Route: Intravenous therapy (any dose) was compared with oral therapy (any dose).
(3) Previous oral or inhaled corticosteroid use.
(4) Severity of asthma. Excluding studies with less severe subjects based on the baseline FEV1 or peak expiratory flow rate on admission. (Severe or life threatening asthma will be defined as peak expiratory flow less than 30% predicted or less than 100 l/min or FEV1 less than 40% predicted or less than 1 litre.)

Sensitivity analysis

Sensitivity analyses were planned based on the following characteristics:

(1) Inclusion criteria of patients in individual studies: Excluding studies which have not supported the diagnosis of asthma by patients previously or subsequently showing short term variability of at least 15% in forced expiratory volume in one second (FEV1) or the exclusion of patients with a greater than 15 pack year history of smoking or history of chronic bronchitis or emphysema.
(2) Methodological quality: Based on the Jadad methodological quality scale, studies with scores of 3 or less were excluded.
(3) Methods of meta-analysis: Random and fixed effects models were compared.

RESULTS

Description of studies

Results of the search

There were 719 abstracts identified by the computerised ARG search and 21 of these were selected for full text review (Kappa 0.77; substantial agreement). Following the full text review, 9 studies were selected for inclusion in the review (Kappa 0.9; almost perfect agreement). Twelve studies were excluded for the following reasons: Not randomised (2), not primary research paper (2), equivalent doses of corticosteroids used (4), single dose comparison only (2), intervention period too short (1) and duplicate citation (1). Contact with the primary authors, experts in the field and pharmaceutical companies and bibliographic searches did not reveal any further relevant studies that were not previously identified by the original search.

Included studies

POPULATIONS:

Most of the included studies applied the American Thoracic Society criteria to define asthma (ATS 1962) [Tanaka 1982; Haskell 1983; Pedersen 1987; Engel 1990; Morell 1992]. Two of the studies specified that to be included in the study subjects had to demonstrate a 15% short term variability in FEV1 on previous or subsequent review visits [Bowler 1992; Marquette 1995]. One of the studies included only patients with demonstrable reversibility of airflow as measured by peak flow or spirometry at previous admissions [Ratto 1988]. Only one of the studies did not specify adequate diagnostic criteria for asthma, however they did not include any subjects over the age of 50 years [Harrison 1986].

All studies included adult patients with acute severe asthma who were admitted to hospital for ongoing management. None of the studies included patients who required ventilation or intensive care on admission. Only 4 of the studies clearly specified objective severity criteria for inclusion in the study [Haskell 1983; Harrison 1986; Ratto 1988; Marquette 1995]. All the studies described similar co-interventions including regular inhaled beta-agonists, oxygen, and intravenous or oral theophylline. In one of the studies subcutaneous adrenaline was used during the first hour of treatment [Morell 1992]. Two of the studies included regular inhaled corticosteroids in the treatment [Pedersen 1987; Bowler 1992] but the remainder of the studies did not comment on the use of inhaled corticosteroids.

Only one of the studies specifically excluded patients who had taken corticosteroids in the last 7 days [Haskell 1983]. Two of the studies excluded patients taking regular oral corticosteroids if they were receiving greater than 10 mg/day [Engel 1990; Bowler 1992]. Two of the studies included only a small numbers of subjects on oral corticosteroids but did not comment on the dose [Tanaka 1982; Marquette 1995]. One of the studies included a total of 8 subjects who were taking more than 10 mg/ day (but not more than 40 mg/day) of prednisolone on a regular basis, however they did not provide data on the total number of patients on any dose of oral corticosteroid [Ratto 1988]. Another of the studies did not specify the dose of regular oral corticosteroid used by the relevant participants but included relatively large numbers of subjects receiving such treatment [Morell 1992]. Regular corticosteroid use was not mentioned in one of the studies [Pedersen 1987]. One of the studies included subjects who had received intravenous or intramuscular corticosteroids prior to inclusion in the study [Harrison 1986].

INTERVENTIONS:
Four of the studies were designed specifically to compare different doses of corticosteroids (same type & route) [Tanaka 1982; Haskell 1983; Bowler 1992; Marquette 1995]. Two of the studies compared intravenous corticosteroids with oral corticosteroids (different doses) [Harrison 1986; Ratto 1988]. Two of the studies were designed to compare pulse intravenous methylprednisolone therapy with regular corticosteroids, but provided potentially relevant data for the first few days of treatment [Pedersen 1987; Engel 1990]. One of the studies, in addition to comparing 2 different doses of corticosteroid had a placebo arm [Morell 1992]. Two studies compared 3 different corticosteroid doses in 3 arms [Haskell 1983; Bowler 1992]. Six of the studies compared different doses of methylprednisolone [Tanaka 1982; Haskell 1983; Pedersen 1987; Ratto 1988; Morell 1992; Marquette 1995]. One of the studies used methylprednisolone and prednisolone [Engel 1990], while

the remainder used hydrocortisone and/or prednisolone [Harrison 1986; Bowler 1992].

OUTCOMES:
Most studies reported data on PEFR or FEV1 and these data form the basis for the quantitative analysis in the review. FVC could not be included as an outcome due to limited reporting of this variable in the primary studies. Three studies did not provide sufficient data to be included in the quantitative analysis and the primary authors have not been able to provide further details as yet [Tanaka 1982; Morell 1992; Pedersen 1987]. The results for pulmonary function data are presented as a percentage of predicted and where specified in the primary studies the post bronchodilator values have been used. For several studies some data were extrapolated from graphs. Authors have been asked to confirm data extraction however none have provided this information as yet. Contact has been established with all but 1 author [Haskell 1983]. For the main results data was extracted by 2 reviewers (RM & DR) and the values did not differ by more than 1% predicted FEV1 or PEFR for means or standard errors for any of the values. One of the studies measured pulmonary function at 44 hours rather than 48 hours and this data has been included for the time period 48 hours [Marquette 1995].

DESIGN:
Most of the studies provided some information on losses to follow up but none of them provided an intention to treat analysis. All were randomised controlled trials.

Excluded studies

See Characteristics of excluded studies.

Risk of bias in included studies

The methodological quality of the studies was generally high. The results for the initial quality assessments are listed below.

The Jadad quality scores were as follows:
4 points: [Harrison 1986; Haskell 1983; Marquette 1995; Bowler 1992].
3 points: [Engel 1990; Pedersen 1987; Morell 1992]
2 points: [Tanaka 1982]
1 point: [Ratto 1988]

All the studies [except Ratto 1988] were described as double blind, however only 4 of them adequately documented the method of blinding [Marquette 1995; Bowler 1992; Harrison 1986; Engel 1990]. All the studies were described as randomised but only 2 provided an adequate description of the method [Haskell 1983; Morell 1992]. The method of randomisation was inadequate in 1 study [Ratto 1988]. Three papers did not provide adequate details on withdrawals and dropouts [Engel 1990; Morell 1992; Tanaka 1982].

Only 1 study reported adequate allocation concealment [Marquette 1995]. In 1 study the allocation concealment was inadequate [Ratto 1988] & in the remainder concealment was unclear.

Following contact with authors the Jadad scores were changed for 2 of the studies. In one study the method of randomisation was by random number table and the score was increased to 5 [Harrison 1986]. In another study the method of randomisation was computer generated [Morell 1992] and the score became 4. Further information regarding allocation concealment was also obtained and found to be adequate in one study [Bowler 1992] and inadequate in another [Morell 1992].

The level of agreement between the 2 reviewers undertaking the quality assessment was good. Kappa statistics for each of the components are presented below:

COCHRANE SCORE:
Allocation concealment kappa = 1 (perfect agreement)

JADAD SCALE:
Study described as randomised (k =1; perfect agreement)
Methods or randomisation (k = 0.61; good agreement)
Study described as double-blind (k = 1; perfect agreement)
Methods of blinding (k = 1; perfect agreement)
Withdrawals & drop outs (k= 0.77; good agreement)
Overall Jadad scale (Kw = 0.92; very good agreement)

Effects of interventions

PULMONARY FUNCTION

There were no clinically important or statistically significant differences between varying doses of corticosteroids (L vs M, M vs H and L vs H). The results for FEV1 at 24 and 48 hours for each comparison group are presented below as the WMD with 95% CI using the fixed effects model.
24 hours:
L vs M: + 0.1% predicted (- 11.4 to + 11.7)
M vs H: - 0.9 % predicted (- 8.4 to + 6.7)
L vs H: + 5.9 % predicted (- 1.4 to + 13.2)
48 hours
L vs M: -3.3 % predicted (-12.4 to + 5.8)
M vs H: -1.9 % predicted (-8.1 to + 4.3)
L vs H: + 0.5 % predicted (-7.8 to + 8.8)

Only 2 studies included FEV1 data for 72 hours [Haskell 1983, Ratto 1988], for the M vs H comparison the pooled WMD was 3.8 % predicted (- 14.7 to + 7.0).

The pooled WMDs for PEFR at 48 hours and 72 hours for the comparison between medium and high doses were - 2.9 (-16.2 to + 10.3), 2.7 % predicted (-16.3 to + 21.7), respectively. Several papers did not measure PEFR [Haskell 1983; Marquette 1995], and it was not possible to perform quantitative analysis for other time points or comparison categories.

It should be noted that for one of the studies [Ratto 1988] the standard deviations for PEFR and FEV1 data at 72 hours were very wide. This has not been explained in the original paper. The data has been taken from a graph and rechecked several times. We have been unable to confirm the data extraction with the authors.

7-14 days
There was insufficient data for this analysis. One study included FEV1 and PEFR data up to day 10 but did not include standard deviations in the report [Tanaka 1982]. Another study followed patients post discharge with serial PEFR measures up to 12 days but the drop out rate was high at this time point [Bowler 1992].

CLINICAL OUTCOMES

Length of stay

Only 2 studies reported length of stay [Ratto 1988; Marquette 1995], for the comparison L or M vs H there was no statistically significant difference in length of stay. The pooled WMD was 0.36 (-0.17 to + 0.89), the confidence intervals correspond to 4 hours in favour of the higher dose or 21 hours in favour of the lower dose. The average length of stay was very different between these two studies and this may reflect institutional differences.

Respiratory failure

Four studies did not specifically comment on respiratory failure [Tanaka 1982; Pedersen 1987; Engel 1990; Morell 1992]. Three studies reported no episodes of respiratory failure in any of the treatment groups [Haskell 1983; Harrison 1986; Marquette 1995]. In one study a patient in the medium dose group required ICU and was excluded from the analysis [Bowler 1992]. For the M vs H comparison there was no statistically significant difference between treatment groups, however the confidence intervals are wide and incorporate potentially clinically relevant differences in favour of either dose.

Deaths

None of the studies reported any deaths.

Symptom scores

Only one of the studies presented data on symptom scores [Bowler 1992]. They used a visual analogue scale (100 mm = no symptoms, 0 mm = maximum symptoms) to assess dyspnoea and found no significant differences between the groups at 24 hours or on day 12.

Vital signs and arterial blood gases

Although many of the studies reported vital signs or arterial blood gases in the baseline data few presented follow up data. One study reported the respiratory rate at 24 hours and found no significant difference between the low and high dose group [Marquette 1995]. Another study reported that there were no significant differences in the changes in PaO2 and PaCO2 at 6 or 48 hours between the high and low dose groups, but did not provide sufficient data for this to be included in the analysis [Morell 1992].

SIDE EFFECTS

There was no consistent reporting of side effects and quantitative analysis could not be performed. Four studies made no specific comment on side effects [Tanaka 1982; Haskell 1983; Harrison 1986; Bowler 1992]. Three studies stated that there were no serious side effects reported [Pedersen 1987; Ratto 1988; Engel 1990]. One study reported that one of the patients in the lower dose group (840 mg methylprednisolone in 24 hours) developed a bleeding duodenal ulcer and another patient in the same group developed a transient sinus tachycardia [Morell 1992]. Another study reported that one patient in the low dose group, with a history of psychiatric illness, developed an acute delirium, however neuroleptic medication had been inadvertently stopped on admission [Marquette 1995]. Despite limited data, in general, the use of varying doses of corticosteroids in acute asthma appear to be well tolerated.

Hyperglycaemia

One study reported that a patient in the high dose group, with known glucose intolerance developed severe hyperglycemia requiring prolonged insulin treatment [Marquette 1995]. Five studies reported that there were no significant differences found between high and low dose groups in terms of blood glucose levels, however there was insufficient data provided for a quantitative analysis [Haskell 1983; Pedersen 1987; Ratto 1988; Engel 1990; Marquette 1995].

HETEROGENEITY

Using a cut off level of significance of P<0.05 no statistical heterogeneity was detected for any of the outcomes. This test is considered weak when the number of studies and total information in the review is small (Hardy 1998). Nonetheless, visual inspection of the analyses shows considerable overlap of 95% CIs and all CIs of individual studies cross the pooled WMD line.

SUBGROUP ANALYSES

A further analysis was conducted on the studies that used very low doses of corticosteroids (200 mg hydrocortisone or 40 mg methylprednisolone equivalent) compared with high dose. Data for this analysis was limited to 24 hours (FEV1) and included 2 studies only. The pooled WMD was + 7.2 % predicted (-2.3 to 16.7) in favour of very low dose using the fixed effects model. A subgroup analysis could not be performed on those subjects who were receiving prior oral or inhaled corticosteroids due to insufficient data (refer to included studies section).
For the comparison oral vs intravenous (any dose) there were no statistically significant differences in FEV1 at 24 hours. The pooled WMD was 7.5 % predicted (-0.3 to + 15.2) in favour of oral therapy. There are only 2 studies in this comparison and one of these was rated as methodologically poor [Ratto 1988] and therefore this analysis should be interpreted with caution. The study by Harrison was not included because some patients in both groups received initial parenteral corticosteroids.

A sub group analysis was performed based on the severity of asthma however the proposed severity criteria could not be applied due to insufficient data. This analysis included 2 studies that only included subjects with an initial post bronchodilator FEV1 of 50% or less and a subgroup of patients from another study [Bowler 1992] who had an initial post bronchodilator FEV1 of 30% or less. For the L vs H comparison at 48 hours the pooled WMD (FEV1) was +2.3 % predicted (-6.6 to + 11.2) in favour of low dose.

SENSITIVITY ANALYSIS

Most of the studies applied appropriate diagnostic criteria for asthma and therefore it was not necessary to perform a sensitivity analysis based on this trial characteristic (Refer to table of included studies). A sensitivity analysis was performed based on methodological quality using both the Jadad scale (excluding studies that scored less than 4) and the Cochrane score for allocation concealment. This did not alter the results significantly in any of the main comparison categories. In addition using different methods for the meta-analysis did not alter the results significantly. For each of the 3 main comparison categories there were no statistically or clinically significant differences between high and low dose treatment groups using either fixed or random effects models.

DISCUSSION

GENERALISABILITY

Patients

The studies included in the review did not include patients presenting with respiratory failure. Although some of the studies included some subjects on regular oral corticosteroids the total number was small and sub-group analysis was not possible. The findings may therefore, not be generalisable to patients on regular oral corticosteroids or those presenting in ventilatory failure.

In chronic asthma, some patients have been reported to require relatively high doses of oral maintenance corticosteroids and others are classified as steroid resistant (Barnes 1995b). Consequently, these results may not apply to this small subset of patients.

Corticosteroid type

Methylprednisolone was the main corticosteroid used in the studies in the review. Some studies used hydrocortisone or prednisolone (See table of included studies). There have been few studies directly comparing the efficacy of different corticosteroids in acute asthma (Sue 1986 (ii); Hall 1995). While the relative anti-inflammatory potencies of different corticosteroids are well established, different potencies for lymphocyte suppression have been shown in in-vitro studies (Langhoff 1983). While this theoretical concern exists, applying these relative potencies to convert those studies using hydrocortisone or prednisolone to methylprednisolone did not significantly alter the results.

Setting

These results are applicable to the admitted severe asthmatic. Although the results may apply to asthmatics not requiring hospitalisation, dose responses should be assessed, where possible, by other reviews including patients treated on an outpatient basis.

SIDE EFFECTS

There was insufficient data to determine trends in relation to dose and the risk of serious but rare side effects. Previous narrative reviews have suggested that total steroid dose may be a risk factor in peptic ulcer disease and acute myopathy (Pecora 1996; Shee 1990) however, very large numbers of participants would be required to detect differences in these outcomes.

STRENGTH OF EVIDENCE

The results are consistent across each of the comparison groups and indicate that methylprednisolone doses above 60 to 80 mg per day provide no added benefit for lung function response in acute asthma. Furthermore, for each of the comparison categories the 95% CIs at 24 and 48 hours encompass values of limited clinical significance. For example using the fixed effects model for the L vs H comparison at 48 hours the maximum potential mean improvement in % predicted FEV1 was 8% in favour of the high dose group or 9% in favour of the low dose group. In most of the original studies a clinically significant difference was defined as a difference of 0.5 litre or 20% predicted FEV1.

METHODOLOGICAL LIMITATIONS

Design of studies:

The majority of included studies were constructed to assess whether different doses of corticosteroids were equivalent in acute asthma. However, the lack of difference does not guarantee equivalence and the finding of equivalence does not infer that both treatments are effective. Small studies failing to find significance between treatments are under-powered to detect differences and severely underpowered to demonstrate equivalence. This systematic review pools similar studies to address this issue. While the issue of efficacy is not addressed, corticosteroids clearly have an important role in the management of asthma. For example, a recent Cochrane review has shown that corticosteroids reduce the risk of relapse in patients presenting to the emergency department with acute asthma (Rowe 1998).

Missing data:

The exclusion of the three studies that did not provide sufficient data for the quantitative analysis is unlikely to alter the findings of the review given that none of them reported significant differences in outcome for varying corticosteroid doses [Pedersen 1987; Tanaka 1982; Morell 1992].

Size of review

The number of studies included in the meta-analysis for each comparison is small. Guidelines on how much information a meta-analysis should include to be reliable are currently lacking. (Pogue 1998) Some authors have suggested that the role of the small meta-analysis may predominantly be to summarise available information and generate hypotheses for further research. (Flather 1997)

Publication bias

Given that most of the published studies reported no difference between varying doses of corticosteroids publication bias did not appear to be an important factor in this review.

AUTHORS' CONCLUSIONS

Implications for practice

1. Varying doses of corticosteroids used in the treatment of admitted patients with acute asthma appear to result in similar outcomes when pulmonary function data are examined.
2. Doses of 60 to 80 mg per day of methylprednisolone or 300 mg to 400 mg per day of hydrocortisone appear to be sufficient in the initial management of adults with acute asthma requiring hospital admission. Higher doses do not appear to offer an obvious therapeutic advantage.
3. The results appear to be relevant for asthmatics with severe attacks however the applicability to patients requiring ventilatory support could not be assessed due to the exclusion of such patients from the studies in the review.
4. Due to the small number of patients on regular oral corticosteroids in the included studies, clear inferences about the relevance of the findings to this sub-group of patients could not be made.

Implications for research

1. Studies involving children were not included in the review and a separate review is recommended.
2. Further studies that include patients requiring intensive care and or ventilatory support might be useful to clarify the risk-benefit of different doses of corticosteroids in this sub group. Given the increased risk of acute myopathy in these patients it would be important to determine whether higher doses contribute to this risk. Acute myopathy has not been reported in patients receiving

daily doses of corticosteroids of the order used in the low dose groups in the review (Shee 1990), however this may simply be a reflection of historical prescribing practices.
3. Only a small sub group analysis was possible based on very low doses (200 mg per day of hydrocortisone or 40 mg per day of methylprednisolone) but the results suggest that even these doses may be sufficient in the management of acute asthma. However, many clinicians may view the difference between 40 mg of methylprednisolone and 60 to 80 mg to be of limited clinical relevance and not worthy of further research.
4. Future research should consider collecting clinical outcomes such as duration of symptoms, relapse or need for additional treatment and symptom scores in a standardised fashion.

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REFERENCES

References to studies included in this review

Bowler 1992 *{published data only}*

Bowler SD, Mitchell CA, Armstrong JG. Corticosteroids in acute severe asthma: effectiveness of low doses. *Thorax* 1992;**47**:584-7.

Engel 1990 *{published data only}*

Engel T, Dirksen A, Frolund L, Heinig JH, Gerner Svendsen U, et al. Methylprednisolone pulse therapy in acute severe asthma. *Allergy* 1990;**45**:224-30.

Harrison 1986 *{published data only}*

Harrison BDW, Hart GJ, Ali NJ, Stokes TC, Vaughan DA, Robinson AA. Need for intravenous hydrocortisone in addition to oral prednisolone in patients admitted to hospital with severe asthma without ventilatory failure. *Lancet* 1986;**1**:181-4.

Haskell 1983 *{published data only}*

Haskell RJ, Wong BM, Hansen JE. A double-blind, randomised clinical trial of methylprednisolone in status asthmaticus. *Archives of Internal Medicine* 1983;**143**:1324-7.

Marquette 1995 *{published data only}*

Marquette CH, Stach B, Cardot E, Bervar JF, Saulnier F, Lafitte JJ, et al. High dose and low dose systemic corticosteroids are equally efficient in acute severe asthma. *European Respiratory Journal* 1995;**8**:22-7.

Morell 1992 *{published data only}*

Morell F, Orriols R, de Gracia J, Curull V, Pujol A. Controlled trial of intravenous corticosteroids in severe acute asthma. *Thorax* 1992;**47**:588-91.

Pedersen 1987 *{published data only}*

Pedersen BK, Laursen LC, Lervang HH, Stjernebjerg T, Weeke B. Methylprednisolone pulse therapy in severe acute asthma. *Allergy* 1987;**42**:154-7.

Ratto 1988 *{published data only}*

Ratto D, Alfaro C, Sipsey J, Glovsky MM, Sharma OP. Are intravenous corticosteroids required in status asthmaticus?. *Journal of the American Medical Association* 1988;**260**:527-9.

Tanaka 1982 *{published data only}*

Tanaka RM, Santiago SM, Kuhn GJ, Williams RE, Klaustermeyer WB. Intravenous methylprednisolone in adults in status asthmaticus: comparison of two dosages. *Chest* 1982;**82**:438-40.

References to studies excluded from this review

Britton 1976 *{published data only}*

Britton MG, Collins JV, Brown D, Fairhurst NPA, Lambert RG. High-dose corticosteroids in severe acute asthma. *British Medical Journal* 1976;**2**:73-4.

Chapela 1995 *{published data only}*

Chapela R. Comparative study of the effectiveness of 2 oral corticoids in the control of severe crisis of bronchial asthma: deflazacort and prednisone. Article in Spanish [Estudio comparativo de la eficacia de dos corticoides orales en el control de la crisis grave de asma bronquial: deflazacort y prednisona]. *Revista Alergia Mexico* 1995;**42**:64-68.

Emerman 1995 *{published data only}*

Emerman CL, Cydulka RK, A randomised comparison of 100mg vs 500mg dose of methylprednisolone in the treatment of acute asthma. A randomised comparison of 100mg vs 500mg dose of methylprednisolone in the treatment of acute asthma. *Chest* 1995;**107**:1559-63.

Fanta 1983 *{published data only}*

Fanta CH, Rossing TH, Mcfadden ER jr. Glucocorticoids in acute asthma: a critical controlled trial. *American Journal of Medicine* 1983;**74**:845-51.

Hall 1995 *{published data only}*

Hall CM, Louw SJ, Joubert G. Relative efficacy of hydrocortisone and methylprednisolone in acute severe asthma. *South African Medical Journal* 1995;**85**:1153-6.

Loren 1980 *{published data only}*

Loren ML, Chai H, Leung P, Rohr C, Brenner AM. Corticosteroids in the treatment of acute exacerbations of asthma. *Annals of Allergy* 1980;**45**:67-71.

McFadden 1976 *{published data only}*

McFadden ER, Kiser R, deGroot WJ, Holmes B, Kiker R, Viser G. A controlled study of the effects of single doses of hydrocortisone on the resolution of acute attacks of asthma. *American Journal of Medicine* 1976;**60**:52-9.

Prazakova 1988 *{published data only}*

Prazakova J, Vondra V, Tomiska F. Hydrocortisone in the treatment of status asthmaticus - comparison of the effectiveness of major and minor doses. *Casopis Lekaru Ceskych* 1988;**127**(19):593-598.

Raimondi 1986 *{published data only}*

Raimondi AC, Figueroa-Casas JC, Roncoroni AJ. Comparison between high and moderate doses of hydrocortisone in the treatment of status asthmaticus. *Chest* 1986;**89**:832-5.

Sue 1986 *{published data only}*

Sue MA, Kwong FK, Klaustermyer WB. A comparison of intravenous hydrocortisone, methylprednisolone and dexamethasone in acute bronchial asthma. *Annals of Allergy* 1986;**56**:406-9.

Webb 1986 *{published data only}*

Webb JR. Dose response of patients to oral corticosteroid treatment during exacerbations of asthma. *British Medical Journal* 1986;**292**:1045-7.

Additional references

ATS 1962

American Thoracic Society. Definitions and classifications of chronic bronchitis, asthma and pulmonary emphysema.. *American Review in Respiratory Disease* 1962;**85**:762-8.

Barnes 1995a

Barnes PJ. Drug Therapy: Inhaled Glucocorticoids for asthma. *The New England Journal of Medicine* 1995;**332**(13):868-75.

Barnes 1995b

Barnes PJ, Adcock IM. Steroid resistance in asthma. *Quarterly Journal of Medicine* 1995;**88**:455-68.

Barnes 1996

Barnes PJ. Mechanisms of action of glucocorticoids in asthma. *American Journal of Respiratory and Critical Care Medicine* 1996;**154**:S21-27.

Barnes 1998

Barnes PJ, Pedersen S, & Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *American Journal of Respiratory and Critical Care Medicine* 1998;**157**:S1-53.

BCDSP 1972

Boston Collaborative Drug Surveillance Program. Acute adverse reactions to prednisone in relation to dosage. *Clinical Pharmacology and Therapeutics* 1972;**13**:694-8.

Bowyer 1985

Bowyer SL, LaMothe MP, Hollister JR. Steroid myopathy: Incidence and detection in a population with asthma. *Journal of Allergy and Clinical Immunology* 1985;**76**:234-7.

Engel 1991

Engel T, Heinig JH. Glucocorticosteroid therapy in acute severe asthma--a critical review. *European Respiratory Journal* 1991;**4**(7):881-9.

Flather 1997

Flather MD, Farkouh ME, Pogue JM, Yusuf S. Strengths and limitations of meta-analysis: larger studies may be more reliable. *Controlled Clinical Trials* 1997;**18**:568-79.

Hall 1995

Hall CM, Louw SJ, Joubert G. Relative efficacy of hydrocortisone and methylprednisolone in acute severe asthma. *South African Medical Journal* 1995;**85**:1153-6.

Hardy 1998

Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. *Statistics in Medicine* 1998;**17**(8):841-56.

Jadad 1996

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**(1):1-12.

Langhoff 1983

Langhoff E, Ladefoged J. Relative immunosuppressive potency of various corticosteroids measured in vitro. *European Journal of Clinical Pharmacology* 1983;**25**:459-62.

McFadden 1992

McFadden ERJ. Microvasculature and airway responses. *American Review in Respiratory Disease* 1992;**145**:S42-43.

McFadden 1993

McFadden ER, Jr. Dosages of corticosteroids in asthma. *American Review of Respiratory Disease* 1993;**147**(5):1306-10.

Pecora 1996

Pecora PG, Kaplan B. Corticosteroids and ulcers: is there and association?. *Annals of Pharmacotherapy* 1996;**30**:870-2.

Persson 1986

Persson CGA. Role of plasma exudation in asthmatic airways. *Lancet* 1986;**2**:1126-9.

Pogue 1998

Pogue J, Yusuf S. Overcoming limitations of current meta-analysis of randomised controlled trials. *Lancet* 1998;**351**:47-52.

Rowe 1992

Rowe BH, Keller JL, Oxman AD. Effectiveness of steroid therapy in acute exacerbations of asthma: a meta-analysis. *American Journal of Emergency Medicine* 1992;**10**(4):301-10.

Rowe 1998

Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. The effectiveness of corticosteroids in the treatment of acute exacerbations of asthma: a meta-analysis of their effect on relapse following acute assessment (Cochrane Review). In: The Cochrane Library, Issue 4, 1998. *The Cochrane Library* 1998, Issue 4.

Shee 1990

Shee CD. Risk factors for hydrocortisone myopathy in acute severe asthma. *Respiratory Medicine* 1990;**84**:229-33.

Stein 1990

Stein LM, Cole RP. Early administration of corticosteroids in emergency room treatment of acute asthma. *Annals of Internal Medicine* 1990;**112**:822-7.

Strauss 1997

Strauss L, Hejal R, Galan G, Dixon L, McFadden ER Jr. Observations on the effects of aerosolized albuterol in acute asthma. *American Journal of Respiratory and Critical Care Medicine* 1997;**155**:454-8.

Sue 1986 (ii)

Sue MA, Kwong FK, Klaustermyer WB. A comparison of intravenous hydrocortisone, methylprednisolone and dexamethasone in acute bronchial asthma. *Annals of Allergy* 1986;**56**:406-9.

Svedmyr 1990

Svedmyr N. Action of corticosteroids on beta-adrenergic receptors. Clinical aspects. *American Review of Respiratory Disease* 1990;**141**(2Pt2):S31-8.

Ward 1986

Ward MJ. Clinical trials in acute severe asthma: are type II errors important?. *Thorax* 1986;**41**:824-9.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bowler 1992

Methods	Randomised double-blind controlled clinical trial comparing 3 different doses of intravenous hydrocortisone (3 arms). Method of randomisation or allocation concealment was not described in the paper. First author stated that the pharmacy was responsible for randomisation and envelopes were used consistent with adequate concealment. The method of double blinding was well described and appropriate. Study duration: 12 days.
Participants	Patients with an unequivocal history of asthma who had previously or subsequently showed short term variability in FEV1 of at least 15%. Subjects were eligible if they required hospital admission after treatment in the emergency room with 10mg of nebulised salbutamol and intravenous aminophylline. Exclusions: Patients with pneumothorax or consolidation on chest x-ray, asthma that warranted admission to intensive care unit or other major illnesses. Subjects taking more than 10mg of prednisolone a day before admission. Ages: 18-65 years. PFTs: the mean baseline % predicted FEV1 & PEFR after emergency department treatment for the whole group was 32.7% & 48.8% respectively.
Interventions	Group 1: 50mg intravenous hydrocortisone 6 hourly (equivalent methylprednisolone dose in 24 hours 40mg); Group 2: 200mg intravenous hydrocortisone 6 hourly (methylprednisolone equivalent dose 160mg); Group 3: 500mg intravenous hydrocortisone 6 hourly (methylprednisolone equivalent dose 400mg). After 48 hours oral treatment with prednisolone was commenced with the following doses: group1; 20mg initially reducing to 5 mg over 12 days, group 2; 40mg initially reducing to 10mg over 12 days, group 3; 60mg initially reducing to 20mg over 12 days. Cointerventions: 4 hourly nebulised salbutamol and IV aminophylline or oral theophylline. All subjects received metered dose inhaled beclomethasone 400mcg BD.
Outcomes	The primary outcome was pulmonary function. FEV1 was measured daily for the first 48 hours. PEFR was measured daily (morning and evening) for 12 days. Severity of dyspnoea was assessed using a visual analogue scale. Treatment failures were recorded but not included in the final analysis.
Notes	Losses to follow up: 10 subjects were excluded after randomisation; 1 subject from the medium dose group required ICU; 2 patients in the low dose group and 3 in the medium dose group improved rapidly and requested discharge prior to the first 48 hours. There were 4 protocol violations due to either failure to collect data or the wrong steroid dose being administered; 1 in the high dose group and 3 in the low dose group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	First author stated that the pharmacy was responsible for randomisation and envelopes were used consistent with adequate concealment

Engel 1990

Methods	Randomised double-blind controlled clinical trial comparing intravenous methylprednisolone pulse therapy with oral corticosteroids. Allocation concealment and method of randomisation not described. Method of blinding well described and appropriate. Primary author has responded to initial correspondence but has not been able to provide further details yet. Study duration: 12 weeks.
Participants	Patients presenting to an allergy clinic with acute severe asthma. Patients were given nebulised salbutamol 2.5mg followed by standard treatment including beta-agonists and intravenous theophylline, if after 1 hour of treatment, the FEV1 was less than 60% predicted and corticosteroids were indicated, patients were offered participation in the study following hospitalisation. All patients fulfilled the American Thoracic Society criteria for asthma. Exclusions: pregnancy or patients with diabetes mellitus, cardiac failure or hypertension. Ages: Criteria not specified, mean age for whole group was 47 years. PFTs: the mean % predicted FEV1 & PEFR for the whole group at baseline was 38% & 45% respectively.
Interventions	MP group: received 1g of intravenous methylprednisolone (single dose) followed by placebo daily tablets. OP group: received daily oral prednisolone tablets starting at a dose of 50mg and reducing to zero within 18 days. Cointerventions: beta-agonists and intravenous theophylline were administered in a standardised fashion for at least the first 24 hours.
Outcomes	Outcomes considered included pulmonary function (FEV1 and PEF), need for subsequent prednisolone treatment, medication use and side effects. Peak expiratory flow was measured hourly (while awake) for the first 24 hours. FEV1was measured at 24 hours, then 1,2,4,8 and 12 weeks.
Notes	Losses to follow up: There was no clear statement on withdrawals or losses to follow up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

Harrison 1986

Methods	Randomised double-blind controlled clinical trial comparing oral prednisolone alone with oral prednisolone and intravenous hydrocortisone. Method of randomisation was not described in the paper and allocation concealment was unclear. Method of double blinding was well described & appropriate. The primary author stated that a random number table was used to randomise subjects and the pharmacist was responsible for randomisation. Coded unnamed ampoules were used to conceal allocation. Study duration: 24 hours
Participants	Patients with acute asthma admitted to the ward were eligible if they satisfied 2 of the following: (a) PEF less than or equal to 30% predicted; (b) heart rate greater than or equal to 110 bpm; (c) systolic arterial paradox greater than or equal to 10mmHg. Exclusions: patients with a PaCO2 of more than 6.4kPa or those who the admitting doctor believed were to ill to take part in the trial. Ages: 16 to 50 PFTs: mean PEF on admission 21%.
Interventions	Both groups received 45 mg oral prednisolone followed by 15 mg orally 8 hourly. The control group received placebo intravenous therapy. (Methylprednisolone equivalent dose in 24 hours: up to 72 mg) The intervention group received hydrocortisone sodium phosphate 3mg/kg intravenous bolus fol-

Harrison 1986 *(Continued)*

	lowed by 3mg/kg 6 hourly by continuous infusion for 24 hours. (Methylprednisolone equivalent dose in 24 hours 240mg). Cointerventions: both groups received terbutaline 5 mg nebulised 4 hourly and IV aminophylline.
Outcomes	The primary outcome was Peak expiratory flow rate at 2 to 6 hourly intervals up to 24 hours. Peak expiratory flow rate presented as a percentage of normal but not specified whether pre or post bronchodilator. Pulse rate, respiratory rate, systolic blood pressure and systolic paradox were recorded but detailed data not described. Arterial blood gases were measured at 1 to 2 hours after the start of treatment and thereafter only if clinically indicated.
Notes	Included patients who had received intravenous or intramuscular corticosteroids prior to admission. Subjects were stratified into 2 groups: A) those who had received pre-admission intravenous or intramuscular glucocorticoids and B) those who had not. Separate data for group B not presented. Some patients in both groups were on regular oral corticosteroids but numbers not specified by group, (total 7). Losses to follow up: 52 subjects were admitted to the study & 47 included in the analysis. 3 protocol violations & 2 did not satisfy entry criteria. No withdrawals due to hypercapnia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Pharmacist was responsible for randomisation

Haskell 1983

Methods	Randomised double-blind controlled clinical trial comparing different doses (3 arms) of intravenous methylprednisolone. Patients were randomised using a table of random numbers, however the authors did not describe whether allocation was concealed. Method of double blinding was not well described. Authors have not responded to correspondence as yet. Study duration: 72 hours.
Participants	Patients with status asthmaticus. Asthma defined according to American Thoracic Society criteria. Status asthmaticus defined as severe asthma that did not respond adequately (FEV1 less than 50% predicted) to conventional treatment with subcutaneous beta-agonists, IV aminophylline and inhaled bronchodilators. Exclusions: chronic bronchitis, emphysema, pneumonia, heart failure, pulmonary embolism, upper airway obstruction, pneumothorax, pleural effusion, lung cancer, previous long term mechanical ventilation, any other cause of an abnormal FEV1. Those with relative or absolute contraindication to corticosteroids & patients treated in the previous 7 days with corticosteroids or barbiturates. Ages: Criteria not described, mean age for whole group was 39 years. PFTs: the mean baseline FEV1 for the whole group was 26% predicted.
Interventions	Group 1: 15 mg intravenous methylprednisolone 6 hourly. Group 2: 40 mg intravenous methylprednisolone 6 hourly. Group 3: 125 mg intravenous methylprednisolone 6 hourly. Cointerventions: (1) IV aminophylline, loading dose; 3 to 6 mg/kg and infusion 0.6 to 0.9 mg/kg/hr adjusted to daily levels (10 to 20 mg/L) (2) Inhaled beta-agonist every 4 hours. (3) intravenous or oral fluids. (4) Supplemental oxygen if oxygen saturation less than 90%.
Outcomes	The primary outcome was pulmonary function (FEV1 % predicted). Blood glucose levels measured.
Notes	Losses to follow up: 25 subjects were randomised & 24 included in the final analysis. One patient was removed after less than 1 day due to refusal to perform spirometry.

Haskell 1983 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

Marquette 1995

Methods	Randomised double-blind controlled clinical trial comparing 2 different doses of intravenous methylprednisolone. Method of randomisation was not described but allocation was concealed by the use of opaque vials which could be identified by a random number only. Method of blinding was adequate. The primary author has responded to initial correspondence but has not been able to provide further details as yet. Study duration: 44 hours after the first dose was given.
Participants	Patients with acute severe asthma. The diagnosis of asthma was based on a typical history, together with airway obstruction, defined as a change in FEV1 > or = 15% of predicted value, or > or = 25% of baseline value (during previous or subsequent follow up visits). Initial treatment included: salbutamol 5mg, via nebuliser, together with salbutamol 0.25 mg/hour via continuous intravenous infusion. The baseline FEV1 was measured 30 minutes after the nebuliser and only patients with an FEV1 of less than or equal to 50% of predicted were included. Exclusions: parenteral corticosteroids prior to admission, need for prompt ventilatory support, fever or chest x-ray abnormalities on admission, or chronic bronchitis, emphysema, extrapulmonary infection, pregnancy, diabetes mellitus, peptic ulcer, smoking history with more than 15 pack-years, psychiatric history. Ages: 18 to 65 years. PFTs: Mean baseline post bronchodilator FEV1 30% for the whole group.
Interventions	Low dose group: received a total daily dose of 1mg/kg of intravenous methylprednisolone in 4 divided doses over 48 hours. High dose group: received a total daily dose of 6mg/kg intravenous methylprednisolone in 4 divided doses over 48 hours. Cointerventions: Concurrently with the above all patients received a standard treatment which included intravenous fluids, intravenous aminophylline, supplemental oxygen, nebulised and intravenous salbutamol. Antibiotics were prescribed only if bronchial infection was suspected by history and by the presence of purulent sputum.
Outcomes	The primary outcome was pulmonary function. Spirometry (pre and post bronchodilator) performed every 4 hours during the first 24 hours of the study, and then every 6 hours until the end of the study. Other outcomes considered included respiratory failure or need for mechanical ventilation. Worsening bronchospasm/need for increased bronchodilator therapy. Vital signs at 24 and 48 hours. Side effects: hypokalaemia, hyperglycaemia, white cell count, psychiatric reactions.
Notes	Losses to follow up: 52 subjects entered the trial 1 dropped out at 12 hours due to fever, 4 patients (2 in each group) were excluded because of erroneous inclusion (subsequently diagnosed with acute exacerbation of chronic obstructive pulmonary disease). 47 patients included in the analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Opaque vials which could be identified by a random number only

Morell 1992

Methods	Randomised double blind controlled clinical trial with three arms comparing placebo and 2 different doses of methylprednisolone. The method of randomisation was not described ; the primary author stated that the method used to randomise subjects was computer generated. Allocation concealment was not described; but the person responsible for randomising subjects was the principal investigator suggesting inadequate concealment but not described further. Study duration: 48 hours
Participants	Patients with acute asthma defined by the American Thoracic society guidelines. Those who were admitted to the emergency service of a general hospital. Exclusions: Pregnancy, cardiac disease, diabetes, active peptic ulcer and hypertension (with a diastolic blood pressure greater than 120mm Hg). Ages: Criteria not described but mean age for the whole group was 46 years. PFTs: Mean baseline FEV1 0.61L and PEF 156 L/min for the whole group. (Not clear whether these were taken before or after any bronchodilator treatment)
Interventions	Group A: intravenous methylprednisolone 10mg/kg every 4 hours for 48 hours. (Total daily methylprednisolone equivalent dose for a 70kg person; 4200mg). Group B: intravenous methylprednisolone 2mg/kg every 4 hours for 48 hours. (Total daily methylprednisolone equivalent dose for 70kg person; 840mg). Group C: placebo (normal saline). Patients receiving maintenance oral corticosteroids continued this treatment throughout the study period. Cointerventions: Initial bronchodilator treatment consisted of 3 doses of 0.3 mg subcutaneous adrenaline hydrochloride every 15 minutes, intravenous aminophylline, inhaled hexoprenaline- 5 mg every 4 hours via a Bird Mark 8 ventilator. All patients received oxygen.
Outcomes	The main outcome was pulmonary function; FEV1, FVC, PEF. Spirometry was repeated every hour for the first 6 hours and then at 24 and 48 hours. Arterial blood gases were repeated at the end of the first 6 hours and 24 and 48 hours. Other outcomes such as length of hospital stay and symptom scores not described.
Notes	No standard deviations presented with the data. The primary author was contacted and stated that they were unable to provide further data. Subgroup analysis performed on those patients who failed to show an increase of 15% or more in PEF after 3 hours of treatment. Losses to follow up: 90 patients were included in the trial but 8 were excluded from the analysis due to incomplete data. No further information provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

Pedersen 1987

Methods	Randomised double-blind controlled clinical trial comparing methylprednisolone pulse therapy with low dose daily corticosteroids. Method of randomisation or blinding not described. Study duration: 3 months. Pilot study (total 6 subjects).
Participants	Patients with acute asthma, all patients met the asthma criteria of the American Thoracic Society. Those who failed to respond to 1 hour of intensive bronchodilator therapy were eligible for entry. (Failure not defined). Exclusions: Patients were described as being free from other complicating cardiopulmonary diseases, hypertension, or insulin-dependent diabetes mellitus. Ages: Adults, age criteria not specified.

Pedersen 1987 *(Continued)*

	PFTs: mean FEV1 for whole group; 0.6L, mean FVC for the whole group; 1.12L.
Interventions	Group A were treated with intravenous methylprednisolone initially 1000 mg on 3 consecutive days followed by placebo tablets. Group B received 50 mg of intravenous methylprednisolone on 3 consecutive days followed by a reducing dose of methylprednisolone tablets over 2 weeks. Cointerventions: The initial bronchodilator treatment consisted of terbutaline inhalations, intravenous infusions of terbutaline & intravenous injection of aminophylline. Ongoing treatment consisted of terbutaline inhaled (5 mg every 4 h) during the first 3 days and thereafter as needed. Budesonide aerosol 800 mcg BD, Theodur 300 mcg BD & Bricanyl Retard 7.5 mg BD were given throughout the study period.
Outcomes	Outcomes included pulmonary function, symptom scores and medication use with follow up to 3 months.
Notes	Pulmonary function or symptom scores for the first 3 days not presented in the paper. Authors contacted, but as yet have not been able to provide further data. Recorded day at which PEF or FEV1 was at least 80% of maximum & day when patients fulfilled no criteria for asthma. Losses to follow up: Drop outs occured after the first month of treatment but not the first few days.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

Ratto 1988

Methods	Quasi randomised controlled clinical trial comparing oral methylprednisolone treatment with intravenous methylprednisolone. Study described as randomised. Allocation on a sequential daily basis and hence inadequate concealment. Not blinded. Study duration: 72 hours.
Participants	Patients with status asthmaticus. Patients were considered to have asthma if they were known or suspected asthmatics without underlying emphysema or chronic bronchitis. All patients had to have demonstrable reversibility of airflow as measured by peak flows or spirometry at previous admissions, at admission for study, or at follow-up in the outpatient clinic. All patients were treated in the emergency department with inhaled beta agonist and intravenous aminophylline. Patients were then eligible for the study if the emergency department physician thought they should be admitted and the FEV1 was less than 50% predicted. Exclusions: a history of smoking for greater than ten pack-years, or hospital steroid therapy more than 1 hour prior to the initial spirogram. Ages: 18 to 65 years. PFTs: mean FEV1 for whole group 26.5 % predicted (0.72 L), mean FVC 35% predicted (1.22L).
Interventions	Oral group: 160 mg/day (80mg BD) or 320 mg/day (80mg QID) oral methylprednisolone. Intravenous group: 500mg/day (125mg QID) or 1000 mg/day (250mg QID) of intravenous methylprednisolone. Cointerventions: Inhaled beta-agonist (alupent) 2.5 mls of 0.6% solution, 4 hourly and intravenous aminophylline. Physicians were allowed to administer inhaled atropine and parenteral or oral terbutaline.
Outcomes	The main outcome was pulmonary function measured up to 72 hours. Other outcomes considered were duration of hospitalisation, respiratory failure, side effects, need for additional treatment.
Notes	There were 4 different dose levels in the study but data were only presented for 2 groups: oral vs intravenous. Authors contacted but as yet have not been able to provide additional data.

Ratto 1988 *(Continued)*

	Patients were not excluded on the basis of having used oral prednisone at home. No patient was taking more than 40mg/day as an outpatient. Losses to follow up: 77 patients were entered in the study & 70 were included in the final analysis. Two patients in the intravenous group refused to continue for personal reasons & 5 patients developed respiratory failure, 2 in the oral group & 3 in the intravenous group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	Allocation on a sequential daily basis and hence inadequate concealment.

Tanaka 1982

Methods	Randomised double-blind controlled clinical trial comparing 2 different doses of intravenous methylprednisolone. Method of randomisation was not described and allocation concealment was unclear. Method of blinding not described. Primary author has been contacted, but has not been able to provide further details as yet. Study duration: 10 days
Participants	Patients with status asthmaticus admitted to hospital. Patients had to fulfil the American Thoracic Society criteria for the diagnsosis of asthma. Status asthmaticus was defined as an acute exacerbation of airway obstruction requiring hospitalisation and not responding to emergency room treatment with optimal doses of theophylline, oral and aerosolized beta adrenergic therapy. Exclusions: Patients with an abnormal diffusing capacity or clinical history of bronchitis. Ages: Not specified in advance but the mean age for the whole group was 54 years. PFTs: Mean baseline FEV1 for the whole group 0.7L.
Interventions	Group A received 20mg methylprednisolone QID intavenously for 7 days. Group B received 125mg QID methylprednisolone intravenously for 7 days. Both groups were then given the same regimen of 60, 40, 20 mg of prednisone orally on days 8,9, and 10. Cointerventions both groups received IV aminophylline (adjusted to maintain serum levels between 10 and 20 mcg/ ml), aerosolised isoetharine or isoproterenol every four hours, intravenous fluids and supplemental oxygen.
Outcomes	The primary outcome was pulmonary function. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) were measured each morning for 10 days. Reported as a percentage of each patients best ventilatory function recorded within 6 months of the study. Not reported whether values were pre or post bronchodilator. Other outcomes not discussed.
Notes	Statistical methods not described and standard deviations not presented with post treatment values. Losses to follow up: No clear statement on losses to follow up or withdrawals. One patient in each group was on regular oral glucocorticoids.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Britton 1976	Not randomised.
Chapela 1995	Equivalent doses of prednisolone and deflazacort
Emerman 1995	Pulmonary function measured at 3 and 5 hours only.
Fanta 1983	Randomised control trial of hydrocortisone (single dosage arm) versus placebo in acute asthma.
Hall 1995	Equivalent doses of hydrocortisone and methylprednislone
Loren 1980	Randomised control trial placebo versus prednisolone treatment, participant ages 7 to 17.
McFadden 1976	Data collected for the first 6 hours of treatment only.
Prazakova 1988	Not randomised
Raimondi 1986	Not randomised
Sue 1986	Equivalent doses of hydrocortisone, dexamethasone and methylprednisolone.
Webb 1986	Patients not requiring admission to hospital.

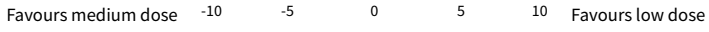
DATA AND ANALYSES

Comparison 1. Low versus medium dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PEF	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 24 hours	1	47	Mean Difference (IV, Fixed, 95% CI)	7.0 [-6.49, 20.49]
1.2 48 hours	1	42	Mean Difference (IV, Fixed, 95% CI)	4.0 [-15.02, 23.02]
1.3 72 hours	1	42	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-20.39, 18.39]
2 FEV1	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 24 hours	2	58	Mean Difference (IV, Fixed, 95% CI)	0.14 [-11.44, 11.72]
2.2 48 hours	2	58	Mean Difference (IV, Fixed, 95% CI)	-3.32 [-12.44, 5.79]
2.3 72 hours	1	16	Mean Difference (IV, Fixed, 95% CI)	-9.5 [-28.35, 9.35]
3 Dyspnoea (VAS)	1	42	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-20.24, 4.24]
4 Respiratory failure	2	59	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.75 [0.15, 390.96]

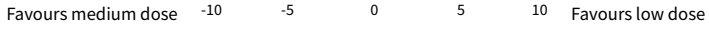
Analysis 1.1. Comparison 1 Low versus medium dose, Outcome 1 PEF.

Study or subgroup	Medium dose N	Medium dose Mean(SD)	Low dose N	Low dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 24 hours							
Harrison 1986	23	-51 (21)	24	-58 (26)		100%	7[-6.49,20.49]
Subtotal ***	**23**		**24**			**100%**	**7[-6.49,20.49]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.02(P=0.31)							
1.1.2 48 hours							
Bowler 1992	20	-71 (24.6)	22	-75 (37.5)		100%	4[-15.02,23.02]
Subtotal ***	**20**		**22**			**100%**	**4[-15.02,23.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.41(P=0.68)							
1.1.3 72 hours							
Bowler 1992	20	-82 (31.3)	22	-81 (32.8)		100%	-1[-20.39,18.39]
Subtotal ***	**20**		**22**			**100%**	**-1[-20.39,18.39]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.1(P=0.92)							
Test for subgroup differences: Chi^2=0.44, df=1 (P=0.8), I^2=0%							

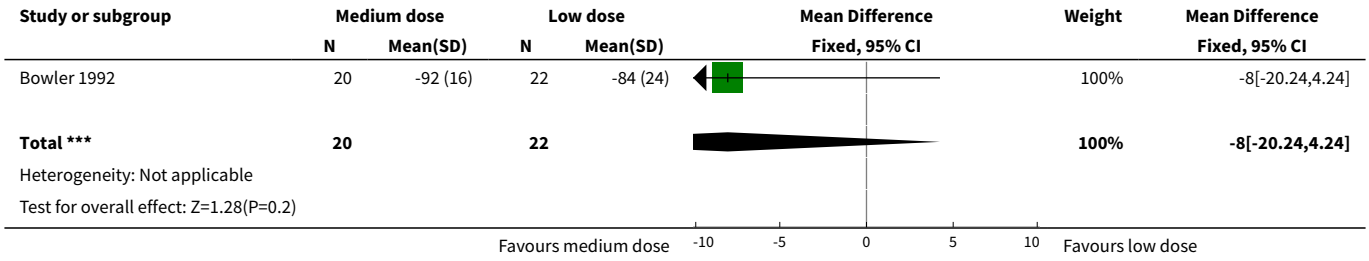


Analysis 1.2. Comparison 1 Low versus medium dose, Outcome 2 FEV1.

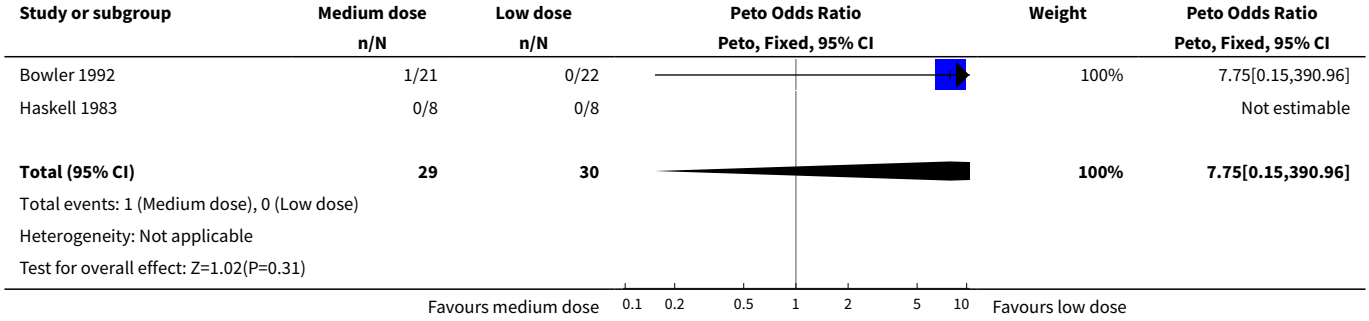
Study or subgroup	Medium dose N	Medium dose Mean(SD)	Low dose N	Low dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.2.1 24 hours							
Bowler 1992	20	-62 (23)	22	-62 (22)		72.06%	0[-13.64,13.64]
Haskell 1983	8	-39.5 (14.1)	8	-40 (28.3)		27.94%	0.5[-21.41,22.41]
Subtotal ***	**28**		**30**			**100%**	**0.14[-11.44,11.72]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%							
Test for overall effect: Z=0.02(P=0.98)							
1.2.2 48 hours							
Bowler 1992	20	-72 (15)	22	-71 (24)		57.79%	-1[-12.99,10.99]
Haskell 1983	8	-58 (8.5)	8	-51.5 (18.4)		42.21%	-6.5[-20.53,7.53]
Subtotal ***	**28**		**30**			**100%**	**-3.32[-12.44,5.79]**
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%							
Test for overall effect: Z=0.71(P=0.48)							
1.2.3 72 hours							
Haskell 1983	8	-66 (12.7)	8	-56.5 (24)		100%	-9.5[-28.35,9.35]
Subtotal ***	**8**		**8**			**100%**	**-9.5[-28.35,9.35]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.99(P=0.32)							
Test for subgroup differences: Chi^2=0.74, df=1 (P=0.69), I^2=0%							



Analysis 1.3. Comparison 1 Low versus medium dose, Outcome 3 Dyspnoea (VAS).



Analysis 1.4. Comparison 1 Low versus medium dose, Outcome 4 Respiratory failure.

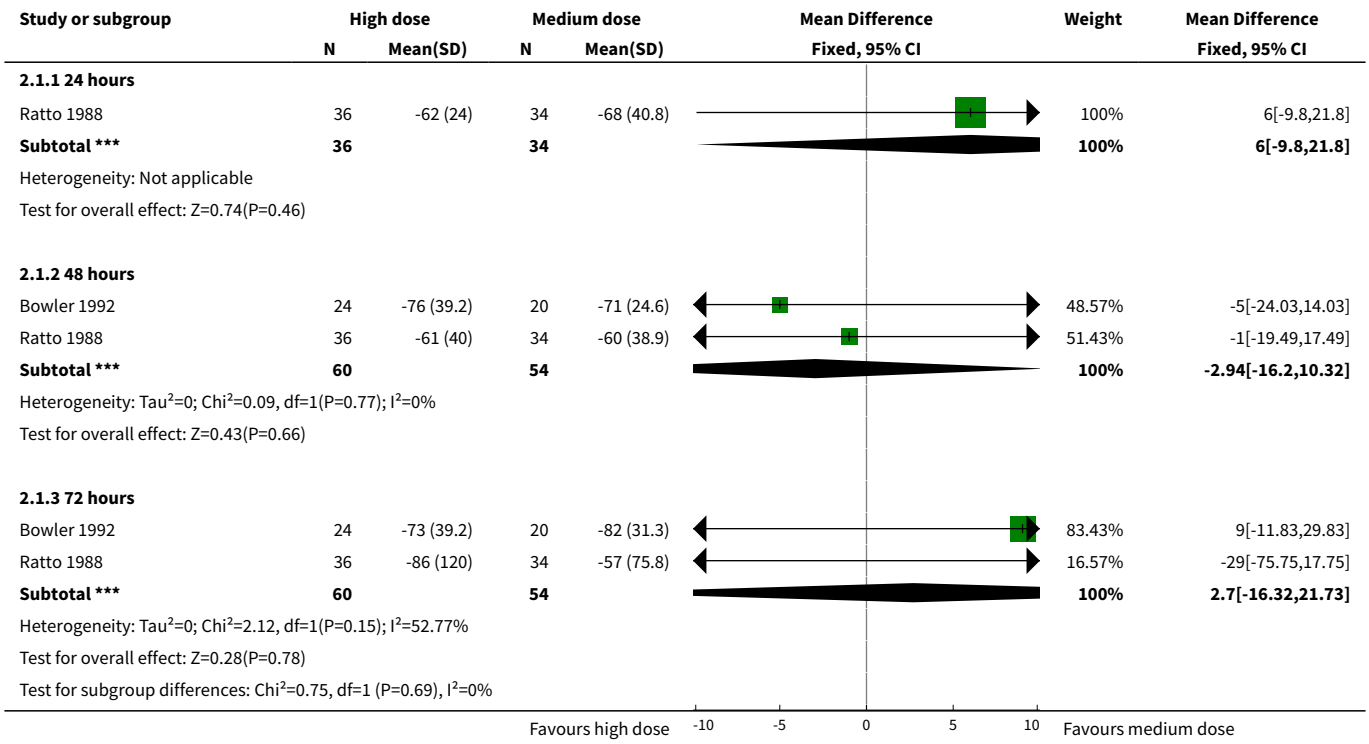


Comparison 2. Medium versus high dose

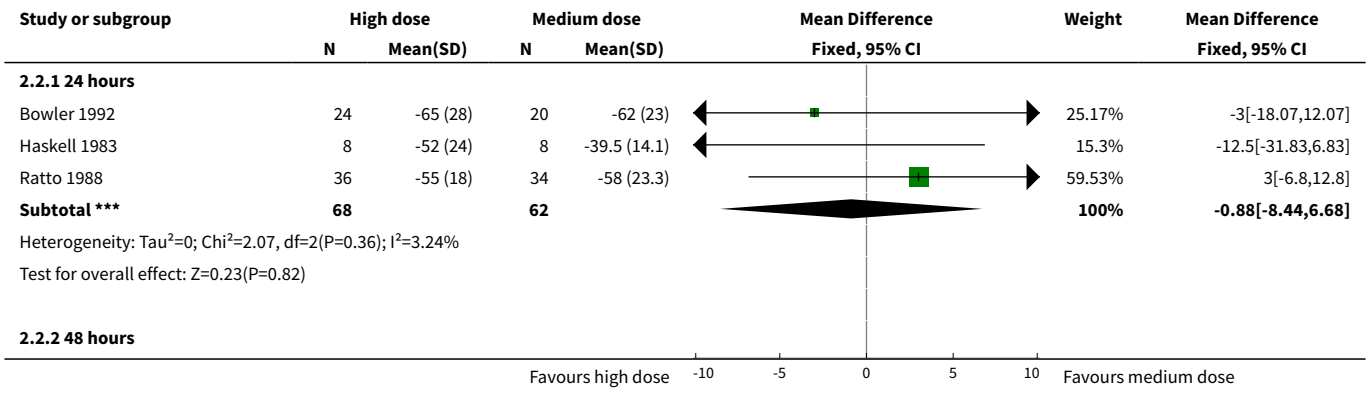
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PEF	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 24 hours	1	70	Mean Difference (IV, Fixed, 95% CI)	6.0 [-9.80, 21.80]
1.2 48 hours	2	114	Mean Difference (IV, Fixed, 95% CI)	-2.94 [-16.20, 10.32]
1.3 72 hours	2	114	Mean Difference (IV, Fixed, 95% CI)	2.70 [-16.32, 21.73]
2 FEV1	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 24 hours	3	130	Mean Difference (IV, Fixed, 95% CI)	-0.88 [-8.44, 6.68]
2.2 48 hours	3	130	Mean Difference (IV, Fixed, 95% CI)	-1.91 [-8.11, 4.29]
2.3 72 hours	2	86	Mean Difference (IV, Fixed, 95% CI)	-3.83 [-14.67, 7.02]
3 Dyspnoea (VAS)	1	44	Mean Difference (IV, Fixed, 95% CI)	4.0 [-5.23, 13.23]
4 High quality studies (FEV1)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 24 hours	2	60	Mean Difference (IV, Fixed, 95% CI)	-6.59 [-18.48, 5.29]

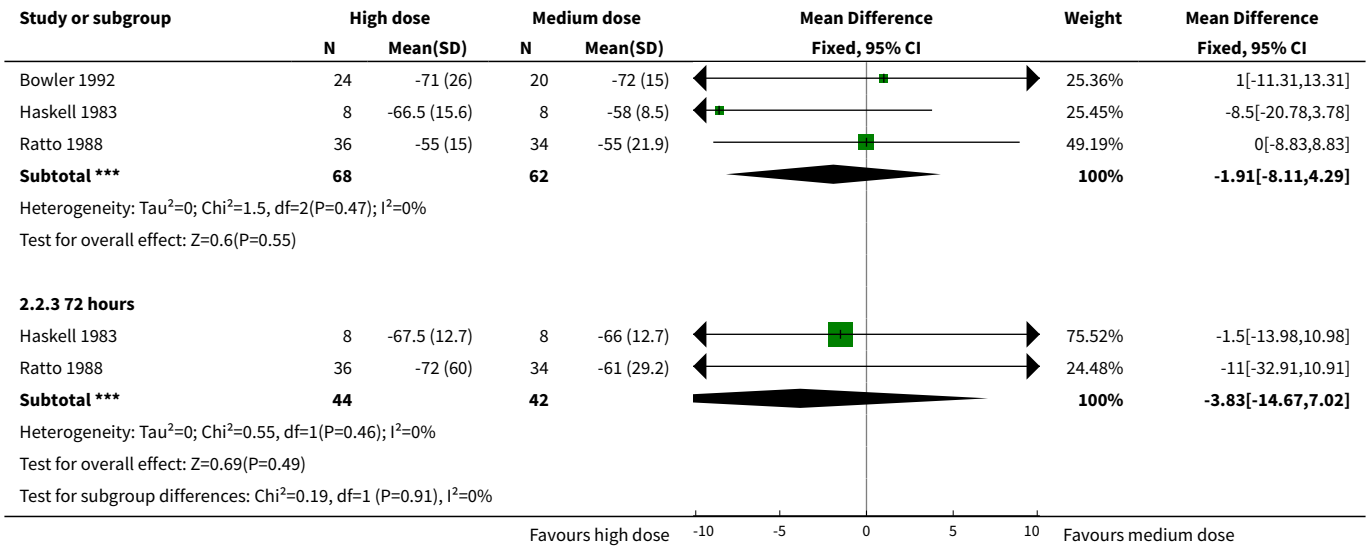
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 48 hours	2	60	Mean Difference (IV, Fixed, 95% CI)	-3.76 [-12.45, 4.93]
4.3 72 hours	1	16	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-13.98, 10.98]
5 Respiratory failure	3	131	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.18, 4.80]

Analysis 2.1. Comparison 2 Medium versus high dose, Outcome 1 PEF.

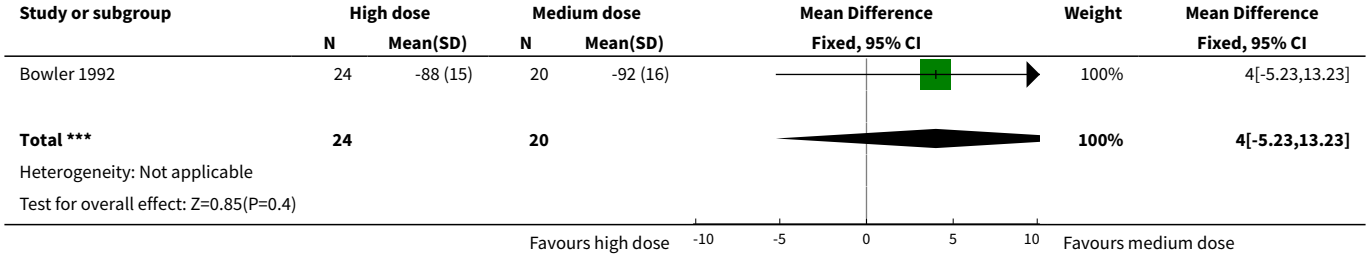


Analysis 2.2. Comparison 2 Medium versus high dose, Outcome 2 FEV1.

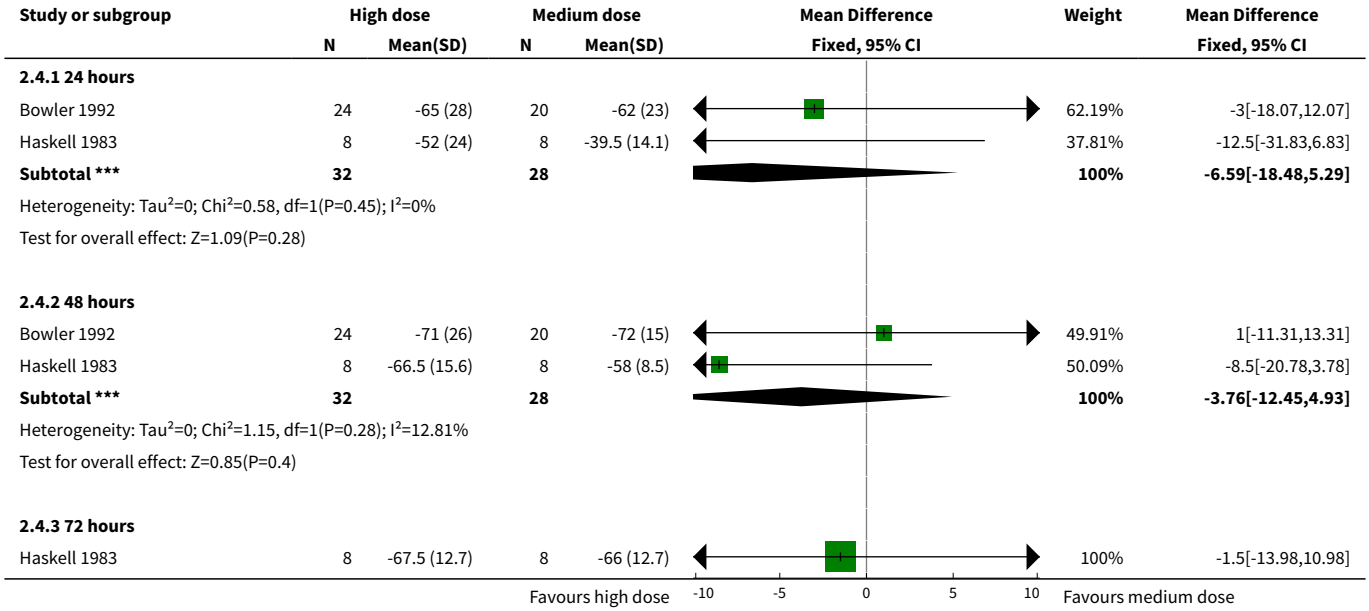


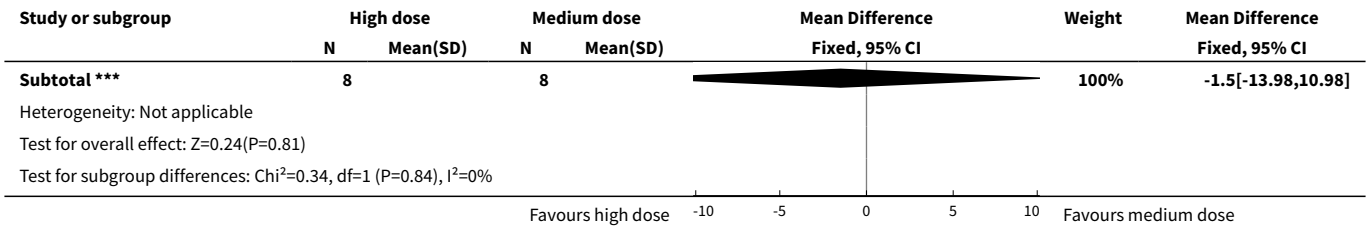


Analysis 2.3. Comparison 2 Medium versus high dose, Outcome 3 Dyspnoea (VAS).

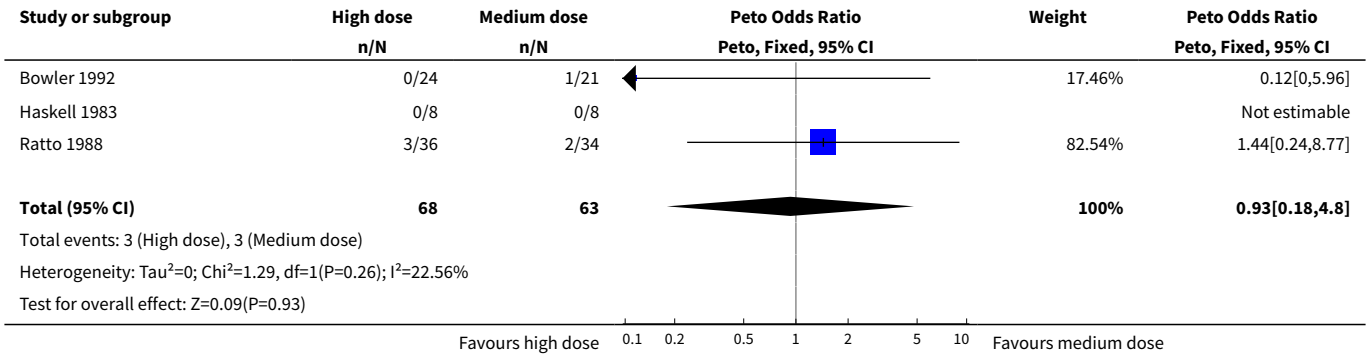


Analysis 2.4. Comparison 2 Medium versus high dose, Outcome 4 High quality studies (FEV1).





Analysis 2.5. Comparison 2 Medium versus high dose, Outcome 5 Respiratory failure.



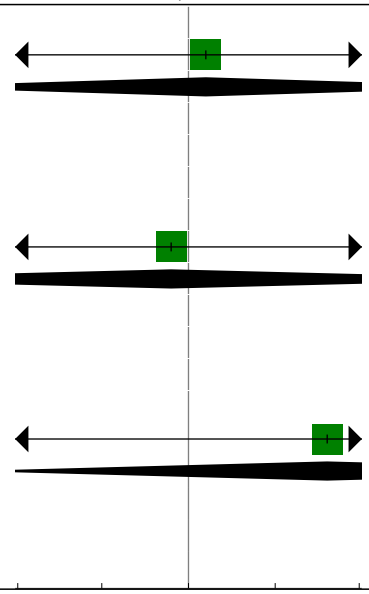
Comparison 3. Low versus high dose

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 PEF	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 24 hours	1	18	Mean Difference (IV, Fixed, 95% CI)	1.0 [-17.08, 19.08]
1.2 48 hours	1	46	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-23.17, 21.17]
1.3 72 hours	1	46	Mean Difference (IV, Fixed, 95% CI)	8.0 [-12.83, 28.83]
2 FEV1	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 24 hours	4	127	Mean Difference (IV, Fixed, 95% CI)	5.92 [-1.38, 13.22]
2.2 48 hours	3	109	Mean Difference (IV, Fixed, 95% CI)	0.52 [-7.77, 8.82]
2.3 72 hours	1	16	Mean Difference (IV, Fixed, 95% CI)	-11.0 [-29.85, 7.85]
3 Dyspnoea (VAS)	1	46	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-15.69, 7.69]
4 High quality studies (FEV1)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 24 hours	3	109	Mean Difference (IV, Fixed, 95% CI)	1.42 [-7.50, 10.34]
4.2 48 hours	3	109	Mean Difference (IV, Fixed, 95% CI)	0.52 [-7.77, 8.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Respiratory failure	3	109	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

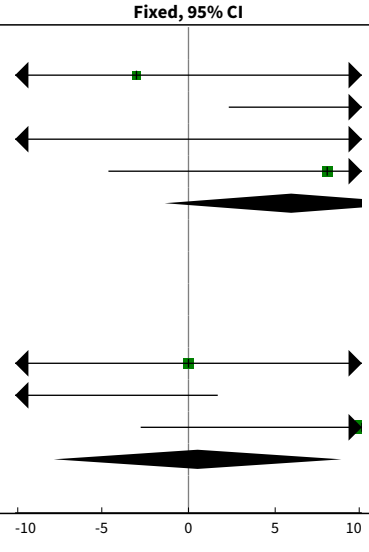
Analysis 3.1. Comparison 3 Low versus high dose, Outcome 1 PEF.

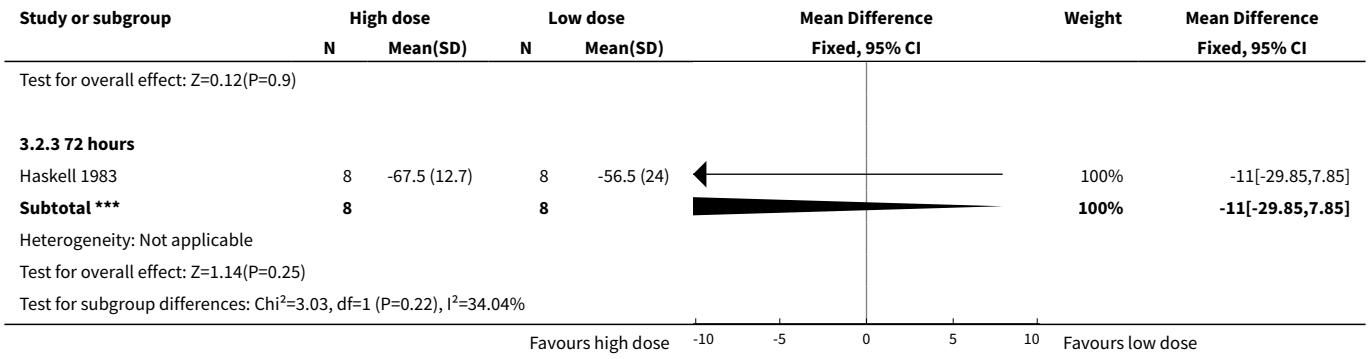
Study or subgroup	High dose N	High dose Mean(SD)	Low dose N	Low dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.1.1 24 hours							
Engel 1990	8	-78 (19)	10	-79 (20)		100%	1[-17.08,19.08]
Subtotal ***	**8**		**10**			**100%**	**1[-17.08,19.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.11(P=0.91)							
3.1.2 48 hours							
Bowler 1992	24	-76 (39.2)	22	-75 (37.5)		100%	-1[-23.17,21.17]
Subtotal ***	**24**		**22**			**100%**	**-1[-23.17,21.17]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.09(P=0.93)							
3.1.3 72 hours							
Bowler 1992	24	-73 (39.2)	22	-81 (32.8)		100%	8[-12.83,28.83]
Subtotal ***	**24**		**22**			**100%**	**8[-12.83,28.83]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.75(P=0.45)							
Test for subgroup differences: Chi^2=0.39, df=1 (P=0.82), I^2=0%							



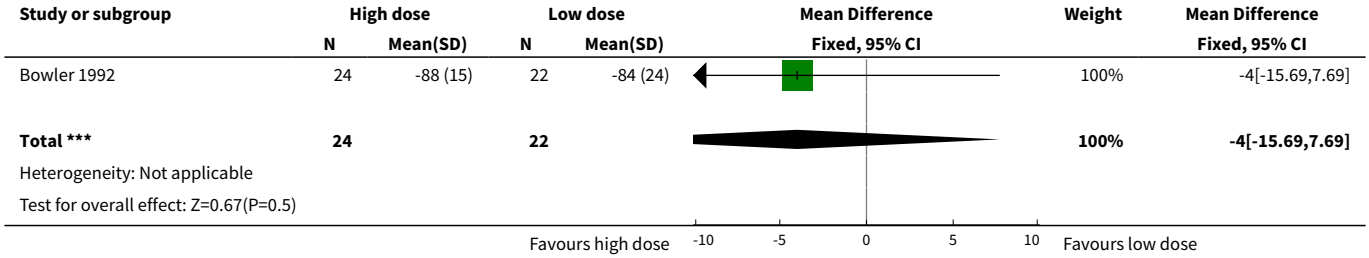
Analysis 3.2. Comparison 3 Low versus high dose, Outcome 2 FEV1.

Study or subgroup	High dose N	High dose Mean(SD)	Low dose N	Low dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.2.1 24 hours							
Bowler 1992	24	-65 (28)	22	-62 (22)		25.36%	-3[-17.49,11.49]
Engel 1990	8	-50.8 (16.2)	10	-65.8 (9.5)		33.14%	15[2.32,27.68]
Haskell 1983	8	-52 (24)	8	-40 (28.3)		8.05%	-12[-37.72,13.72]
Marquette 1995	24	-51 (17)	23	-59 (26)		33.46%	8[-4.62,20.62]
Subtotal ***	**64**		**63**			**100%**	**5.92[-1.38,13.22]**
Heterogeneity: Tau^2=0; Chi^2=5.4, df=3(P=0.15); I^2=44.4%							
Test for overall effect: Z=1.59(P=0.11)							
3.2.2 48 hours							
Bowler 1992	24	-71 (26)	22	-71 (24)		32.97%	0[-14.45,14.45]
Haskell 1983	8	-66.5 (15.6)	8	-51.5 (18.4)		24.72%	-15[-31.69,1.69]
Marquette 1995	24	-50 (16)	23	-60 (27)		42.3%	10[-2.76,22.76]
Subtotal ***	**56**		**53**			**100%**	**0.52[-7.77,8.82]**
Heterogeneity: Tau^2=0; Chi^2=5.45, df=2(P=0.07); I^2=63.3%							

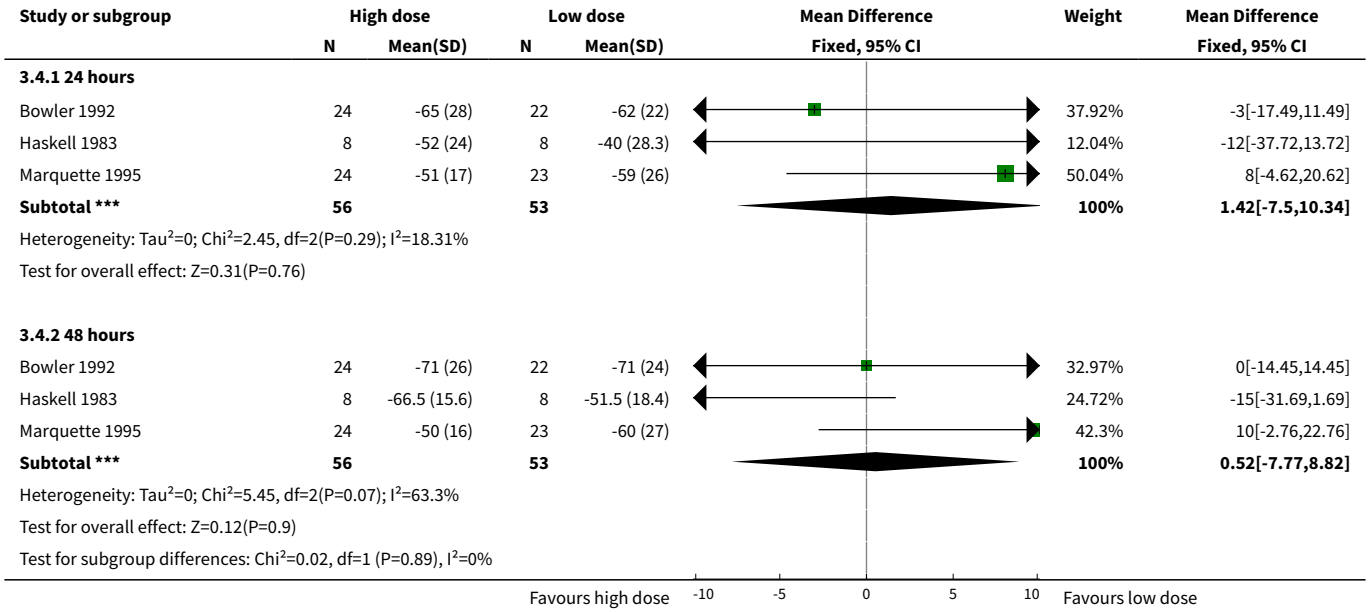




Analysis 3.3. Comparison 3 Low versus high dose, Outcome 3 Dyspnoea (VAS).

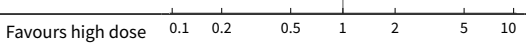


Analysis 3.4. Comparison 3 Low versus high dose, Outcome 4 High quality studies (FEV1).



Analysis 3.5. Comparison 3 Low versus high dose, Outcome 5 Respiratory failure.

Study or subgroup	High dose n/N	Low dose n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bowler 1992	0/24	0/22			Not estimable
Haskell 1983	0/8	0/8			Not estimable
Marquette 1995	0/24	0/23			Not estimable
Total (95% CI)	**56**	**53**			**Not estimable**
Total events: 0 (High dose), 0 (Low dose)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

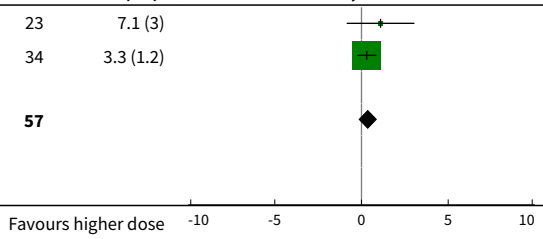


Comparison 4. Low or medium versus high dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of stay	2	117	Mean Difference (IV, Fixed, 95% CI)	0.36 [-0.17, 0.89]

Analysis 4.1. Comparison 4 Low or medium versus high dose, Outcome 1 Length of stay.

Study or subgroup	Higher dose N	Higher dose Mean(SD)	Lower dose N	Lower dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Marquette 1995	24	8.2 (3.8)	23	7.1 (3)		7.48%	1.1[-0.85,3.05]
Ratto 1988	36	3.6 (1.2)	34	3.3 (1.2)		92.52%	0.3[-0.26,0.86]
Total ***	**60**		**57**			**100%**	**0.36[-0.17,0.89]**
Heterogeneity: Tau^2=0; Chi^2=0.6, df=1(P=0.44); I^2=0%							
Test for overall effect: Z=1.32(P=0.19)							

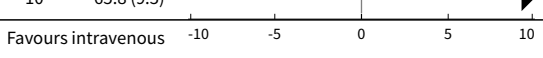


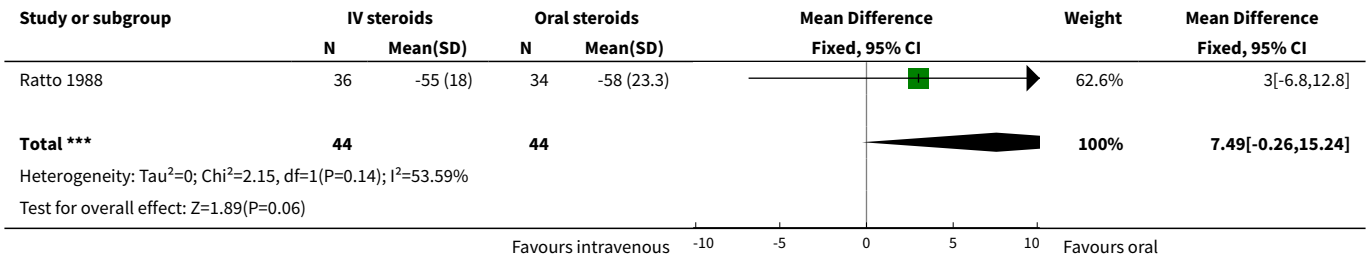
Comparison 5. Oral versus intravenous (any dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 FEV1 at 24 hours	2	88	Mean Difference (IV, Fixed, 95% CI)	7.49 [-0.26, 15.24]

Analysis 5.2. Comparison 5 Oral versus intravenous (any dose), Outcome 2 FEV1 at 24 hours.

Study or subgroup	IV steroids N	IV steroids Mean(SD)	Oral steroids N	Oral steroids Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Engel 1990	8	-50.8 (16.2)	10	-65.8 (9.5)		37.4%	15[2.32,27.68]

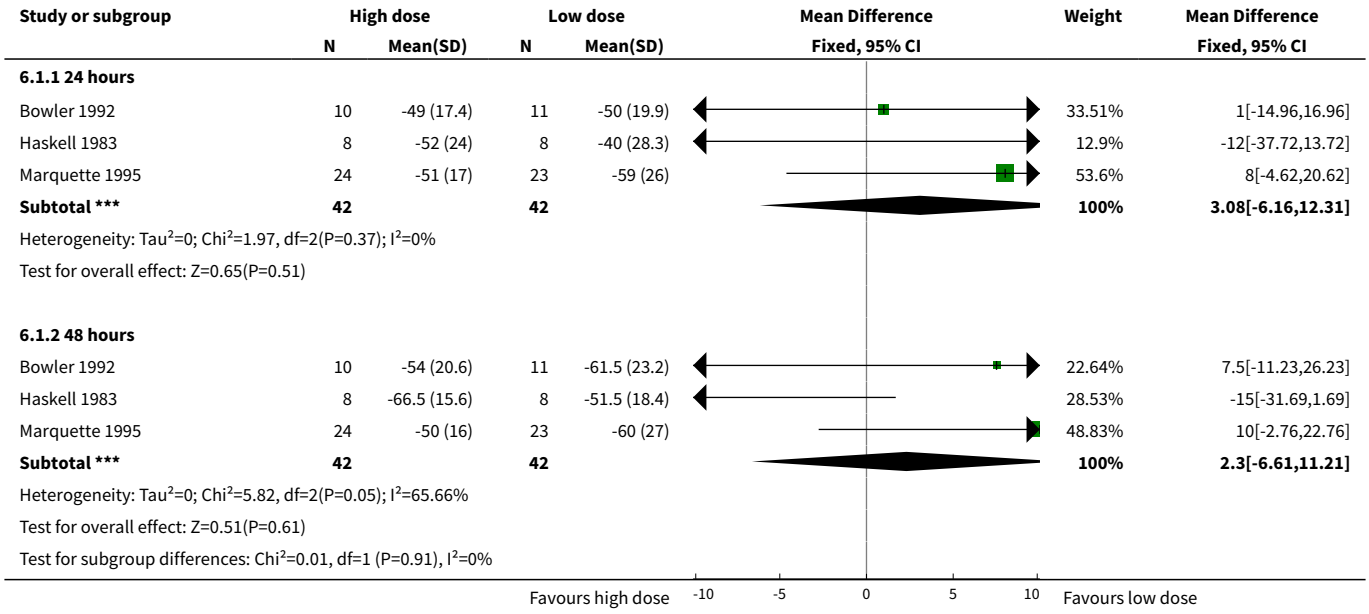




Comparison 6. Severe asthma (low versus high)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 24 hours	3	84	Mean Difference (IV, Fixed, 95% CI)	3.08 [-6.16, 12.31]
1.2 48 hours	3	84	Mean Difference (IV, Fixed, 95% CI)	2.30 [-6.61, 11.21]

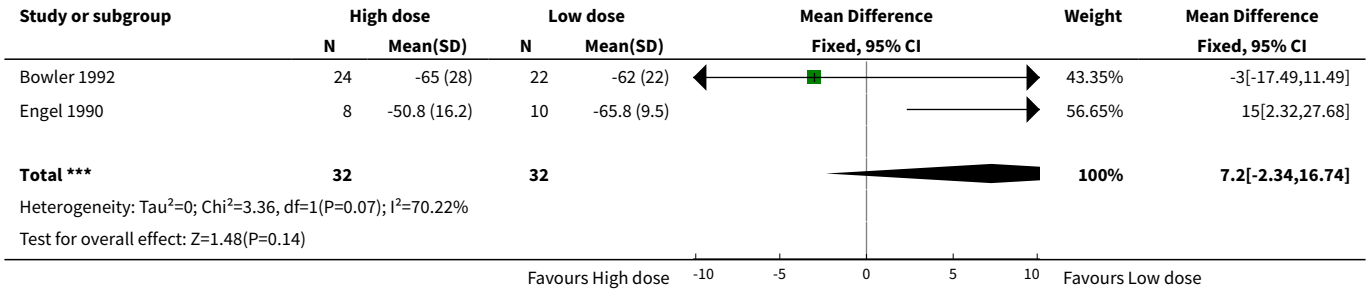
Analysis 6.1. Comparison 6 Severe asthma (low versus high), Outcome 1 FEV1.



Comparison 7. Very low versus high

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 24 hours	2	64	Mean Difference (IV, Fixed, 95% CI)	7.20 [-2.34, 16.74]

Analysis 7.1. Comparison 7 Very low versus high, Outcome 1 FEV1 24 hours.



WHAT'S NEW

Date	Event	Description
23 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1998
Review first published: Issue 4, 1999

Date	Event	Description
5 September 2000	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None. The authors are not involved in the primary research reported in this systematic review and have not represented the producers of these agents in the past.

SOURCES OF SUPPORT

Internal sources

- NHS Research and Development, UK.

External sources

- Victorian Department of Human Services, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hospitalization; Acute Disease; Adrenal Cortex Hormones [*therapeutic use]; Asthma [diagnosis] [*drug therapy]; Randomized Controlled Trials as Topic; Severity of Illness Index

MeSH check words

Adult; Humans