Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 12

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[Intervention Review]

Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

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Editorial group: Cochrane Airways Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 12, 2012.
Review content assessed as up-to-date: 28 September 2012.

Citation: Nair P, Milan SJ, Rowe BH. Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD002742. DOI: 10.1002/14651858.CD002742.pub2.

ABSTRACT

Background

Asthma is a chronic condition in which sufferers may have occasional or frequent exacerbations resulting in visits to the emergency department (ED). Aminophylline has been used extensively to treat exacerbations in acute asthma settings; however, it's role is unclear especially with respect to any additional benefit when added to inhaled beta$_2$-agonists.

Objectives

To determine the magnitude of effect of the addition of intravenous aminophylline to inhaled beta$_2$-agonists in adult patients with acute asthma treated in the ED setting.

Search methods

We identified trials from the Cochrane Airways Group register (derived from MEDLINE, EMBASE, CINAHL standardised searches) and handsearched respiratory journals and meeting abstracts. Two independent review authors screened and obtained potentially relevant articles and handsearched their bibliographic lists for additional articles. In the original version of this review published in 2000 we included searches of the database up to 1999. The 2012 review was updated with a revised search from inception to September 2012.

Selection criteria

Randomised controlled trials comparing intravenous aminophylline versus placebo in adults with acute asthma and treated with inhaled beta$_2$-agonists. We included patients who were treated with or without corticosteroids or other bronchodilators provided this was not part of the randomised treatment.

Data collection and analysis

Two review authors independently extracted data and one review author entered data into RevMan, which was checked by a second review author. Results are reported as mean differences (MD) or odds ratios (OR) with 95% confidential intervals (CI).

Main results

Fifteen studies were included in the previous version of the review, and we included two new studies in this update, although we were unable to pool new data. Overall, the quality of the studies was moderate; concealment of allocation was assessed as clearly adequate in only seven (45%) of the trials. There was significant clinical heterogeneity between studies as the doses of aminophylline and other medications and the severity of the acute asthma varied between studies.

There was no statistically significant advantage when adding intravenous aminophylline with respect to hospital admissions (OR 0.58; 95% CI 0.30 to 1.12; 6 studies; n = 315). In 2000 it was found that there was no statistically significant effect of aminophylline on airflow outcomes at any time period; the addition of two trials in 2012 has not challenged this conclusion. People treated with aminophylline and beta$_2$-agonists had similar peak expiratory flow (PEF) values compared to those treated with beta$_2$-agonists alone at 12 h (MD 8.30 L/min; 95% CI -20.69 to 37.29 L/min) or (MD -1.21% predicted; 95% CI -14.21% to 11.78% predicted) and 24 h (MD 22.20 L/min; 95% CI -56.65 to 101.05 L/min). Two subgroup analyses were performed by grouping studies according to mean baseline airflow limitation (11 studies) and the use of any corticosteroids (nine studies). There was no relationship between baseline airflow limitation or the use of corticosteroids on the effect of aminophylline. Aminophylline-treated patients reported more palpitations/arrhythmias (OR 3.02; 95% CI 1.15 to 7.90; 6 studies; n = 249) and vomiting (OR 4.21; 95% CI 2.20 to 8.07; 7 studies; n = 321); however, no significant difference was found in tremor (OR 2.60; 95% CI 0.62 to 11.02; 5 studies; n = 249).

Authors' conclusions

The use of intravenous aminophylline did not result in significant additional bronchodilation compared to standard care with inhaled beta$_2$-agonists in patients experiencing an asthma exacerbation in the ED setting, or in a significant reduction in the risk of hospital admission. For every 100 people treated with aminophylline an additional 20 people had vomiting and 15 people arrhythmias or palpitations. No subgroups in which aminophylline might be more effective were identified. Our update in 2012 is consistent with the original conclusions that the risk-benefit balance of intravenous aminophylline is unfavourable.

PLAIN LANGUAGE SUMMARY

Does an aminophylline injection in addition to bronchodilators for an asthma attack improve lung function and other outcomes or cause harm?

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 severe or even fatal. The main drugs used to relieve a severe asthma attack are bronchodilators (reliever inhalers to open up the lungs and airways) for the spasms and corticosteroids (preventer medications to decrease the inflammation in the lungs and airways). The drug aminophylline has also been used intravenously (injected into the veins) for many years; however, this review of trials found that aminophylline is not significantly better than other bronchodilator drugs, and has more adverse effects. For every 100 people treated with aminophylline an additional 20 people had vomiting and 15 people arrhythmias or palpitations. This review was first published in 2000 and was updated in 2012 and the addition of two trials in 2012 did not alter the original conclusions.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Aminophylline compared to placebo for adults with acute asthma

Patient or population: patients with adults with acute asthma
Settings: emergency department
Intervention: aminophylline
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Aminophylline				
PEF (L/min) - at 60 min	The mean PEF (L/min) - at 60 min in the placebo group was 208.17 (158 patients)	The mean PEF (L/min) - at 60 min in the intervention group was 219.05 (144 patients)	(MD 6.24 L/min; 95% CI -21.09 to 33.57 L/min)	302 (6 studies)	⊕⊕○○ **low**[1]	
Hospital admissions	**275 per 1000**	**180 per 1000** (102 to 298)	**OR 0.58** (0.3 to 1.12)	315 (6 studies)	⊕⊕⊕○ **moderate**[2]	
Tremor	**349 per 1000**	**582 per 1000** (249 to 855)	**OR 2.6** (0.62 to 11.02)	249 (5 studies)	⊕⊕○○ **low**[3,4]	
Vomiting	**90 per 1000**	**294 per 1000** (178 to 443)	**OR 4.21** (2.2 to 8.07)	321 (7 studies)	⊕⊕⊕○ **moderate**[5]	
Arrhythmia/palpitations	**102 per 1000**	**255 per 1000** (115 to 472)	**OR 3.02** (1.15 to 7.9)	249 (6 studies)	⊕⊕⊕○ **moderate**[6]	
Convulsions	See comment	See comment	Not estimable	21 (1 study)	⊕⊕⊕○ **moderate**[7]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; OR: odds ratio; PEF: peak expiratory flow rate

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1 A point is deducted for the PEF (L/min) at 60-min analysis to reflect the variability in the risk of bias among the contributing studies and a further point is deducted to reflect the level of heterogeneity among the contributing studies (I^2 at 51%)
2 A point is deducted for the hospitalised or admitted analysis to reflect the variability in the risk of bias among the contributing studies
3 A point is deducted for the analysis of tremor side effects to reflect the variability in the risk of bias among the contributing studies
4 An additional point is deducted for the analysis of tremor side effects to reflect the high level of heterogeneity (I^2 at 77%)
5 A point is deducted for the analysis of vomiting side effects to reflect the variability in the risk of bias among the contributing studies
6 A point is deducted for the arrhythmia/palpitations analysis to reflect the variability in the risk of bias among the contributing studies
7 A point is deducted for the convulsions analysis to reflect the uncertainty in the generation of the randomisation sequence process in the one contributing study

BACKGROUND

Description of the condition

Each year in the US over 10 million people experience an asthma exacerbation (Krishnan 2006) and in the UK there were 65,732 hospital admissions for asthma in the period 2005 to 2006 (NHS 2011). In the US approximately 10% to 20% of patients with acute asthma are admitted to hospital, and 10% to 20% of patients discharged from the emergency department relapse within two weeks (Camargo 1998a; Camargo 1998b). A number of national (BTS 1995; Beveridge 1996; NAEPP 2007; Boulet 1999; BTS/SIGN 2011) and international (NHLBI/WHO 1995; GINA 2011) guidelines for the management of acute asthma have been published since the 1990s.

In view of the fairly long history of randomised trial research in this area, going back to the 1970s, there is a large body of evidence on treating acute asthma in the emergency department (ED) setting. The main treatments include short-acting beta$_2$-agonist agents and systemic corticosteroids. The focus of this review is on patients who present to EDs with worsening of their symptoms that usually require systemic corticosteroids. The review examines the effect of intravenous aminophylline in patients who felt ill enough to present to an EDor were admitted to hospitals and the entry criteria for most of the included trials defined asthma as physician-diagnosed.

Description of the intervention

Methylxanthines, such as theophylline (administered orally) and aminophylline (administered intravenously), have been used in the treatment of asthma since the 1960s and remain some of the most prescribed drugs for asthma worldwide. The mechanism of action of the methylxanthines is uncertain; the three main cellular effects are that of translocation of calcium, inhibition of the phosphodiesterase enzyme resulting in the accumulation of cyclic adenosine monophosphate (AMP) and adenosine receptor blockade.

How the intervention might work

Methylxanthines are weak bronchodilators, and they also interact with respiratory muscles to reduce respiratory muscle fatigue. Conventionally, the therapeutic benefit of xanthines has been ascribed to bronchodilation. With the development of safer and more potent bronchodilators, such as inhaled beta$_2$-agonists, there has been a decline in the use of methylxanthines. However, with the growing recognition that theophylline might modulate airway inflammation in asthma, there has been a resurgence in the interest in these agents.

Why it is important to do this review

The use of xanthines varies in different parts of the world. Most international guidelines recommend the use of theophylline only as an additional bronchodilator in chronic asthma that remains difficult to control despite moderate- to high-dose inhaled corticosteroids and long-acting beta-agonists. Its use in acute severe asthma has declined in the past decade due to the systematic review evidence accumulated in the past (Littenberg 1988; Nair 2000). There have been a number of studies comparing intravenous aminophylline with beta$_2$-agonists and the combination of the two with beta$_2$-agonists alone; however, prior to systematic reviews the results have been conflicting. It was widely believed that intravenous aminophylline was effective in relieving bronchoconstriction in acute asthma as an initial treatment drug. There have been several systematic reviews published dealing with the use of methylxanthines in acute asthma. The previous version of this review (Nair 2000) concluded "in acute asthma, the use of intravenous aminophylline did not result in any additional bronchodilation compared to standard care with beta$_2$-agonists. The frequency of adverse effects was higher with aminophylline. No subgroups in which aminophylline might be more effective could be identified. These results should be added to consensus statements and guidelines". The current version of this review aimed to examine this conclusion in relation to any relevant randomised controlled trials (RCTs) that may have been completed since 1999. Separate reviews are available in *The Cochrane Library* for: intravenous aminophylline for acute severe asthma in children over two years of age receiving inhaled bronchodilators (Mitra 2009) and Intravenous beta$_2$-agonists for acute asthma in the emergency department (Travers 2009). In Travers 2009 direct comparisons are made between intravenous aminophylline and intravenous beta$_2$-agonists.

OBJECTIVES

To determine whether intravenous aminophylline has an additional bronchodilation effect in adult patients with acute asthma when used in conjunction with inhaled beta$_2$-agonists with or without systemic corticosteroids (intravenous, oral, inhaled or combinations of these).

METHODS

Criteria for considering studies for this review

Types of studies

We included RCT in this review. Cross-over trials were excluded.

Types of participants

We included studies involving adult patients (over 18 years of age) with acute asthma attending EDs or other acute care settings (asthma clinics, hospital outpatient clinics, etc.). Studies involving only children or patients with COPD were excluded. Studies including both COPD and asthma patients were considered if patients with asthma could be separated by reviewing the study or through correspondence with the authors. Studies involving patients requiring mechanical ventilation at presentation and inpatients for more than 24 h were also excluded.

Types of interventions

The primary comparison was intravenous aminophylline plus inhaled beta$_2$-agonists versus either placebo or inhaled beta$_2$-agonists alone. We accepted interventions of intravenous aminophylline at either an initial loading dose, maintenance infusion or both.

We also included studies comparing intravenous aminophylline plus "standard care" versus placebo plus "standard care" alone. We only included standard care if patients were treated with inhaled beta$_2$-agonists (usually nebulised using oxygen); however,standard care could also include treatment with other agents such as corticosteroids. We excluded studies that compared aminophylline directly to beta$_2$-agonists (i.e. head-to-head trials) as this comparison is the subject of another Cochrane review (Travers 2012). Study co-interventions, such as the use of systemic corticosteroids, beta$_2$-agonists (nebulised or metered-dose inhalers), ipratropium bromide (nebulised or metered-dose inhalers), intravenous magnesium sulfate or other sympathomimetics (e.g. adrenaline) were recorded.

Types of outcome measures

Primary outcomes

Lung (pulmonary) function: change in peak expiratory flow (PEF; absolute and % predicted) or forced expiratory volume in 1 second (FEV_1; absolute and % predicted).

Secondary outcomes

- Admission to hospital;.
- Effect on vital signs (pulse rate, respiratory rate, blood pressure (BP));
- Presence of adverse outcomes (including side effects: tremor, palpitations, cardiac arrhythmias and vomiting).

The analysis was performed from data collected at 0, 0.5, 1, 12 and 24 h or as close to them as possible.

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). All records in the CAGR coded as 'asthma' were searched using the following terms:

(aminophylline* or Phyllocontin or Truphylline OR theophylline* or ethylenediamine or methyl-xanthin* OR methylxanthin* OR "methyl xanthin*") AND (emergenc* or acute* or status or severe* or exacerb* or hospital*).

A search of ClinicalTrials.gov was also conducted using the terms in Appendix 2 from inception to the present and there was no restriction on the language of publication. The search was conducted in November 2011 and updated in September 2012. Search methods used in the previous version of the review are in Appendix 3.

Searching other resources

We searched all reference lists of available primary studies and review articles to identify other potentially relevant citations. We contacted authors of published or unpublished studies scientific advisors of the various pharmaceutical industries that manufacture methylxanthines; and colleagues, collaborators and other trialists working in the field of asthma to identify potentially relevant studies.

Data collection and analysis

Selection of studies

In 2000 in a preliminary stage of the process, two review authors (PN and BR) screened the retrieved references using the abstract, title and MeSH headings, and independently assessed studies for potential relevance. At the next stage, using the full text of the study, two review authors (PN, BR) independently selected trials for inclusion in the review. At this point, if there was a disagreement between review authors, this was resolved using an independent third party adjudicator (JB).

In 2012 the preliminary stage was completed independently by two out of three people (SM, Melissa Bota and Lindsay Lovstrom), and the following stage was completed by two review authors independently (PN, SM). Had there been disagreements, we planned to involve an independent third party adjudicator; however, this was not necessary.

Data extraction and management

In 2000 data for included trials were extracted independently by two review authors (PN, JB) and entered into the Cochrane Collaboration software program (RevMan 2011). In some cases, information regarding outcomes was estimated from graphs. This was also performed independently by both review authors. In 2012 the narrative update of the review with two trials, unsuitable for statistical aggregation, was completed by SM and PN.

Assessment of risk of bias in included studies

In 2000 trials were assessed according to the Jadad criteria (Jadad 1996). In the 2012 update (SM and PN or Chris Cates) assessed the trials with respect to selection bias, performance and detection bias, attrition bias, reporting bias and other potential sources of bias using the Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011).

Measures of treatment effect

For dichotomous variables, we expressed data as odds ratios (OR) with 95% confidence intervals (CI). Data for continuous variables were reported as mean differences (MD) with 95% CIs or standardised mean differences (SMD) with 95% CIs in analyses where it was necessary to pool data from different measures.

Unit of analysis issues

The unit of analysis was the patient.

Dealing with missing data

We planned to contact authors if outcome data or information on trial design was missing in the 2012 update of this review; however, this issue did not arise.

Assessment of heterogeneity

We tested heterogeneity among pooled estimates using the DerSimonian and Laird method; and we considered $P < 0.05$ as the threshold for statistical significance. Heterogeneity was assessed at first using visual inspection of forest plots. The Chi^2 test was similarly considered ($P < 0.10$) but interpreted with caution owing to the low power associated with this test. I^2 was also considered and interpreted in relation to the following guidance (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Where we encountered heterogeneity according to the above mentioned criteria, we applied the fixed- and random-effects models and commented on any differences, reporting the random-effects model in the review.

Assessment of reporting biases

We planned to examine publication bias using funnel plots if we had included an adequate number of trials (10 or more) aggregated in a single meta-analysis. We recognise that an asymmetric funnel plot can reflect heterogeneity, outcome reporting bias and small study effects and is therefore not necessarily a reflection of publication bias.

Data synthesis

Trials were combined using Cochrane Review Manager software (RevMan 2011). Results are reported using the fixed-effect model where there was no significant heterogeneity.

Subgroup analysis and investigation of heterogeneity

Subgroup and sensitivity analysis were performed by pooling absolute and relative data, in order to include sufficient studies at each time point. In these cases, we calculated individual and pooled statistics as SMD and 95% CIs using a random-effects model. Subgroup analysis was performed using the following subgroups:

1. severity at presentation (based on the mean airflow limitation of patients in both the placebo or control group). Severe asthma was considered FEV_1 lower than 40% or 1 L or PEF lower than 40% or 150 L/min; and
2. co-intervention with intravenous corticosteroids versus none.

Sensitivity analysis

Sensitivity analyses were performed using the following domain:

- random-effects versus fixed-effect modelling.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

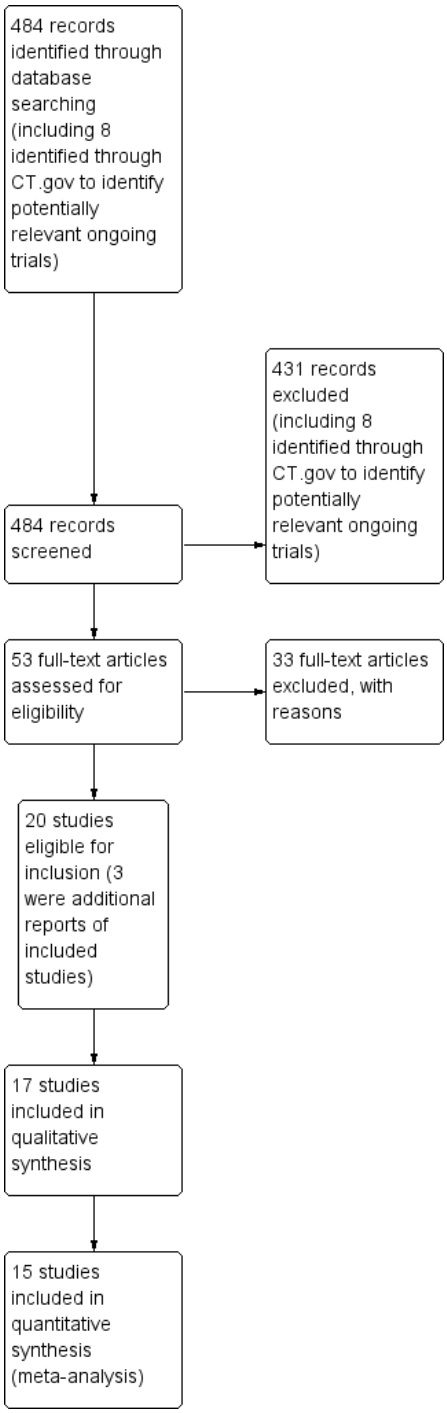
Results of the search

In 2000, a total of 210 abstracts were identified using the CAGR. Two independent review authors identified a total of 27 potentially eligible studies for further review. Following full-text review, 12 trials were excluded and 15 were included. Two trials (Fanta 1986; Coleridge 1993) had data available to form two different substudies, and were reported in two parts. Results from a total of 17 trial comparisons formed the basis for this review in 2000. At that time, a total of 739 patients (353 aminophylline; 386 standard

care) had been involved in the trials in this review. Only three trials had sample sizes larger than 30 subjects per group.

In 2012, 484 references (including the 210 found in the original searches) were identified from which a further 26 were judged to be potentially relevant to the review (see Figure 1). Two new trials (Whig 2001; Pavalakou 2006) were independently considered by PN and SM as relevant for inclusion, although it was not possible to combine data from these studies with the original analyses. In Whig 2001 this was because the age range of participants included children who were younger than our inclusion criteria and we were not able to obtain separate data on adults over 18 years of age. Pavalakou 2006 was reported as a conference abstract and therefore subject to a paucity of usable data; however, the findings from these trials are narratively included in the review. Combined they introduced a further 78 patients, bringing the overall total of included participants to 817. Three of the remaining 24 studies were additional reports of studies already included in the review (Emerman 1986; Coleridge 1993; Zainudin 1994) and a further 20 did not meet the inclusion criteria for the review (Muittari 1978; Wolfe 1978; Carrier 1985; Aggarwal 1986; Haahtela 1986; Magnussen 1986; Jonsson 1988; Kino 1991; Montserrat 1991; Alanko 1992; Janson 1992; Janson 1992a; Nayyer 1994; Djukanovic 1995; Dal Negro 1997; Schwartz 1998; Filiz 2002; Kato 2004; Taqweem 2004; Yamauchi 2005). In was not possible to obtain a trial report from a further study (Barradas 1986).

Figure 1. Study flow diagram.



Included studies

The included studies in were published between 1979 and 2006. Eleven trials were from centres in North America, one from Australia, one from the UK, one from Uruguay, one from Malaysia, one from Greece and one from India. Detailed descriptions of each study are given in Characteristics of included studies.

Populations: studies were mainly conducted in adults (older than 18 years) but two studies included subjects older than 15 years (Evans 1980; Coleridge 1993), two older than 16 years (Josephson 1979; Wrenn 1991) and one did not report the age range (Appel 1981). One trial had an age range from two to 25 years (Whig 2001) and another reported as a conference abstract where the mean age was 28 years (Pavalakou 2006). The upper limit of age among included trials was from 25 to 60 years. The populations were defined as people attending emergency departments with "acute asthma" or "acute exacerbation of asthma" and who were previously diagnosed with asthma. However, a detailed definition of "acute" was described in only three trials (Evans 1980; Appel 1981;Siegel 1985). Three studies included subjects with a chief complaint of asthma (Josephson 1979; Rossing 1981; Fanta 1982). Asthma criteria were generally established according to American Thoracic Society (ATS) criteria (ATS 1987).

Several of the studies were small, so matching of severity at baseline was not always achieved. This led to difficulties where results were presented as measurements at a time point rather than as changes from baseline. Baseline differences in severity may thus bias results between groups. To adjust for this, baseline differences were calculated and added to the disadvantaged group. The analysis was then repeated, using the original standard deviation (SD).

Severity of exacerbation: severity of the exacerbation was generally based on symptoms and the degree of airflow limitation of participants; however, this was not always specified in the manuscript. The airflow limitation was classified as "severe" in 11 trials as defined by PEF (< 40 % predicted or 150 L/min) or FEV_1 (< 40% predicted or 1 L).

Interventions: the doses of aminophylline and other medications varied among studies. Trials specified different $beta_2$-agonists (five used epinephrine, five salbutamol, three meta-isoproterenol, two isoproterenol and two albuterol). Similarly, co-intervention with corticosteroids was clearly documented and varied among trials; five trials used hydrocortisone, four methylprednisolone and the remaining nine trials did not use systemic corticosteroids.

Outcomes: a variety of outcomes were reported. Whenever feasible, the most commonly reported outcomes are reported and include: pulmonary functions (e.g. PEF, % PEF, FEV_1 and % FEV_1), admissions and adverse effects.

Excluded studies

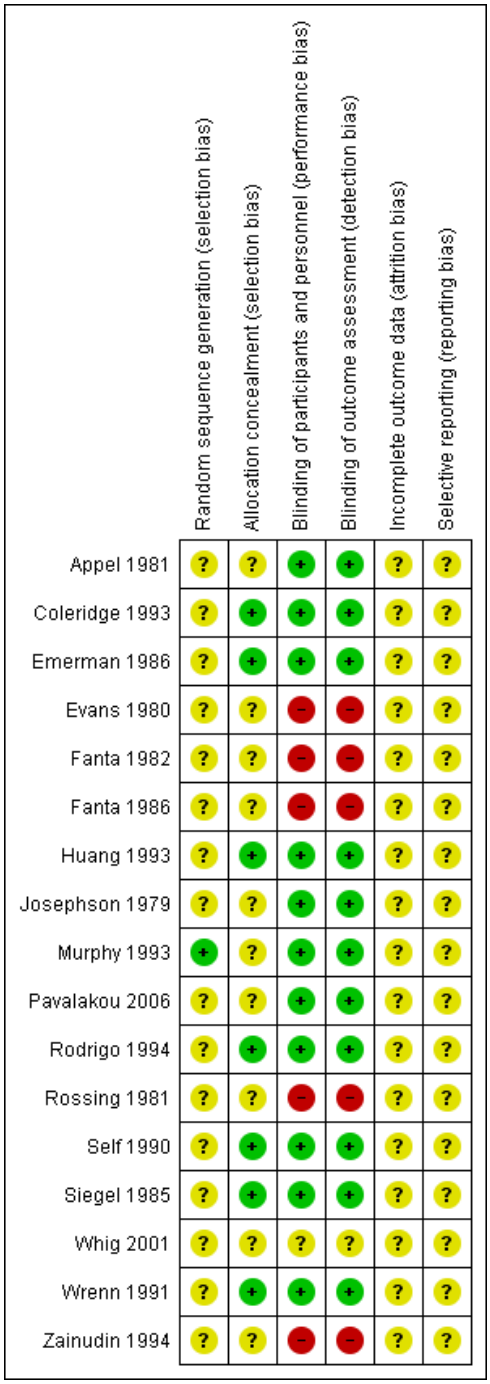
In total 33 studies have been excluded and reasons for exclusion have been provided in Characteristics of excluded studies. The main reasons for exclusion were as follows: 13 (39%) made a direct comparison between aminophylline and $beta_2$-agonists (rather than comparing the additive effect of intravenous aminophylline to $beta_2$-agonists); seven (21%) were non-randomised; six (18%) focused on stable asthma rather than acute asthma; two (6%) compared oral aminophylline versus intravenous aminophylline; one compared inhaled $beta_2$-agonists versus intravenous $beta_2$-agonists and one (3%) compared intravenous theophylline alone versus intravenous theophylline plus intravenous corticosteroid. In one trial (3%) the setting was ICU and insufficient information was available concerning ED treatment, another trial (3%) focused on paediatric patients and in another trial (3%) data were unavailable.

Risk of bias in included studies

Allocation

Only one trial was judged to be low in risk of bias with respect to random sequence generation (selection bias) (Murphy 1993 Figure 2). The risk of bias for the remaining 16 trials was judged as unclear as details of the random sequence generation were not described in the trial report. In seven trials the risk of bias regarding allocation concealment (selection bias) was considered low (Siegel 1985; Emerman 1986; Self 1990; Wrenn 1991; Coleridge 1993; Huang 1993; Rodrigo 1994) and in the remaining 10 trials it was judged to be unclear (Josephson 1979; Evans 1980; Appel 1981; Rossing 1981; Fanta 1982; Fanta 1986; Murphy 1993; Zainudin 1994; Whig 2001; Pavalakou 2006).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Blinding

Eleven trials were judged to be at low risk of bias with respect to the blinding of participants and personnel (performance bias) (Josephson 1979; Appel 1981; Siegel 1985; Emerman 1986; Self 1990; Wrenn 1991; Coleridge 1993; Huang 1993; Murphy 1993; Rodrigo 1994; Pavalakou 2006). In one trial the risk was judged to be unclear Whig 2001; and in the following five the risk was judged to be high (Evans 1980; Rossing 1981; Fanta 1982; Fanta 1986; Zainudin 1994).

Main outcome data were collected during the trial and blinding of study personnel responsible for outcome assessment, in a double-blind context, indicates the risk of detection bias in the following studies would be low (Josephson 1979; Appel 1981; Siegel 1985; Emerman 1986; Self 1990; Wrenn 1991; Coleridge 1993; Huang 1993; Murphy 1993; Rodrigo 1994; Pavalakou 2006). The risk of detection bias was unclear in Whig 2001. Five studies were not blinded and the risk of detection bias was judged to be high (Evans 1980; Rossing 1981; Fanta 1982; Fanta 1986; Zainudin 1994).

Incomplete outcome data

In all 17 included studies reporting bias was unclear. As these acute asthma trials were very short it is conceivable that all participants would have completed the trial. We evaluated trials where no patients were reported as having been withdrawn to be at no higher risk of bias than those where several failed to complete the trial.

Selective reporting

In all 17 included studies reporting bias was judged to be unclear. There was no apparent indication of selective reporting in any of the trials.

Effects of interventions

See: **Summary of findings for the main comparison** Aminophylline compared to Placebo for adults with acute asthma

The results are discussed with regard to the outcome groupings: pulmonary function, admissions, adverse effects and subgroup/sensitivity analyses.

Pulmonary function

There were no statistically significant differences in PEF or FEV_1 between aminophylline and placebo observed at any time period studied apart from in the one study Rodrigo 1994 contributing FEV_1 data at 30 min (MD -0.26 L; 95% CI -0.49 to -0.03 L; 1 study; n = 94; Analysis 1.4); however, there was also a difference between groups at baseline in this study. At baseline, the aminophylline-treated group recorded marginally lower PEF (MD -7.61 L/min; 95% CI -21.51 to 6.28 L/min; 7 studies; n = 327; Analysis 1.2; MD -1.53 L/min; 95% CI -2.85 to -0.20 L/min; 6 studies; n = 285; Analysis 1.3) and FEV_1 (MD -0.05 L; 95% CI -0.18 to 0.08 L; 8 studies; n = 419; Analysis 1.4; MD -0.36% predicted; 95% CI -4.09 to 3.38% predicted; 5 studies; n = 260; Analysis 1.5) values than the control group. One hour after starting aminophylline, the treated group had similar values to the control group for both PEF (MD 6.24 L/min; 95% CI -21.09 to 33.57 L/min; 6 studies; n = 302; Figure 3; MD -2.28% predicted; 95% CI -4.84 to 0.27% predicted; 6 studies; n = 285; Figure 4) and FEV_1 (MD 0.05 L; 95% CI -0.13 to 0.23 L; 8 studies; n = 419; Figure 5; MD -2.99% predicted; 95% CI -13.05 to 7.07% predicted; 3 studies; n = 176; Figure 6). At 12 h post infusion both PEF (MD 8.30 L/min; 95% CI -20.69 to 37.29 L/min; 3 studies; n = 84; Analysis 1.2; MD -1.21% predicted; 95% CI -14.21 to 11.78% predicted; 2 studies; n = 76; Analysis 1.3) and FEV_1 (MD 0.41 L; 95% CI -0.16 to 0.98 L; 1 study; n = 21; Analysis 1.4; MD 4.28% predicted; 95% CI -17.93 to 26.49% predicted; 2 studies; n = 39; Analysis 1.5) failed to demonstrate a difference between the treatment arms. The same results were demonstrated at 24 h for PEF (MD 22.20 L/min; 95% CI -56.65 to 101.05 L/min; 2 studies; n = 40; Analysis 1.2). There were no data available at this time point relating to PEF % predicted). At 24 h FEV_1 was not significantly different (MD 0.42; 95% CI -0.13 to 0.97; 1 study; n = 21; Analysis 1.4; MD 4.35% predicted; 95% CI -16.68 to 25.39% predicted; 2 studies; n = 39; Analysis 1.5). These differences were neither statistically significant nor clinically important.

Figure 3. Forest plot of comparison: 1 Aminophylline vs. placebo, outcome: 1.2 PEF (L/min).

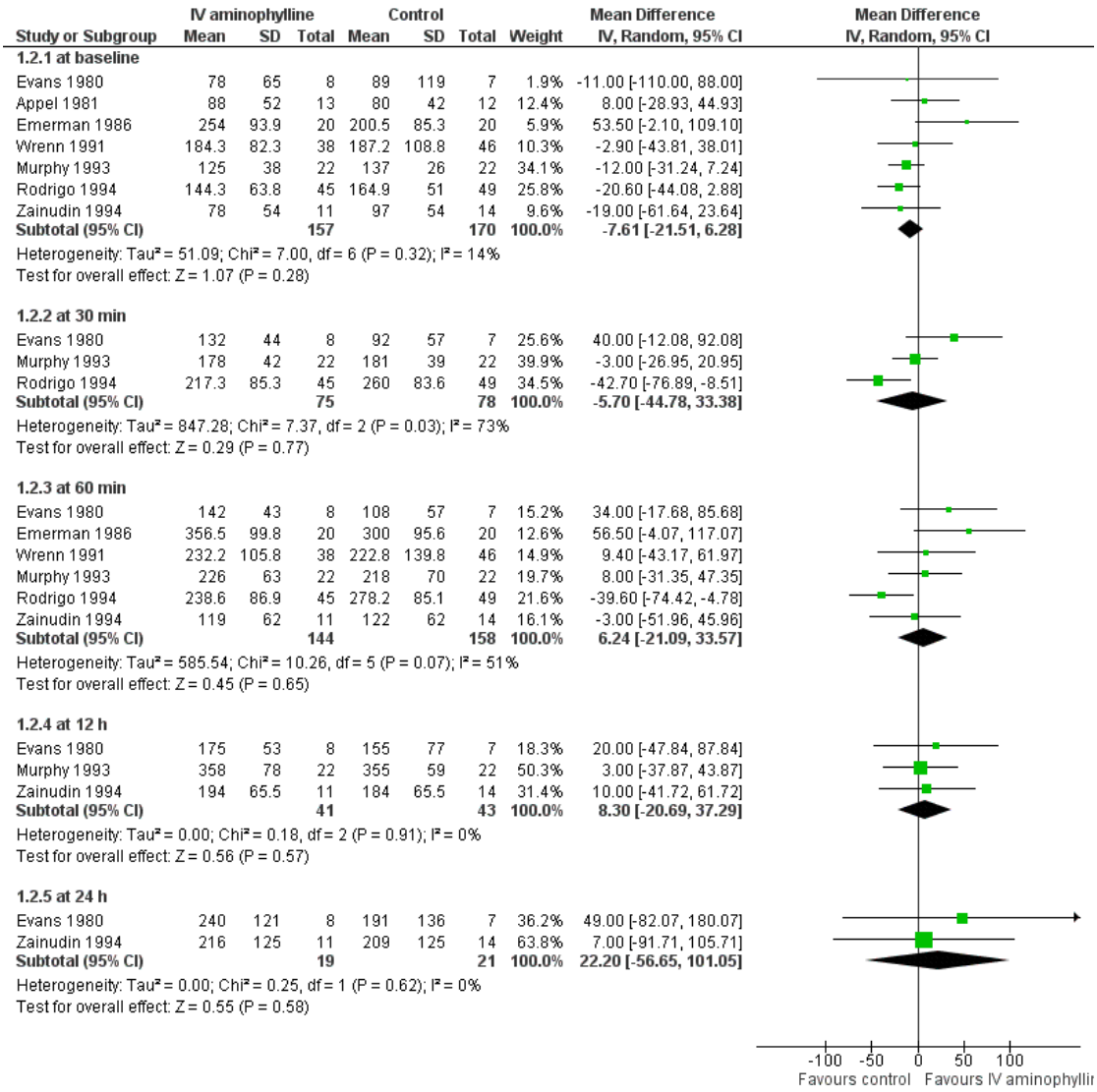


Figure 4. Forest plot of comparison: 1 Aminophylline vs. placebo, outcome: 1.3 PEFR (% predicted).

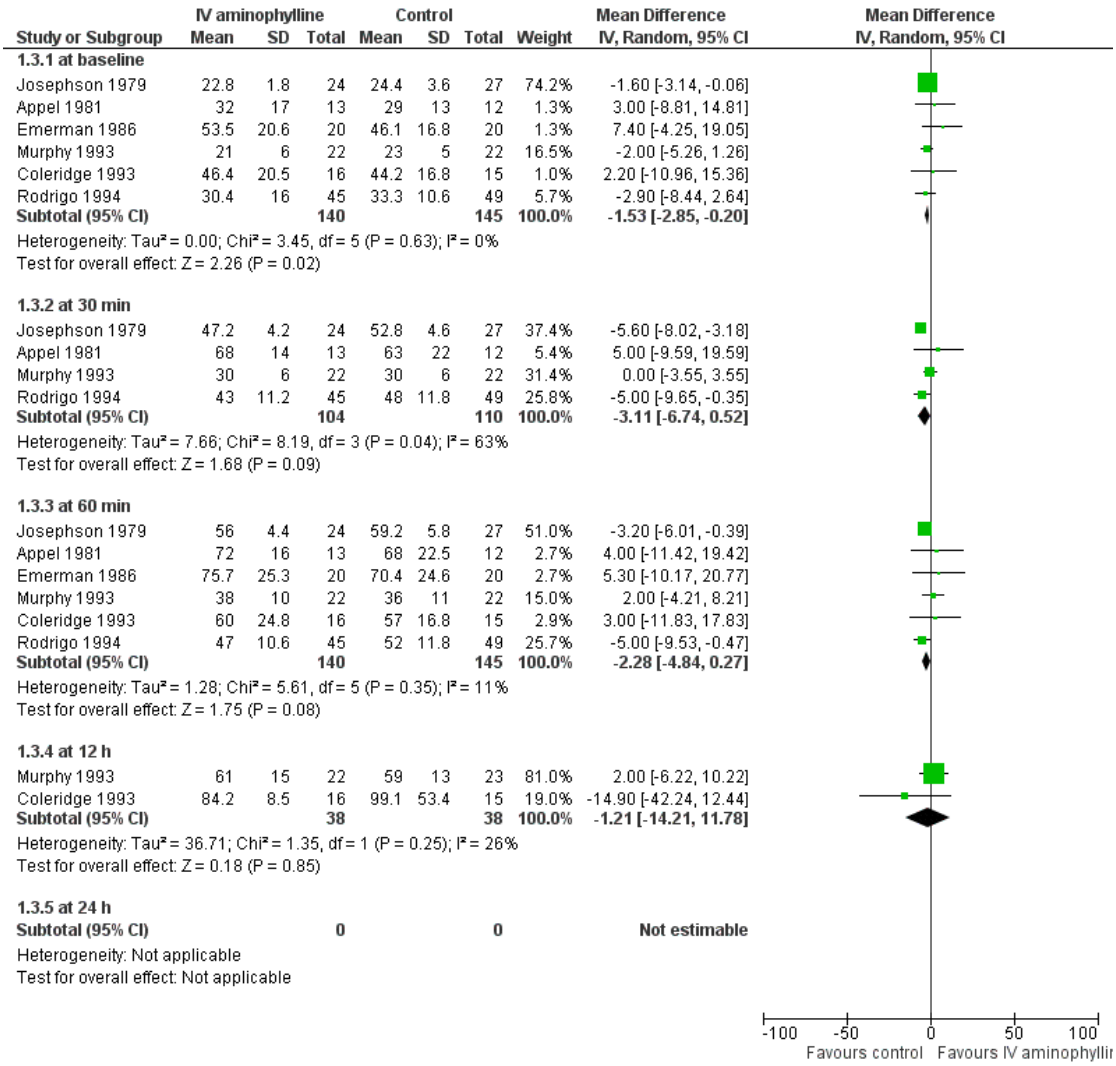


Figure 5. Forest plot of comparison: 1 Aminophylline vs. placebo, outcome: 1.4 FEV1 (L).

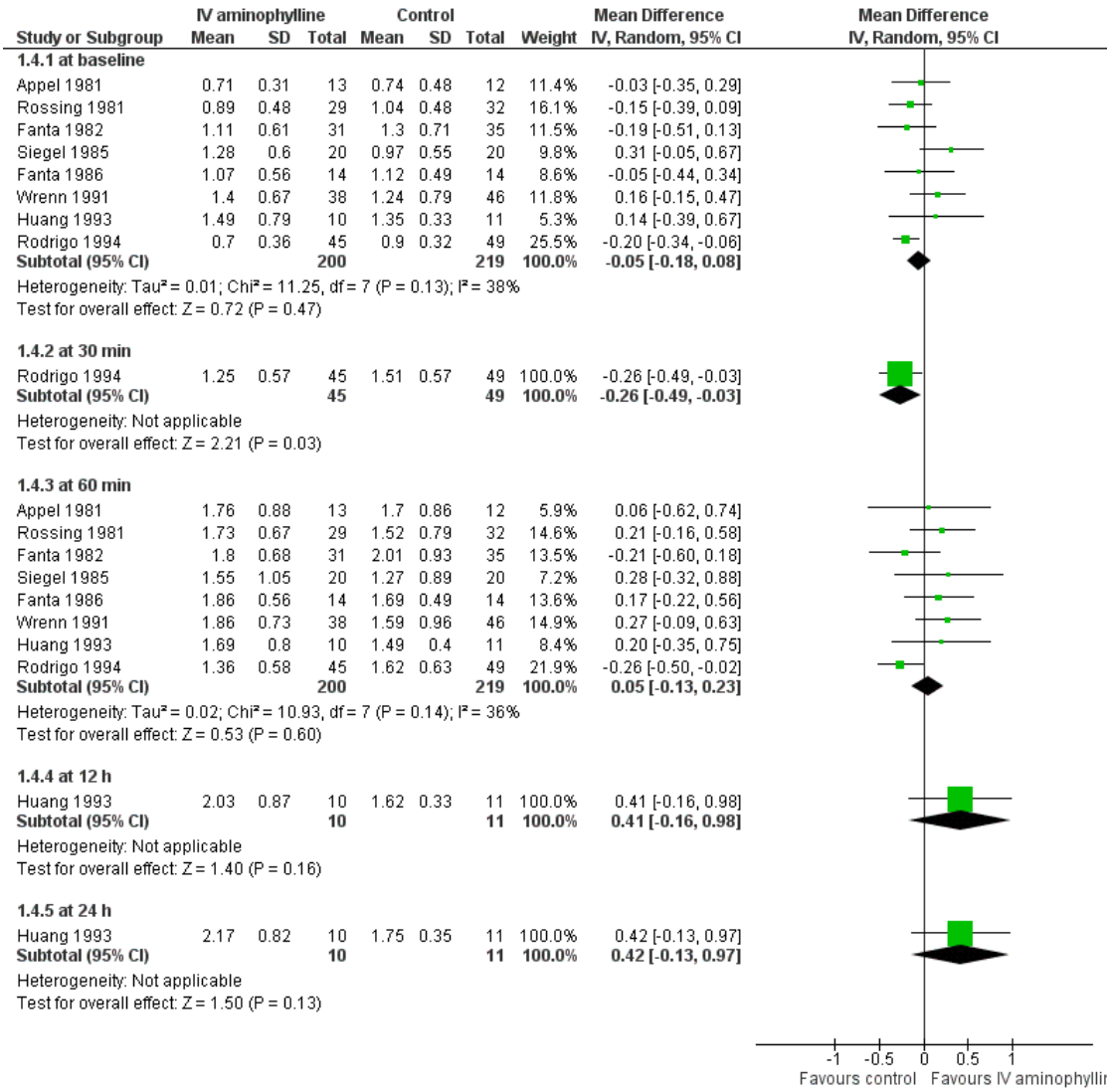
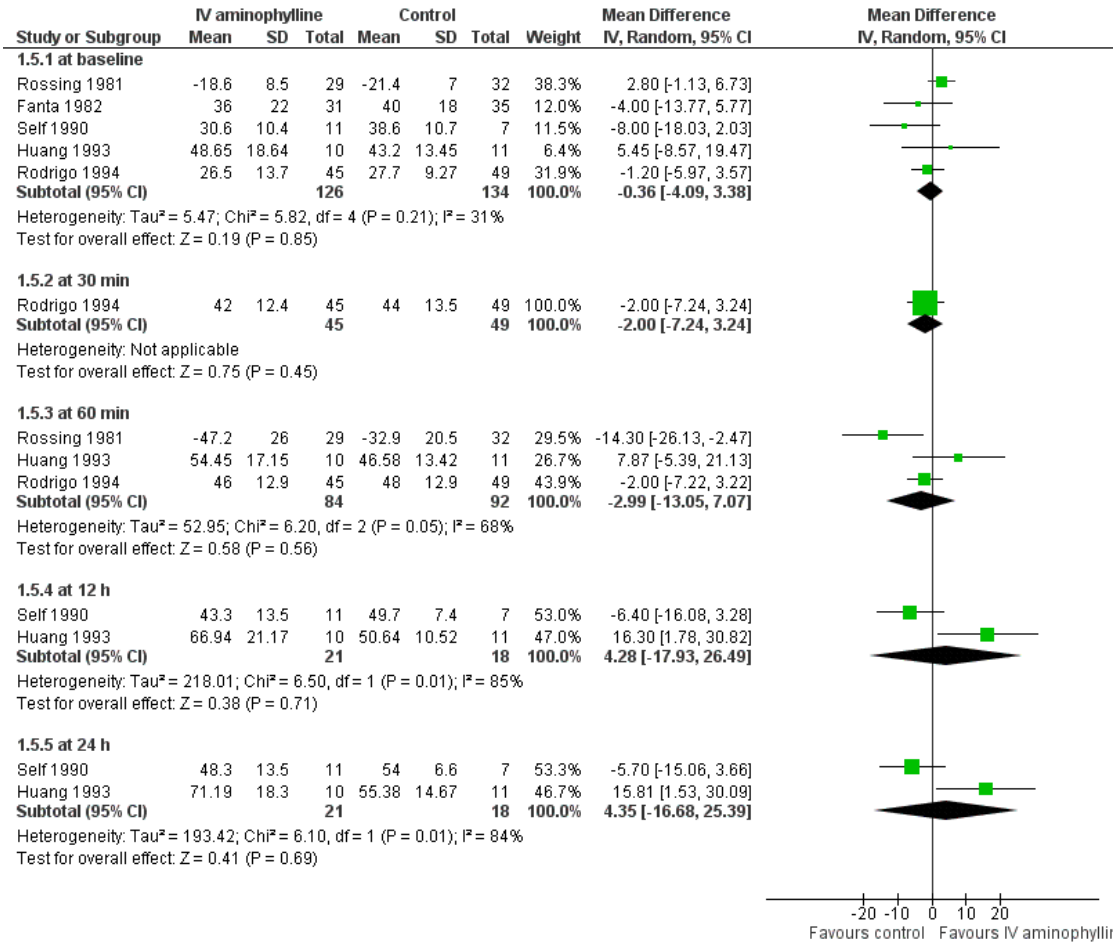


Figure 6. Forest plot of comparison: 1 Aminophylline vs. placebo, outcome: 1.5 FEV_1 (% predicted).



Given that very few studies provided data at 12 or 24 h, the studies were re-analysed by pooling all studies that provided a measurement at either time point using an SMD. If one study had results expressed in both % predicted and absolute values, the latter were used. The results remained unchanged; there was no significant effect of aminophylline.

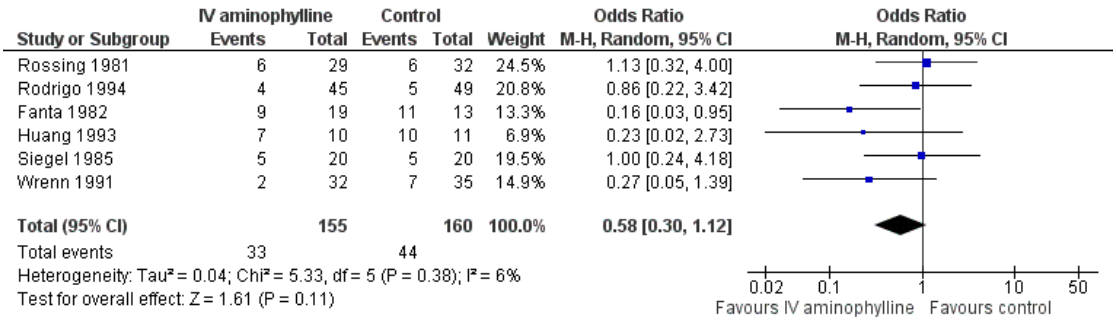
Two trials were identified in the 2012 update of this review that could not be statistically included in the meta-analysis: Pavalakou 2006 stated that the addition of intravenous aminophylline did not contribute benefit to patients experiencing an acute asthma attack. We were not able to obtain data from the adult subset of participants in Whig 2001 although across all the children and adults (aged two to 25 years) there was no significant difference between the two groups on this outcome on any of the five time points monitored.

We acknowledge that PEF and FEV_1 are not directly comparable but both are included here as they are commonly used outcome measures in emergency departments to decide on discharge from the emergency departments and to assess response to treatment. PEF, being a simpler measurement, is used more widely but it is less reproducible than FEV_1.

Hospital admission

Six studies (315 participants) examined the effect of aminophylline on admissions to hospital (Rossing 1981; Fanta 1982; Siegel 1985; Wrenn 1991; Huang 1993; Rodrigo 1994). There was no significant difference in hospitalisations between the aminophylline and $beta_2$-agonist/comparison groups (OR 0.58; 95% CI 0.30 to 1.12; 6 studies; n = 315; Figure 7). This estimate changed slightly when a fixed-effect model was used, owing to significant heterogeneity (OR 0.56; 95% CI 0.31 to 1.03).

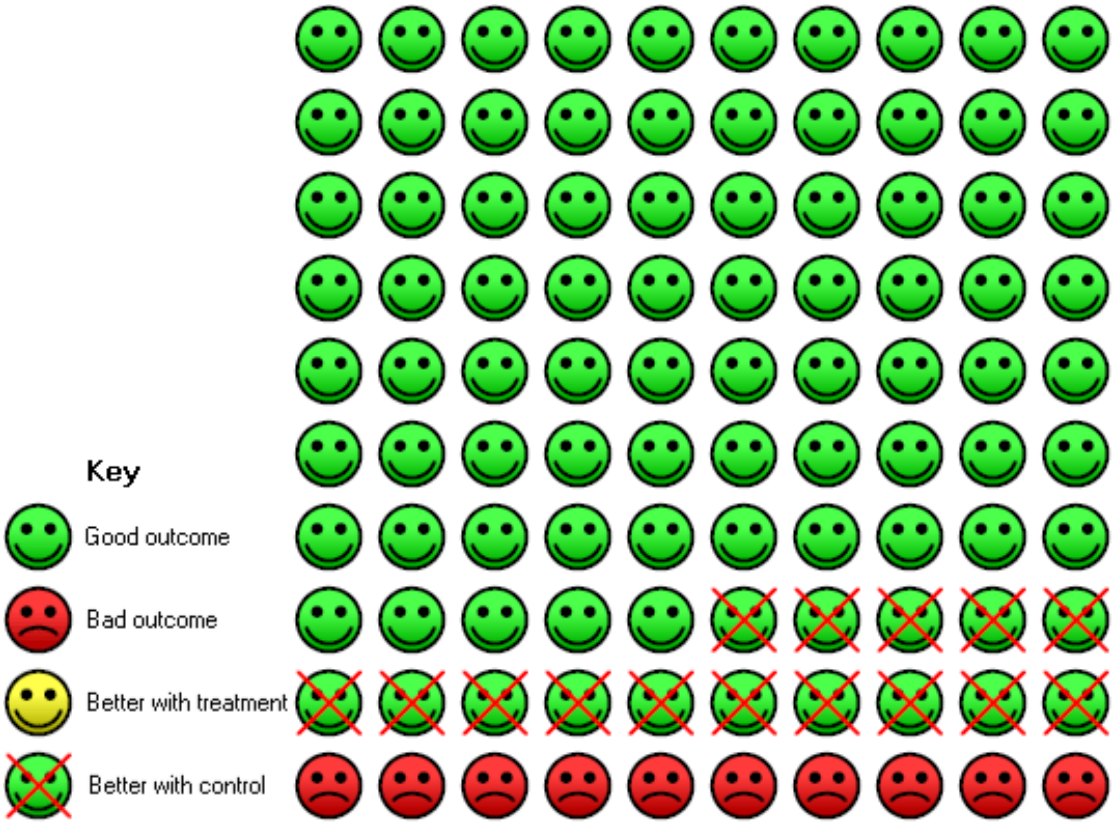
Figure 7. Forest plot of comparison: 1 Aminophylline vs. placebo, outcome: 1.1 Hospital admissions.



Adverse effects

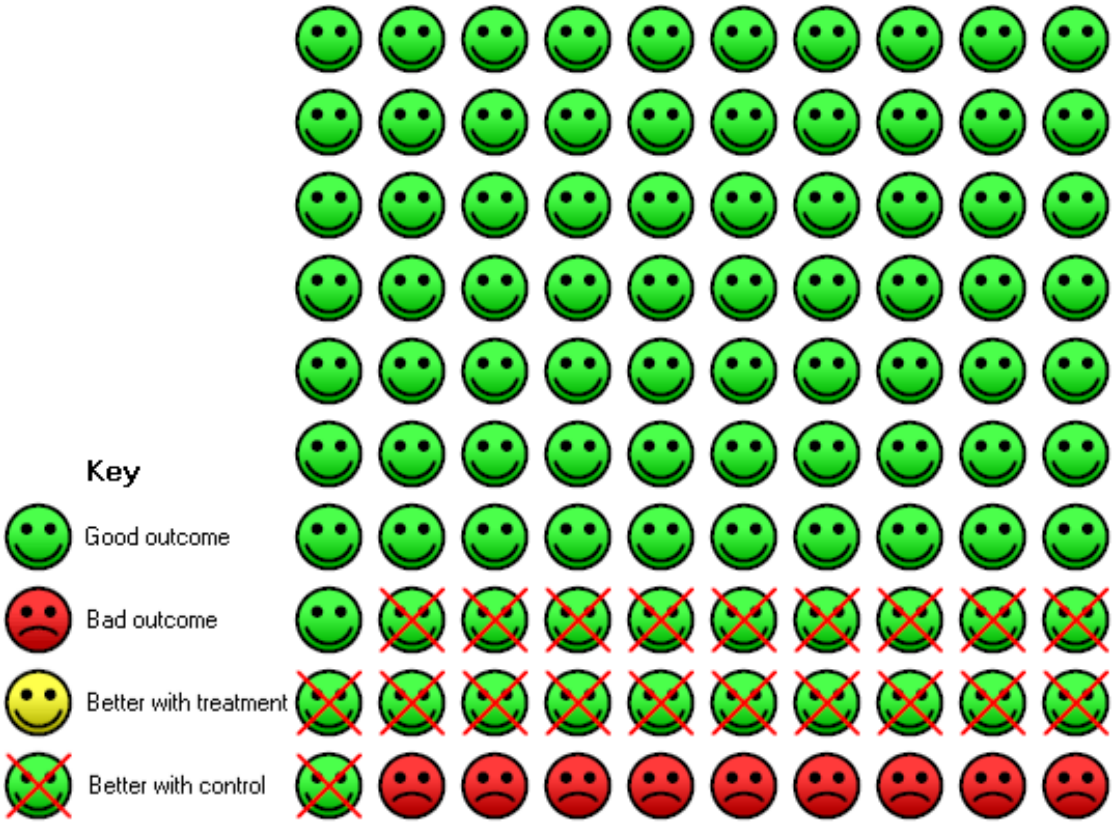
Six studies (249 participants) reported the number of participants experiencing palpitations, arrhythmias or both. There were more events in participants treated with aminophylline plus beta$_2$-agonists than those treated with beta$_2$-agonists alone (OR 3.02; 95% CI 1.15 to 7.90; 6 studies; n = 249; Analysis 1.8). Figure 8 shows that, on average, in the control group, 10 people out of 100 had arrhythmias or palpitations compared to 25 out of 100 (95% CI 11/100 to 47/100) for the intravenous aminophylline group.

Figure 8. Arrhythmia/palpitations: in the control group 10 people out of 100 had arrhythmias or palpitations, compared to 25 out of 100 (95% CI 11 to 47) for the IV aminophylline group.



Similarly, seven trials (321 participants) reported vomiting and there were more events in participants randomised to receive aminophylline (OR 4.21; 95% CI 2.20 to 8.07; 7 studies; n = 321; Analysis 1.7). Figure 9 shows that nine control group participants out of 100 had vomiting compared to 29 out of 100 (95% CI 18/100 to 44/100) participants receiving intravenous aminophylline.

Figure 9. Vomiting: in the control group nine people out of 100 had vomiting, compared to 29 out of 100 (95% CI 18 to 44) for the IV aminophylline group.



There was no difference between the two groups regarding the incidence of tremor (OR 2.60; 95% CI 0.62 to 11.02; 5 studies; n = 249; Analysis 1.6). One study on 21 participants Huang 1993 reported that there were no convulsions in any of the participants and no studies reported hypokalaemia.

In the two studies identified in the 2012 update of this review that could not be statistically included in the meta-analysis, Pavalakou 2006 did not report the effect of aminophylline in relation to adverse effects. Whig and colleagues reported considerably more adverse effects in the aminophylline group among the participants aged 2 to 25 years old (Whig 2001); however, it is important to note that 19 adverse effects (eight nausea, six headache, five anxiety, four vomiting and one ventricular premature beats) were recorded in the aminophylline group whereas there were only five (two nausea, one headache, one anxiety and one vomiting) in the placebo group (Whig 2001).

Subgroup and sensitivity analyses

Subgroup analyses were performed by grouping studies according to mean baseline airflow limitation for our primary outcome, pulmonary function, only. Using our PEF criteria for severity, two studies included subjects classified as mild-moderate asthma and seven as severe asthma. In the studies involving participants with mild-moderate acute asthma there was no difference between treatment groups at baseline (SMD -0.23; 95% CI -0.36 to 0.83; 2 studies; n = 124; Analysis 2.1). This did not change at one hour (SMD 0.26; 95% CI -0.21 to 0.73; 2 studies; n = 124; Analysis 2.3). There was insufficient reporting at 12 or 24 h to conduct further subgroup analyses. The studies that included patients with severe acute asthma indicated a higher PEF level at baseline in the control group (SMD -0.32; 95% CI -0.56 to -0.09; 7 studies; n = 285; Analysis 2.1). There was no difference at one hour (SMD -0.13; 95% CI -0.43 to 0.17; 7 studies; n = 285; Analysis 2.3) or at 24 h (MD 22.20; 95% CI -56.65 to 101.05; 2 studies; n = 40; Analysis 2.5). Using our FEV_1 criteria for baseline asthma severity, four studies were included in the severe group and five in the moderately severe group. Generally very similar (non-significant) results were obtained with the exception of the difference observed at 30 min, with data contributed by only one study, where a higher

FEV_1 level was observed in the control group (SMD -0.45; 95% CI -0.86 to -0.04; 1 study; n = 94; Analysis 2.7).

When studies were grouped according to the use of corticosteroids, the bronchodilator effect of the aminophylline treatment was similar in the corticosteroid-treated group and the non-corticosteroid-treated group. Six studies used corticosteroids and three did not. At baseline, in the patients given corticosteroids, there was no difference in PEF between treatment groups (SMD 0.20; 95% CI -0.43 to 0.03; 6 studies; n = 293; Analysis 3.1); the same was found at one hour (SMD -0.04; 95% CI -0.31 to 0.23; 6 studies; n = 293; Analysis 3.3), at 12 h (SMD -0.02; 95% CI -0.38 to 0.35; 4 studies; n = 115; Analysis 3.4) and at 24 h (SMD 0.17; 95% CI -0.46 to 0.79; 2 studies; n = 40; Analysis 3.5). In the studies in which patients did not receive corticosteroids, there was no difference at baseline (SMD -0.10; 95% CI -0.82 to 0.62; 3 studies; n = 116; Analysis 3.1) and at one hour (SMD 0.04; 95% CI -0.71 to 0.78; 3 studies; n = 116; Analysis 3.3). There was insufficient reporting at 12 or 24 h to conduct further subgroup analyses.

The pooled treatment group had lower values for PEF and FEV_1 than the pooled control group at baseline. Owing to the limitations of the software in 2000, which was unable to deal with repeated measures and to adjust by baseline values, we dealt with this problem by recalculating our results after adding the baseline differences to the disadvantaged group at 30 min and thereafter. Then, we repeated the analysis using these "new adjusted data". Sensitivity analyses were performed adjusting for baseline differences, using methodological criteria and fixed-effect modelling. Given the baseline differences between treated and control groups, adjustment of the aminophylline-treated group pulmonary function measures was performed. One hour after starting aminophylline, there was no difference in PEF (MD 8.9 L/min; 95% CI -10 to 27 L/min; MD -0.8% predicted; 95% CI -3 to 1% predicted) or FEV_1 (MD 0.1 L; 95% CI -0.0 to 0.2 L; MD -4.7% predicted; 95% CI -15 to 6% predicted). Similarly, 12 and 24 h after aminophylline infusion, there were neither statistically nor clinically important differences between treatments.

DISCUSSION

Summary of main results

This systematic review examined the use of aminophylline in the early management of acute asthma in the ED. The meta-analysis is based on 15 studies that included 739 patients (353 aminophylline versus 386 standard treatment) after a comprehensive search for high-quality evidence on the topic, and in the 2012 update a further two trials (Whig 2001; Pavalakou 2006) were narratively included to provide additional context from a further 78 participants. The pooled results demonstrated no clear benefit of aminophylline therapy in improving pulmonary function or preventing hospital admission. Overall, this review identified no additional bronchodilator effect of intravenous aminophylline when added to $beta_2$-agonists in acute asthma. The side effects associated with aminophylline treatment were more common than in the groups treated with $beta_2$-agonists alone. For every 100 people treated with intravenous aminophylline, 20 more people had vomiting and 15 more had arrhythmias or palpitations.

Overall completeness and applicability of evidence

Despite subgroup analyses based on corticosteroid use and asthma severity, no groups in which aminophylline would be of benefit were identified. The lack of heterogeneity in the overall pooled results suggests these findings are consistent over a number of trials. However, subgroup comparisons should be interpreted with caution in this meta-analysis, as all comparisons were made among studies rather than within studies, and the differences in effect sizes were small (Oxman 1992).

Most of the 17 identified RCTs concluded that the addition of intravenous aminophylline contributed little to the treatment of acute asthma in the ED setting and there is a clear indication that the addition of aminophylline leads to a higher incidence of vomiting (Analysis 1.7) and arrhythmia/palpitations (Analysis 1.8).

Quality of the evidence

With regards to random sequence generation only one trial was judged to be at low risk of bias (selection bias) (Murphy 1993). The risk of bias for the remaining 16 trials was judged as unclear as details of the random sequence generation were not described in the trial report. In terms of the blinding of participants and personnel 11 trials were judged to be at low risk of bias (performance bias) (Josephson 1979; Appel 1981; Siegel 1985; Emerman 1986; Self 1990; Wrenn 1991; Coleridge 1993; Huang 1993; Murphy 1993; Rodrigo 1994; Pavalakou 2006). In one trial the risk was judged to be unclear (Whig 2001); and in five trials the risk was judged to be high (Evans 1980; Rossing 1981; Fanta 1982; Fanta 1986; Zainudin 1994).

Potential biases in the review process

There is a possibility of publication bias in this meta-analysis, in that by missing unpublished negative trials, the (albeit non-significant) effect of aminophylline therapy may be overestimated and missing unpublished positive trials may underestimate the therapeutic benefit. However, we feel we have identified the majority of the research available dealing with this clinical question by employing a comprehensive systematic search and our attempts to find unpublished trials, including extensive correspondence with the authors of six of the included studies as well as other experts

in the field, searching of abstracts from conferences and contact with pharmaceutical companies.

There were several methodological limitations to this review. There was the problem associated with the variety of pulmonary function outcomes and assessments. For example, airflow limitation was expressed as PEF as well as FEV_1 and each one could be reported as absolute or relative values. We combined absolute and relative scores using SMDs in our subgroup analyses. Although it has some recognised limitations, by broadening the analysis at the cost of losing specific focus, we attempted to address this problem by providing absolute and % predicted (FEV_1 or PEF) values using the SMD for the outcome reported. This approach confirmed the results from the analyses that used absolute measurements or % predicted results aggregated using an MD. In addition, most trials reported data until the first hour preventing us from commenting with confidence on the one- to 12-h period; however, the lack of change at 12 h is reassuring.

There was also a possibility of study selection bias; however, we employed two independent review authors, and feel confident that the studies excluded were evaluated on consistent and appropriate criteria.

It would be worthwhile to produce a systematic review of the anti-inflammatory effects of aminophylline either on its own or additive to those of inhaled corticosteroids, when used in low or high dose.

Agreements and disagreements with other studies or reviews

This is not the first meta-analysis to evaluate the benefits of the addition of aminophylline to beta$_2$-agonist treatment. Littenberg 1988 published a meta-analysis that yielded similar conclusions. However, many debates arose from this review owing to concerns regarding methodology. We believe our review dealt with these problems by following the Cochrane methodology and excluding non-randomised clinical trials. The conclusions in this update accord with the previous version of this review (Nair 2000).

AUTHORS' CONCLUSIONS

Implications for practice

1. There is insufficient evidence to support the routine use of aminophylline in the management of acute asthma when adequate inhaled beta$_2$-agonist treatment is provided.

2. The development of side effects is significantly higher with aminophylline treatment than inhaled beta$_2$-agonist therapy alone.

3. Treatments with efficacious agents (e.g., beta$_2$-agonists and anticholinergic agents, systemic and inhaled corticosteroids, magnesium sulfate, etc) should be encouraged before consideration is given to intravenous aminophylline therapy.

Implications for research

1. Most of the studies in this review did not provide data beyond the first hour of follow-up and there were only small differences demonstrated at 12 and 24 h. It is possible that aminophylline provides some additional late bronchodilator effects or benefits aside from airway relaxation. However, the magnitude of this effect would be clinically irrelevant in the emergency department and such small potential benefit in bronchodilation would not justify a new emergency department study.

2. Owing to the small samples in certain subgroups, the conclusions from these analyses require further evaluation. For example, the most severe subgroup data may be the only area in which aminophylline treatment would justify additional trials. One subgroup in particular that may benefit from further empirical consideration through randomised trials is those who experience no relief from nebulised beta$_2$-agonists.

3. It is possible that aminophylline may provide benefits in asthma beyond bronchodilation, particularly by exerting an anti-inflammatory effect by increasing intracellular cyclic AMP. This can be evaluated only by studying markers of inflammation in airway lumen or in biopsy samples.

ACKNOWLEDGEMENTS

The original version of this review in 2000 included the following acknowledgment: the authors wish to acknowledge the assistance of Stephen Milan, Anna Bara and Jane Dennis of the Cochrane Airways Review group. We would also like to acknowledge the assistance of the corresponding authors: Drs. Emerman, Huang, Rodrigo, Siegel, Wrenn and Zainudin. Finally, the assistance of Professor Paul Jones (Cochrane Airways Review Group Co-ordinating Editor) was greatly appreciated.

In 2012 we would like to thanks Melissa Bota and Lindsay Lovstrom from the Emergency Medicine Research Group (EMeRG) in the Department of Emergency Medicine at the University of Alberta for assistance in screening the search. We would particularly like to acknowledge the excellent support and assistance from Emma Welsh, Liz Stovold and Emma Jackson of the Cochrane Airways Review group, together with the greatly appreciated guidance from Chris Cates (Cochrane Airways Review Group Coordinating Editor). We would also like to thank Dr Luis Nannini for help with the translation of one study. The support provided by librarians Judith Scammel, Jane Appleton and Hilary Garrett at St Georges University London is also greatly appreciated.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Appel 1981

Methods	RCT with adequate description of inclusion and exclusion criteria. Randomisation not explained. Adequate description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients is uncertain. Method to assess adverse events described. Jadad quality score 4
Participants	Inclusion: age not specified, acutely ill (severe dyspnoea, chest tightness, anxiety and wheezing) with previous asthma (according to ATS 1962) and severe airflow obstruction (FVC $\leq$ 50% predicted, FEV_1/FVC $\leq$ 40% and PEF $\leq$ 150 L/min) in emergency department. Exclusion: unable to cooperate, history of ischaemic cardiac disease, liver disease, epilepsy or previous history of hypertension, theophylline 500 mg or more taken 24 h prior to admission. None was taking corticosteroids n = 42 but 37 analysed, age 33, 33 and 54 years (means by group), 27/9 (M/F). Severity assessed by FEV_1 28, 26, 26% of predicted or PEF 28, 29, 32% of predicted (means by group). Theophylline levels: 3.4, 3.2, 3.6 (means by group)
Interventions	WARNING: semi-cross-over changing treatments after 60 min. First hour: Study group: aminophylline IV: 6 mg/kg for 15 min epinephrine SC: 1:1000: 0.3, 0.4 or 0.5 mL according to body weight every 20 min Placebo group: placebo of aminophylline: volutrol infusion (volutrol is the IV infusion set. Both aminophylline and placebo infusions were administered using this device) epinephrine SC 1:1000: 0.3, 0.4 or 0.5 ml according to body weight every 20 min Third group: aminophylline IV: 6 mg/kg for 15 min placebo of epinephrine Second hour: Study group: placebo of aminophylline: volutrol infusion epinephrine SC 1:1000: 0.3, 0.4 or 0.5 mL according to body weight every 20 min Placebo group: aminophylline IV: 6 mg/kg for 15 min epinephrine SC 1:1000: 0.3, 0.4 or 0.5 mL according to body weight every 20 min Third group: not clear (seems placebo + placebo)
Outcomes	PEF (L/min, %) and FEV_1 (L, %) at times 0, 30, 60 min and 12 and 24 h. Only reported PEF % of personal best and FEV_1 in L Pulse rates at these same times
Notes	Study data were obtained from graphs. Used PEF % of personal best as predicted. Because of semi-crossover design only data from the first hour were analysed

Risk of bias

Bias	Authors' judgement	Support for judgement

Appel 1981 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 patients withdrawn. 2 from group 2 (epinephrine alone for first hour), 1 from group 3 (epinephrine and aminophylline for first hour) had therapeutic plasma theophylline levels (10 to 20 μg/mL). 1 from group 1 (aminophylline for first hour) became severely tremulous and nauseous. 1 further patient was excluded as reversible airways obstruction was not demonstrated in 4 months from initial presentation
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Coleridge 1993

Methods	RCT with adequate description of inclusion and exclusion criteria. Blinded. Adequate description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients was adequate. Methods used to assess adverse events not described. Jadad quality score 5 Secondary effects were assessed
Participants	Inclusion: aged 15 to 55 years, acute exacerbation and previously diagnosed of asthma according to ATS 1987 in emergency department and failed to respond at 30 min after admission to salmeterol INH and ipratropium bromide INH Exclusion: requiring intubation, cardiovascular, renal or hepatic impairment, pregnancy, pneumothorax or chest infection (fever more than 38^{o}C, discoloured sputum or suggestive x-ray) n = 59, age 33, 34 (means by group), 21/38 (M/F). Severity assessed by PEF 32%, 37% (means by group)
Interventions	First 30 min: ALL: salbutamol 1 mL (0.5%) and ipratropium bromide 1 mL (0.025%) in 1 mL of glycol diluent driven by O_2 (6 L/min) After 30th min:

Coleridge 1993 (*Continued*)

	ALL: hydrocortisone IV: 250 mg every 6 h O_2 6 L/min Study group: aminophylline IV: bolus dose is not specified (Wiggins method and no loading dose if theophylline level > 55 μg/L). Maintenance 0.5 mg/kg/h in non-smokers or 0.75 mg/kg/h in smokers salbutamol 1 mL (0.5%) and ipratropium bromide 1 mL (0.025%) in 1 mL of glycol diluent driven by O_2 (6 L/min) at 0, 2, 4, 6, 8 and 12 h and then every 6 h Placebo group: placebo of aminophylline IV: same saline solution salbutamol 1 mL (0.5%) and ipratropium bromide 1 mL (0.025%) in 1 mL of glycol diluent driven by O_2 (6 L/min) at 0, 2, 4, 6, 8 and 12 h and then every 6 h
Outcomes	PEF (% predicted) at 0, 1, 3, 5, 7, 9, 12 (discharged patients) and same plus 18, 24, 30, 36, 42 and 48 h (hospitalised patients)
Notes	Data are post-bronchodilator. Study describes discharged and hospitalised patients independently and at different times. Therefore, study split up in 2 parts. We also used discharged patients followed during 12 h

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 patients excluded. 2 because hydrocortisone was omitted, 1 randomised to aminophylline withdrew owing to nausea and vomiting. A further 3 were excluded as their PEF measurements were reported as chaotic and inconsistent
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Emerman 1986

Methods	RCT with adequate description of inclusion and exclusion criteria. Randomisation confirmed through contact with the authors. Blinded. Adequate description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients was clarified by mail. Method to assess adverse events described. Jadad quality score (disagreement between review authors) 4 and 5 Secondary effects were assessed
Participants	Inclusion: aged 18 to 45 years, acute exacerbation and previously diagnosed of asthma according to ATS 1962 in emergency department Exclusion: history of cardiac disease or arrhythmia n = 52 presented 60 acute episodes of asthma and were considered as patients, age 33, 29, 26 years (means by group), 28/42 (M/F). Severity assessed by PEF 48%, 46% and 53% (means by group). Theophylline levels: 0.51, 0.43 and 0.56 mg/dL (means by group). Also reported results prior to theophylline, beta$_2$-agonist and corticosteroid use
Interventions	ALL: O_2 by nasal cannula administered at a flow of 3 L/min Study group: aminophylline IV: 5.6 mg/kg in administered over 20 min epinephrine SC: 1:1000: 0.3 every 20 min Placebo group: placebo of aminophylline IV: saline epinephrine SC: 1:1000: 0.3 mL every 20 min Third group: aminophylline IV: 5.6 mg/kg in administered over 20 min placebo of epinephrine SC: 1:1000: saline NOTE: loading dose of aminophylline reduced 50% in patients with any previous use of theophylline in the preceding 6 h
Outcomes	PEF (L/min and % predicted) at 0, 90 min Ventricular arrhythmias measured by Holter
Notes	Authors contacted by mail. They gave details about allocation that shifted from unclear to adequate (randomised blocks of 15 with treating physicians and investigators blinded until study completion). Other data (SD) were facilitated Time 90 will be assumed as 60

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind

Emerman 1986 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears from trial report not to be an issue
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Evans 1980

Methods	RCT with adequate description of inclusion and exclusion criteria. Randomisation not explained. Not blinded. No description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients was uncertain. Method to assess adverse events not described. Jadad quality score 1
Participants	Inclusion: aged > 15 years, with acute asthma (no details) and pulse rate > 120/min, PEF < 25% predicted and pO_2 < 9.3 kPa (70 mm Hg) admitted to hospital (no details) Exclusion: age and bronchodilator therapy less than 3 h prior to admission n = 21, aged 22, 33 and 28 years (means by group), 9/12 (M/F). Severity assessed by PEF 131, 89, 78 L/min
Interventions	ALL: hydrocortisone 4 g and potassium chloride 4 g in 2 L of 5% dextrose infused over 24 h and 35% O_2 via Ventimask Study group: aminophylline IV: 0.285 mg/kg/min (4.275 mg/kg) for 15 min followed by 0.014 mg/kg/min (0.84 mg/kg/h) for 24 h salbutamol IV: 0.285 μg/kg/min for 15 min followed by 0.057 μg/kg/min for 24 h Placebo group: not placebo of aminophylline: nothing salbutamol IV: 0.285 μg/kg/min for 15 min followed by 0.057 μg/kg/min for 24 h Third group: aminophylline IV: 0.285 mg/kg/min (4.275 mg/kg) for 15 min followed by 0.014 mg/kg/min (0.84 mg/kg/h) maintenance for 24 h
Outcomes	PEF (L/min) at times 0, 30, 60 min and 12 and 24 h Pulse rates at these same times
Notes	Study data were obtained from graphs and are changes (change to absolute by simple addition of means) and SE changed to SD. Because of low-quality rate authors were not contacted for further data (PEF %)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Unclear risk	Insufficient information available

Evans 1980 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial was not double blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial was not double blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears from trial report not to be an issue
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Fanta 1982

Methods	RCT with adequate description of inclusion and exclusion criteria. Randomisation not explained. Not blinded. No description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients was uncertain but it would appear that sequential randomisation took place. Method to assess adverse events not described. Jadad quality score 1
Participants	Inclusion: aged 18 to 45 years, complaint of asthma (based on ATS 1962) in emergency department Exclusion: complicated respiratory or cardiac disease n = 102, age 30, 31, 30 years (means by group), 86/21 (M/F). Severity assessed by FEV_1 38% of predicted. Theophylline levels: 8.1 (isoproterenol group), 8.3 (isoproterenol + aminophylline group), 8.4 ((isoproterenol + Exilophyllin group)
Interventions	ALL: O_2 by nasal prongs Study group: aminophylline IV: 6 mg/kg in 20 min followed by 0.6 mg/kg/h maintenance. Reduced 50-75% in previous 12 h isoproterenol INH 0.5%: 2.5 mg in 2.5 cc of saline every 20 min (3 doses) Placebo group: no placebo of aminophylline IV: nothing isoproterenol INH 0.5%: 2.5 mg in 2.5 cc of saline every 20 min (3 doses) Third group: theophylline OR: single dose of elixir at 7 mg/kg or reduced as aminophylline IV isoproterenol INH 0.5%: 2.5 mg in 2.5 cc of saline every 20 min (3 doses)
Outcomes	FEV_1 (L) at times 0 and 60 min Serum theophylline concentrations Tremor, palpitations, nausea/vomiting, blood pressure, heart rate and discharge rates at different times are discussed but not data are given
Notes	Study data were obtained from graphs and SE changed to SD Side effects are discussed in results section of paper but no data were reported
Risk of bias	

Fanta 1982 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears from trial report not to be an issue
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Fanta 1986

Methods	RCT with NO description of inclusion and exclusion criteria. Not double blinded. No description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients is uncertain. Method to assess adverse events not described. Jadad quality score 1
Participants	Inclusion: aged 18 to 45 years, acute episodes of asthma (according to ATS 1962) in emergency department. Exclusion: multiple emergency visits (second and further), cardiopulmonary diseases other than asthma, pneumonia, chronic bronchitis or emphysema n = 157, aged 30, 37 males and 120 females. Severity assessed by FEV_1 1.23 L. Theophylline levels: 11 μg/mL (100 were on xanthines prior to study)
Interventions	ALL: O_2 4 L/min by nasal prongs Study group: aminophylline IV: 5.6 mg/kg in 20 min followed by 0.9 mg/kg/h maintenance (bolus reduced by 50-75% if taking xanthines in the preceding 24 h) epinephrine SC: 1:1000: 0.3 mL every 20 (3 doses) Placebo group: no placebo of aminophylline IV: nothing epinephrine SC: 1:1000: 0.3 mL every 20 (3 doses) There were 4 more groups: aminophylline alone, isoproterenol alone, isoproterenol + aminophylline, isoproterenol + elixophyllin
Outcomes	FEV_1 (L and % predicted) at times 0 and 60 min Serum theophylline concentrations Vomiting/nausea Discussion about tremor, nausea and palpitations were discussed with no data reported

Fanta 1986 (*Continued*)

Notes	Study divided into 2 parts. This is the first for aminophylline associate with epinephrine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears from trial report not to be an issue
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Huang 1993

Methods	RCT with adequate description of inclusion and exclusion criteria. Blinded. Adequate description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients was clarified by phone. Method to assess adverse events described. Jadad quality score 5 Secondary effects were assessed
Participants	Inclusion: aged 18 to 50 years, acute exacerbation and previously diagnosed of asthma according to ATS 1987 in emergency department and failed to respond to 3 or more doses of inhaled albuterol (with or without terbutaline SC) and corticosteroids IV (methylprednisone IV 125 mg followed by 60 mg every 6 h) Exclusion: unable to perform spirometry, intubated, pregnant, lower respiratory tract infection, PCO_2 > 50 mmHg, chronic cardiopulmonary disease, chronic bronchitis or emphysema or FEV_1 > 80% of predicted at time 0 n = 21, aged 32.8, 33.9 years (means by group), 10/11 (M/F). Severity assessed by FEV_1 49%, 43% (means by group). Theophylline levels: 1.9, 3.8 μg/mL (means by group)
Interventions	ALL: O_2 flow was adjusted to keep saturation over 92% methylprednisolone 125 mg bolus followed by 60 mg/6 h Study group: aminophylline IV: 1 mg/kg in 5% dextrose in 30 min for each 2 μg/L desired increase in serum theophylline to achieve a target of 15 μg/mL. Followed by 0.6 mg/kg/h and adjusted to maintain theophylline concentration within 10 to 20 μg/mL

Huang 1993 (*Continued*)

	albuterol INH: 2.5 to 5.0 mg in 4 mL of saline as-needed based in FEV_1 and clinical response and side effects (full details are given for that) Placebo group: placebo of aminophylline IV: 5% dextrose albuterol INH: 2.5 to 5.0 mg in 4 mL of saline as-needed based in FEV_1 and clinical response and side effects (full details are given for that)
Outcomes	FEV_1 (L/min and % predicted) at 0, 1, 3, 6, 12, 24, 36 and 48 h Nausea Other symptoms are described but actual data were not given
Notes	Authors contacted by mail. They responded and supplied us with raw data. Mean and SD were calculated. No further details were obtained about side effects. By telephone, details were obtained about allocation, which is now adequate. Data for hospitalisation were taken from results computing as hospitalised all resting non-discharged patients in the group (3 discharged in aminophylline and 1 in control group)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 patients were excluded: "1 unable to perform spirometry tests, 3 refused to participate, 1 had a Pco2 value greater than 50, and two patients had FEV_1 values of 80% or more of the predicted value after nebulized albuterol treatments in the emergency department"
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Josephson 1979

Methods	RCT with adequate description of inclusion and exclusion criteria. Double blinded. Description of withdrawals and drop-outs only stated. Statistical methods described. Allocation of the patients is inadequate. Method to assess adverse events described. Jadad quality score 4 but inadequate allocation 4-1 = 3
Participants	Inclusion: aged 16 to 50 years, main complaint of asthma (shortness of breath and wheezing) in adult emergency department Exclusion: cardiovascular disease, cough or sputum during symptoms free periods, no history of asthma or wheezing, theophylline levels above 8 μg/mL at baseline n = 56, age 27.7, 23/28 (M/F). Severity assessed by PEF 23% of predicted. Theophylline levels: 3.5 (epinephrine group), 2.3 (epinephrine + aminophylline group)
Interventions	Study group: aminophylline IV: 5.6 mg/kg in 20 min followed by 0.9 mg/kg/h maintenance epinephrine SC: 1:1000: 0.3 to 0.5 mL at 0, 30 and 60 min depending of weight Placebo group: placebo of aminophylline IV: saline solution epinephrine SC: 1:1000: 0.3 to 0.5 mL at 0, 30 and 60 min depending of weight
Outcomes	PEF (% predicted) at times 0, 30, 60 and 90 min Serum theophylline concentrations Vomiting/nausea
Notes	Data on hospitalisation cannot be used because no details are given about the distribution of patients by groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Unclear risk	Study investigators aware/potentially aware of order of treatment group assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 patients with 13 episodes of acute asthma were excluded as their baseline theophylline levels were in excess of 8 μg/mL (5 in the epinephrine group and 8 were in the aminophylline-epinephrine group)

Josephson 1979 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Murphy 1993

Methods	RCT with adequate description of inclusion and exclusion criteria. Double blinded. Partial description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients was uncertain but it seemed to be sequential. Method to assess adverse events described. Jadad quality score (disagreement between review authors) 4 and 5 Some secondary effects were assessed
Participants	Inclusion: aged 18 to 45 years, acute exacerbation and previously diagnosed of asthma (no details) in emergency department and PEF remained less than 40% predicted after 1 h of initial dose of metaproterenol Exclusion: febrile, pregnant, currently taking oral corticosteroids, so severe exacerbation that patients required continuous nebulisation or epinephrine, onset of disease after 35 years of age n = 44, aged 28 years, 36/8 (M/F). Severity assessed by PEF 125, 137 L (means by group) . Theophylline levels: 5, 6 μg/L (means by group)
Interventions	Study group: Initial: metaproterenol sulfate nebulised: 15 mg dissolved in 2.5 mL of normal saline 1 h later: aminophylline IV: 8 mg/kg in 30 min followed by 0.6 (weight less than 70 kg) or 0.8 mg/kg/h maintenance metaproterenol sulfate nebulised: 15 mg dissolved in 2.5 mL of normal saline every hour for 5 h methylprednisolone IV: 125 mg in bolus Placebo group: initial: metaproterenol sulfate nebulised: 15 mg dissolved in 2.5 mL of normal saline 1 h later: placebo of aminophylline IV: normal saline metaproterenol sulfate nebulised: 15 mg dissolved in 2.5 mL of normal saline every hour for 5 h methylprednisolone IV: 125 mg in bolus
Outcomes	PEF 15 min after metaproterenol (L/min and % predicted) at times 0, 25 min, 1 h 25 min, 2 h 25 min, 3 h 25 min, 4 h 25 min and 5 h 25 min Tremor Vomiting/nausea Palpitations
Notes	Data were 15 min post beta$_2$ treatment. There were no pre beta$_2$ data Time 25 min was assumed to be 30 min and 1 h 25 min as 1 h. There were no data for 12 h but 5 h 25 min. Given that these data show the bigger effect we can consider as low estimate of 12 h

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Murphy 1993 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomisation table in hospital pharmacy
Allocation concealment (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Limited information on exclusions--
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Pavalakou 2006

Methods	Both groups received IV methylprednisolone and inhaled salbutamol
Participants	38 patients with acute asthma admitted in emergency department. Mean age of sample: 28 years (SD 8 years); no specific details included in report for the 2 groups although there were no significant baseline differences between the groups with respect to age, PEF, SO_2, pulse rate, blood pressure, clinical score of asthma, previous admission to hospital and emergency department
Interventions	IV aminophylline
Outcomes	IV normal saline 0.9% for 72%
Notes	Clinical asthma scores, PEF, SO_2, pulse rate, blood pressure appear to have been taken at 6, 12, 24, 48 and 72 h after admission. Spirometry was performed every 24 h. Specific details on these outcomes are not available in the trial report (conference abstract)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Unclear risk	Unclear in trial report

Pavalakou 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears from trial report not to be an issue
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Rodrigo 1994

Methods	RCT with adequate description of inclusion and exclusion criteria. Double blinded. No description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients was uncertain but it seemed to be sequential. Method to assess adverse events described. Jadad quality score 3
Participants	Inclusion: aged 18 to 50 years, acute exacerbation and previously diagnosed of asthma according to ATS 1987 criterion in emergency department and PEF or FEV_1 below 50% predicted. Exclusion: chronic cough, cardiac, hepatic, renal or other medical disease or pregnancy n = 94, age 35, 36.2 years (means by group), 33/61 (M/F). Severity assessed by PEF 164.9, 144.3 L/min (means by group) (also available PEF %, FEV_1 and FEV_1 %. Theophylline levels: 3.3, 3.5 μg/L (means by group) 18 in control group and 15 in the study group used corticosteroids within the past 7 days
Interventions	ALL: O_2 by nasal prongs 4 L/min Study group: aminophylline IV: 5.6 mg/kg in 20 min followed by 0.9 mg/kg/h maintenance salbutamol INH: 400 μg (4 puffs) from MDI through spacer device every 10 min hydrocortisone IV: 500 mg bolus Placebo group: placebo of aminophylline IV: 0.9% sodium chloride solution salbutamol INH: 400 μg (4 puffs) from MDI through spacer device every 10 min
Outcomes	FEV_1 (L) and % predicted at 0, 30, 60 min PEF L/min and % predicted at 0, 30, 60 min Admission/discharge rate Tremor Vomiting/nausea Palpitations Anxiety

Rodrigo 1994 (*Continued*)

Notes	Authors contacted by mail. They provided data (mean and SD) for absolute values but they pointed out that we can obtain % data from graphs, which were not given. Randomisation and allocation were confirmed by correspondence. They were both performed adequately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears from trial report not to be an issue
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Rossing 1981

Methods	RCT with adequate description of inclusion and exclusion criteria. Randomisation not explained. Not blinded. No description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients was uncertain but it appeared to have been sequential. Method to assess adverse events was described. Jadad quality score 1 Secondary effects were assessed
Participants	Inclusion: aged 18 to 45 years, complaint of asthma and diagnosed of asthma according to ATS 1962 criteria in emergency department Exclusion: onset of asthma symptoms after 35 years of age, history of cardiac disease, chronic cough, purulent sputum or fever (> 37.2°C) n = 89, age 30, 30, 29 years (means by group), 15/74 (M/F). Severity assessed by FEV_1 1.09, 0.89, 0.86 L (means by group). Baseline theophylline levels 7.9, 8.2 and 8.4 mg/L
Interventions	ALL: O_2 by nasal prongs 4 L/min Study group: aminophylline IV: 5.6 mg/kg administered over 20 min followed by 0.9 mg/kg/h maintenance epinephrine SC: 1:1000: 0.3 at 0, 20 and 40 min

Rossing 1981 (*Continued*)

	Placebo group: no placebo of aminophylline IV: nothing epinephrine SC: 1:1000: 0.3 mL at 0, 20 and 40 min Third group: isoproterenol 1:200 dilution: 0.5 mL (2.5 mg) by hand-held nebuliser at 0, 20 and 40 min aminophylline IV: 5.6 mg/kg administered over 20 min followed by 0.9 mg/kg/h maintenance NOTE: loading dose of aminophylline reduced 25% to 50% in patients with any previous use of theophylline in the preceding 24 h
Outcomes	FEV_1 (L and % predicted) at times 0 and 60 min Serum theophylline concentrations if previous use of theophylline Discharge/admission (see notes) Tremor Vomiting/nausea
Notes	Data of third group could not be used because there was no control group After 1 h of study physician in charge was allowed to change treatment Discharge or admission are described following unclear criteria

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears from trial report not to be an issue
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Self 1990

Methods	RCT with adequate description of inclusion and exclusion criteria. Randomisation only stated. Double blinded. Adequate description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients was inadequate. Method to assess adverse events unclear (review authors' discrepancy). Jadad quality score 4
Participants	Inclusion: aged 18 to 49 years, with asthma and previously diagnosed of asthma (according to ATS 1987 criteria) in emergency department, who failed to respond to oxygen, albuterol 2.5 mg/h during 4 doses and methylprednisolone IV 125 mg/monodose and deemed in need of hospitalisation according to ATS criteria Exclusion: cardiovascular disease, chronic bronchitis, emphysema, pregnancy, respiratory failure, other complicating cardiopulmonary diseases (pneumonia, decompensated heart failure) n = 46 (but only 11 and 7 were analysed), age 31.3 and 32.8 years (means by group), 19/20 (M/F). Severity assessed by FEV_1 41.5% and 34.7% of predicted (means by group). Theophylline levels: 4.1 (placebo group), 5.3 (theophylline group)
Interventions	First 4 h: ALL: albuterol INH: 2.5 mg nebulised every hour for 4 h methylprednisolone IV: 125 mg monodose O_2 flow was adjusted to maintain saturation above 90% After 4 h: Study group: aminophylline IV: bolus and maintenance were not specified only aimed to reach blood levels of 10 to 20 μg/mL albuterol INH: 2.5 mg in 3 mL saline nebulised every 2 h for 4 doses and then every 4 h until 32 h (if needed could be increased to every 1 or 2 h) prednisone PO: 0.5 mg/kg every 6 h O_2: nasal prongs to reach 90% saturation Placebo group: placebo of aminophylline IV: same IV solution albuterol INH: 2.5 mg in 3 mL saline nebulised every 2 h for 4 doses and then every 4 h until 32 h (if needed it could be increased to every 1 or 2 h) prednisone PO: 0.5 mg/kg every 6 h O_2: nasal prongs to reach 90% saturation
Outcomes	FEV_1 (L and % predicted) at times 0, 8, 16, 24 and 32 h Serum theophylline concentrations Nausea/vomiting Tremor Palpitations Nervousness/anxiety
Notes	Study data were obtained from graphs and SE changed to SD Data at 16 h were considered as 12 h for analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report

Self 1990 (*Continued*)

Allocation concealment (selection bias)	Low risk	Randomisation code retained by pharmacy and not revealed to investigators prior to completion of study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 patients became severely ill and were withdrawn, and 3 were discharged against medical advice
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Siegel 1985

Methods	RCT with adequate description of inclusion and exclusion criteria. Randomisation not explained. Double blinded. No description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients is uncertain (maybe sequentially). Method to assess adverse events described. Jadad quality score 4
Participants	Inclusion: aged 18 to 45 years, acute exacerbation of asthma (previous history of recurrent shortness of breath, chest tightness and wheezing and diagnosed by a physician) in emergency department Exclusion: chronic bronchitis, cardiac disease, onset of symptoms after 35 years of age n = 40, age 31, 29 years (means by group), 25/15 (M/F). Severity assessed by FEV_1 0.75 L. Theophylline levels: 8.8 (metaproterenol + aminophylline group), 7.3 metaproterenol group)
Interventions	ALL: metaproterenol INH: 15 mg in 2 cc saline by nebuliser 100% O_2 After 30 min Study group: aminophylline IV: 5.6 mg/kg in 20 min followed by 0.7 mg/kg/h maintenance (in treated with xanthines in prior 24 h or 12 h the bolus was 2.8 mg/kg) metaproterenol INH: 15 mg/h in 2 cc saline by nebuliser (total 3 doses) Placebo group: placebo of aminophylline IV: 5% dextrose solution metaproterenol INH: 15 mg/h in 2 cc saline by nebuliser (total 3 doses)
Outcomes	FEV_1 (L) at times 0, 60, 120 and 180 min Serum theophylline concentrations Vomiting/nausea Palpitations Tremor Anxiety

Siegel 1985 (*Continued*)

	Heart rate
Notes	Authors contacted by mail. Authors do not have further data but they gave details about concealment and randomisation, which clarified the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears from trial report not to be an issue
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Whig 2001

Methods	RCT with description of inclusion and exclusion criteria. Information on method of randomisation (generation of sequence or allocation concealment) is not included in trial report. Information on whether trial was blinded is not included in trial report. No description of withdrawals and drop-outs. Statistical methods described
Participants	Inclusion: aged 2 to 25 years, with acute bronchial asthma in casualty department Exclusion: "patients with theophylline intake in last 24 hours, significant renal or hepatic disease, regular smokers, pregnant women, those on drugs likely to interfere with the pharmacokinetics or pharmacodynamics of theophylline were excluded from the study". Patients were excluded if they were relieved within 60 min of admission following nebulised salbutamol and hydrocortisone succinate n = 40, information on age and M/F in each group not included in trial report but reported as comparable. Severity assessed by PEF and Woods asthma score, and groups reported as comparable
Interventions	ALL: on admission each patient received nebulised salbutamol 0.15 mg/kg (repeated after 4 h). Also, on admission, hydrocortisone succinate 4 mg/kg

Whig 2001 (*Continued*)

	After 60 min (if patient was not relieved): Study group: aminophylline IV: 6 mg/kg followed by 0.5 mg/kg/h aminophylline infusion for at least 12 h Placebo group: received equivalent amounts of placebo as slow injection and as infusion
Outcomes	Improvement in Woods asthma score Improvement in PEF Serum theophylline concentrations Adverse reactions (nausea, headache, anxiety, vomiting, ventricular premature beats) Woods asthma score, PEF, ECG, blood sugar, serum electrolytes determined/recorded just prior to at aminophylline/placebo at 0 h and then at 1, 5, 9 and 13 h. Plasma theophylline concentrations determined at 2 and 8 h
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Unclear risk	Unclear in trial report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear from trial report whether any aspect of the study was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear from trial report whether any aspect of the study was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears from trial report not to be an issue
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Wrenn 1991

Methods	RCT with adequate description of inclusion and exclusion criteria. Randomisation only stated. Double blinded but only stated not described. Adequate description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients is uncertain. Method to assess adverse events described. Jadad quality score 4
Participants	Inclusion: aged > 16 years, with asthma exacerbation or wheezing (no details) in emergency department. Asthma defined as under 45 years of age, have smoked for < 20 pack-years, had a duration of disease for < 20 years or had onset of asthma in childhood Exclusion: theophylline-containing product within the preceding 24 h, past history

	of adverse reaction to theophylline, contraindication to the use of corticosteroids or beta$_2$-agonists, insulin-dependent diabetes, possible myocardial ischaemia or pulmonary oedema Age 31, 36 years (means by group). Severity assessed by FEV_1 1 and 1.5 L and PEF 151 and 178 L/min (means by group)
Interventions	First hour: ALL: metaproterenol INH: 0.3 mL of 5% solution in 2.2 mL of saline nebulised every 15 to 20 min for 3 back-to-back treatments methylprednisolone IV: 80 mg monodose After first hour: Study group: aminophylline IV: 5.6 mg/kg in 20 min followed by 0.9 mg/kg/h maintenance metaproterenol INH: 0.3 mL of 5% solution in 2.2 mL of saline nebulised every 30 to 60 min as deemed necessary by a house officer Placebo group: placebo of aminophylline IV: saline metaproterenol INH: 0.3 mL of 5% solution in 2.2 mL of saline nebulised every 30 to 60 min as deemed necessary by a house officer
Outcomes	FEV_1 and PEF (L and L/min, respectively) at times 0, 60 and 120 min Serum theophylline concentrations at the end of treatment (since none of the patients had taken any theophylline for 24h before the study, baseline measurements were not made) Vomiting/nausea Tremor Anxiety Seizure Palpitations/arrhythmia
Notes	Authors contacted by mail. Details of randomisation and blinding were sent by mail. Study passed from unclear to adequate. New data used from asthma group given by the authors. There are no relative values only absolute FEV and PEF. Clarifications were received by mail

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind

Wrenn 1991 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 patients were excluded from the analysis. 5 patients were excluded as the study code was lost, no spirometric data was obtained for 3, it was not possible to establish an intravenous line for 1 and infusion of study drug was terminated in 1 when blood glucose was found to be elevated and new T-wave inversions were observed
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

Zainudin 1994

Methods	RCT with no description of inclusion and exclusion criteria. Not double blinded. No description of withdrawals and drop-outs. Statistical methods described. Allocation of the patients is uncertain. Method to assess adverse events not described. Jadad quality score 1
Participants	Inclusion: aged 18 to 60 years, severe asthmatic attack (no other details) in emergency department Exclusion: no details n = 25, there was no demographic data. Severity assessed by PEF: 78 and 97 L/min (means by group) and ABG (no reported). Theophylline levels: 5.7 and 9.7 μg/mL (means by group, 23 patients were on theophylline. Moreover in 5 cases they had received a previous bolus of aminophylline)
Interventions	ALL: O_2 45% by Hudson mask for 24 h hydrocortisone IV: 100 mg every 6 h for 24 h and then prednisolone 30, 20 and 10 mg daily for 2 days, respectively Study group: aminophylline IV: aminophylline was given as a continuous infusion over 48 h. There was no bolus injection in either the active or placebo arm salbutamol INH: 5 mg in 3 mL of saline every hour (first 3 h), then every 3 h (next 9 h) , then every 4 h (next 12 h) and thereafter every 6 h Placebo group: given as a continuous infusion over 48 h. There was no bolus injection in either the active or placebo arm salbutamol INH: 5 mg in 3 mL of saline every hour (3 first h), then every 3 h (next 9 h) , then every 4 h (next 12 h) and thereafter every 6 h
Outcomes	PEF (L/min) at times 0, 1, 3, 6, 12, 24, 36 and 48 h Serum theophylline concentrations Tremor Vomiting/nausea Palpitations/arrhythmia

Zainudin 1994 (*Continued*)

	Discussion about tremor, nausea and palpitations are discussed with no actual data	
Notes	Authors contacted by mail. There is not SD or SE available (estimated from average of other studies)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear in trial report
Allocation concealment (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial was not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appears from trial report not to be an issue
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting

ATS; American Thoracic Society: ECG: electrocardiogram; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; INH: inhaled; IV: intravenous; M/F: male/female ratio; MDI: metered-dose inhaler; PEF: peak expiratory flow rate; PO: oral; SC: subcutaneous; SD: standard deviation; SE: standard error.

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

Study	Reason for exclusion
Aggarwal 1986	This study was excluded as not randomised
Alanko 1992	This study was excluded because it was a direct comparison between salbutamol and aminophylline, rather than an investigation of the benefits of adding aminophylline to salbutamol
Beswick 1975	This study was excluded because of intervention issues. It was a randomised, blinded comparison between aminophylline IV and salbutamol IV

(*Continued*)

Carrier 1985	This study was excluded because it was a comparison between IV and oral aminophylline
Dal Negro 1997	This study was excluded as classified as a non-RCT, and comparisons being between theophylline IV at 12 and 36 h and with betamethasone at 12 h
Djukanovic 1995	Study used oral theophylline and was performed on mild to moderately severe atopic asthmatics, who were not experiencing acute asthma
Femi-Pearse 1977	This study was excluded because of intervention issues. It was a randomised, blinded comparison between aminophylline IV and salbutamol IV
Filiz 2002	This study was performed on patients who were not experiencing acute asthma
Greif 1985	This study was excluded because of intervention issues. It was a randomised, blinded comparison between aminophylline IV and salbutamol IV
Haahtela 1986	This study was excluded because it did not assess the added benefit of IV aminophylline to inhaled beta$_2$-agonists
Ikeda 1990	Study excluded because it did not show lung function data at the times required in our review. In addition, the study was classified as a non-RCT by a Japanese translator
Janson 1992	This randomised part of this study compared inhaled salbutamol with IV salbutamol and the relationship with theophylline was examined in correlational analyses
Janson 1992a	This study was excluded because it was not randomised and it was a comparison between inhaled and IV beta$_2$-agonists
Johnson 1978	This study did not compare aminophylline to standard care or placebo. It was a randomised and blinded comparison between IV aminophylline and IV salbutamol for patients who did not improve after initial care (combined regimen of aminophylline bolus, 2 inhalations of salbutamol through IPPB and hydrocortisone 200 mg plus oral prednisone 40 mg)
Jonsson 1988	This study was excluded because of intervention issues. It was a randomised comparison of methylprednisolone IV plus aminophylline IV versus oral methylprednisolone + oral aminophylline
Kato 2004	This study was excluded because of intervention issues. It was a randomised comparison of theophylline IV versus theophylline IV plus corticosteroid IV versus corticosteroid IV alone. The only reported outcomes were reduction of eosinophils and eosinophil cationic protein levels
Kino 1991	This study was excluded because it was non-randomised and compares 2 protocols for the use of aminophylline IV in the emergency department
Magnussen 1986	This study was performed on patients with stable asthma, who were not experiencing acute asthma
Montserrat 1991	No indication of randomisation in trial report

(*Continued*)

Montserrat 1995	Study excluded because authors did not report lung function data at the times required in our review. The settings are ICU after 24 h of admission and no data were provided on previous treatment
Muittari 1978	This study was performed on asthma outpatients and does not meet the intervention criteria
Nayyer 1994	This study was excluded because it did not assess the added benefit of IV aminophylline to inhaled beta$_2$ agonists
Ohta 1996	This study did not meet the intervention criteria: it was a randomised, blinded and partial cross-over comparison between aminophylline IV and salbutamol INH
Pierson 1971	This study was performed on children
Rossing 1980	This study did not meet the intervention criteria. It was a randomised, non-blinded comparison between aminophylline IV, epinephrine SC and nebulised salbutamol
Schwartz 1998	This study was performed on patients with chronic asthma and did not meet the intervention criteria
Sharma 1984	This study did not meet the intervention criteria. It was a randomised, non-blinded comparison between aminophylline IV, salbutamol IV and terbutaline INH
Svedmyr 1982	Study was performed on stable moderate to severe asthmatics, who were not experiencing acute asthma
Taqweem 2004	This study was excluded because it was a non-randomised design
Tribe 1976	This study was excluded because of intervention issues. It was a randomised, blinded comparison of aminophylline IV and salbutamol IV
Williams 1975	This study was excluded because of intervention issues. It was a randomised, blinded comparison between aminophylline IV and salbutamol IV
Wolfe 1978	This study was performed on patients with stable asthma
Yamauchi 2005	It has not been possible to obtain data for those patients in the trial who were receiving beta$_2$ agonists

ICU: intensive care unit; INH: inhaled; IPPB: intermittent positive-pressure breathing; IV: intravenous; RCT: randomised controlled trial; SC: subcutaneous.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Barradas 1986

Methods	
Participants	
Interventions	
Outcomes	
Notes	Trial report unobtainable. January 2012

DATA AND ANALYSES

Comparison 1. Aminophylline vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admissions	6	315	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.30, 1.12]
2 PEF (L/min)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 at baseline	7	327	Mean Difference (IV, Random, 95% CI)	-7.61 [-21.51, 6.28]
2.2 at 30 min	3	153	Mean Difference (IV, Random, 95% CI)	-5.70 [-44.78, 33.38]
2.3 at 60 min	6	302	Mean Difference (IV, Random, 95% CI)	6.24 [-21.09, 33.57]
2.4 at 12 h	3	84	Mean Difference (IV, Random, 95% CI)	8.30 [-20.69, 37.29]
2.5 at 24 h	2	40	Mean Difference (IV, Random, 95% CI)	22.20 [-56.65, 101.05]
3 PEF (% predicted)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 at baseline	6	285	Mean Difference (IV, Random, 95% CI)	-1.53 [-2.85, -0.20]
3.2 at 30 min	4	214	Mean Difference (IV, Random, 95% CI)	-3.11 [-6.74, 0.52]
3.3 at 60 min	6	285	Mean Difference (IV, Random, 95% CI)	-2.28 [-4.84, 0.27]
3.4 at 12 h	2	76	Mean Difference (IV, Random, 95% CI)	-1.21 [-14.21, 11.78]
3.5 at 24 h	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 FEV_1 (L)	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 at baseline	8	419	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.18, 0.08]
4.2 at 30 min	1	94	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.49, -0.03]
4.3 at 60 min	8	419	Mean Difference (IV, Random, 95% CI)	0.05 [-0.13, 0.23]
4.4 at 12 h	1	21	Mean Difference (IV, Random, 95% CI)	0.41 [-0.16, 0.98]
4.5 at 24 h	1	21	Mean Difference (IV, Random, 95% CI)	0.42 [-0.13, 0.97]
5 FEV_1 (% predicted)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 at baseline	5	260	Mean Difference (IV, Random, 95% CI)	-0.36 [-4.09, 3.38]
5.2 at 30 min	1	94	Mean Difference (IV, Random, 95% CI)	-2.0 [-7.24, 3.24]
5.3 at 60 min	3	176	Mean Difference (IV, Random, 95% CI)	-2.99 [-13.05, 7.07]
5.4 at 12 h	2	39	Mean Difference (IV, Random, 95% CI)	4.28 [-17.93, 26.49]
5.5 at 24 h	2	39	Mean Difference (IV, Random, 95% CI)	4.35 [-16.68, 25.39]
6 Tremor	5	249	Odds Ratio (M-H, Random, 95% CI)	2.60 [0.62, 11.02]
7 Vomiting	7	321	Odds Ratio (M-H, Random, 95% CI)	4.21 [2.20, 8.07]
8 Arrythmia/palpitations	6	249	Odds Ratio (M-H, Random, 95% CI)	3.02 [1.15, 7.90]
9 Convulsions	1	21	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Aminophylline vs placebo (grouped by baseline severity)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PEF (L/min) or PEF (%) if missing at baseline	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 at baseline mild-moderate subgroups	2	124	Std. Mean Difference (IV, Random, 95% CI)	0.23 [-0.36, 0.83]
1.2 at baseline severe subgroup	7	285	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.56, -0.09]
1.3 at baseline total pooled result	9	409	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.39, 0.05]
2 PEF (L/min) or PEF (%) if missing at 30 min	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 at 30 min mild-moderate subgroups	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 at 30 min severe subgroup	5	229	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.83, 0.33]
2.3 at 30 min total pooled result	5	229	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.83, 0.33]
3 PEF (L/min) or PEF (%) if missing at 60 min	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 at 60 min mild-moderate subgroups	2	124	Std. Mean Difference (IV, Random, 95% CI)	0.26 [-0.21, 0.73]
3.2 at 60 min severe subgroup	7	285	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.43, 0.17]
3.3 at 60 min total pooled result	9	409	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.28, 0.27]
4 PEF (L/m) or PEF (%) if missing at 12 h	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 at 12 h mild-moderate subgroups	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 at 12 h severe subgroup	4	115	Mean Difference (IV, Fixed, 95% CI)	-3.98 [-23.87, 15.91]
4.3 at 12 h total pooled result	4	115	Mean Difference (IV, Fixed, 95% CI)	-3.98 [-23.87, 15.91]
5 PEF (L/min) or PEF (%) if missing at 24 h	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 at 24 h mild-moderate subgroups	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 at 24 h severe subgroup	2	40	Mean Difference (IV, Fixed, 95% CI)	22.20 [-56.65, 101.05]
5.3 at 24 h total pooled result	2	40	Mean Difference (IV, Fixed, 95% CI)	22.20 [-56.65, 101.05]
6 FEV_1 (L) or FEV_1 (%) if missing at baseline	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 at baseline mild-moderate subgroups	4	151	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.30, 0.39]
6.2 at baseline severe subgroup	5	286	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.55, 0.16]
6.3 at baseline total pooled result	9	437	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.39, 0.14]

7 FEV_1 (L) or FEV_1 (%) if missing at 30 min	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 at 30 min mild-moderate subgroups	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 at 30 min severe subgroup	1	94	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.86, -0.04]
7.3 at 30 min total pooled result	1	94	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.86, -0.04]
8 FEV_1 (L) or FEV_1 (%) if missing at 12 h	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 at 12 h mild-moderate subgroups	2	39	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-1.05, 1.17]
8.2 at 12 h severe subgroup	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 at 12 h total pooled result	2	39	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-1.05, 1.17]
9 FEV_1 (L) or FEV_1 (%) if missing at 60 min	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 at 60 min mild-moderate subgroups	3	157	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.08, 0.58]
9.2 at 60 min severe subgroup	5	286	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.33, 0.26]
9.3 at 60 min total pooled result	8	443	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.17, 0.31]
10 FEV_1 (L) or FEV_1 (%) if missing at 24 h	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 at 24 h mild-moderate subgroups	2	39	Std. Mean Difference (IV, Random, 95% CI)	0.10 [1.00, 1.21]
10.2 at 24 h severe subgroup	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 at 24 h total pooled result	2	39	Std. Mean Difference (IV, Random, 95% CI)	0.10 [1.00, 1.21]

Comparison 3. Aminophylline vs placebo (grouped by corticosteroid use)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PEF (L/min) or PEF (%) if missing at baseline	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 at baseline subgroup with CS	6	293	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.43, 0.03]
1.2 at baseline subgroup without CS	3	116	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.82, 0.62]
1.3 at baseline total pooled result	9	409	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.39, 0.05]
2 PEF (L/min) or PEF (%) if missing at 30 min	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 at 30 min subgroup with CS	3	153	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.69, 0.49]
2.2 at 30 min subgroup without CS	2	76	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [0.00, 0.97]
2.3 at 30 min total pooled result	5	229	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.83, 0.33]

3 PEF (L/min) or PEF (%) if missing at 60 min	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 at 60 min subgroup with CS	6	293	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.31, 0.23]
3.2 at 60 min subgroup without CS	3	116	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.71, 0.78]
3.3 at 60 min total pooled result	9	409	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.28, 0.27]
4 PEF (L/min) or PEF (%) if missing at 12 h	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 at 12 h subgroup with CS	4	115	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.38, 0.35]
4.2 at 12 h subgroup without CS	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 at 12 h total pooled result	4	115	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.38, 0.35]
5 PEF (L/min) or PEF (%) if missing at 24 h	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 at 24 h subgroup with CS	2	40	Std. Mean Difference (IV, Random, 95% CI)	0.17 [-0.46, 0.79]
5.2 at 24 h subgroup without CS	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 at 24 h total pooled result	2	40	Std. Mean Difference (IV, Random, 95% CI)	0.17 [-0.46, 0.79]
6 FEV_1 (L) or FEV_1 (%) if missing at baseline	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 at baseline subgroup with CS	4	217	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.72, 0.33]
6.2 at baseline subgroup without CS	5	220	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.56, -0.02]
6.3 at baseline total pooled result	9	437	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.39, 0.14]
7 FEV_1 (L) or FEV_1 (%) if missing at 30 min	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 at 30 min subgroup with CS	1	94	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.86, -0.04]
7.2 at 30 min subgroup without CS	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 at 30 min total pooled result	1	94	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.86, -0.04]
8 FEV_1 (L) or FEV_1 (%) if missing at 60 min	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 at 60 min subgroup with CS	3	199	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.53, 0.57]
8.2 at 60 min subgroup without CS	5	244	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.14, 0.37]
8.3 at 60 min total pooled result	8	443	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.17, 0.31]
9 FEV_1 (L) or FEV_1 (%) if missing at 12 h	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 at 12 h subgroup with CS	2	39	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-1.05, 1.17]
9.2 at 12 h subgroup without CS	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 at 12 h total pooled result	2	39	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-1.05, 1.17]

10 FEV_1 (L) or FEV_1 (%) if missing at 24 h	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 at 24 h subgroup with CS	2	39	Std. Mean Difference (IV, Random, 95% CI)	0.10 [1.00, 1.21]
10.2 at 24 h subgroup without CS	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 at 24 h total pooled result	2	39	Std. Mean Difference (IV, Random, 95% CI)	0.10 [1.00, 1.21]

Analysis 1.1. Comparison 1 Aminophylline vs Placebo, Outcome 1 Hospital admissions.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 1 Aminophylline vs Placebo

Outcome: 1 Hospital admissions

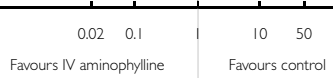
Study or subgroup	IV aminophylline n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Rossing 1981	6/29	6/32		24.5 %	1.13 [0.32, 4.00]
Rodrigo 1994	4/45	5/49		20.8 %	0.86 [0.22, 3.42]
Fanta 1982	9/19	11/13		13.3 %	0.16 [0.03, 0.95]
Huang 1993	7/10	10/11		6.9 %	0.23 [0.02, 2.73]
Siegel 1985	5/20	5/20		19.5 %	1.00 [0.24, 4.18]
Wrenn 1991	2/32	7/35		14.9 %	0.27 [0.05, 1.39]
Total (95% CI)	**155**	**160**		**100.0 %**	**0.58 [0.30, 1.12]**

Total events: 33 (IV aminophylline), 44 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 5.33$, df = 5 (P = 0.38); $I^2 = 6\%$

Test for overall effect: Z = 1.61 (P = 0.11)

Test for subgroup differences: Not applicable

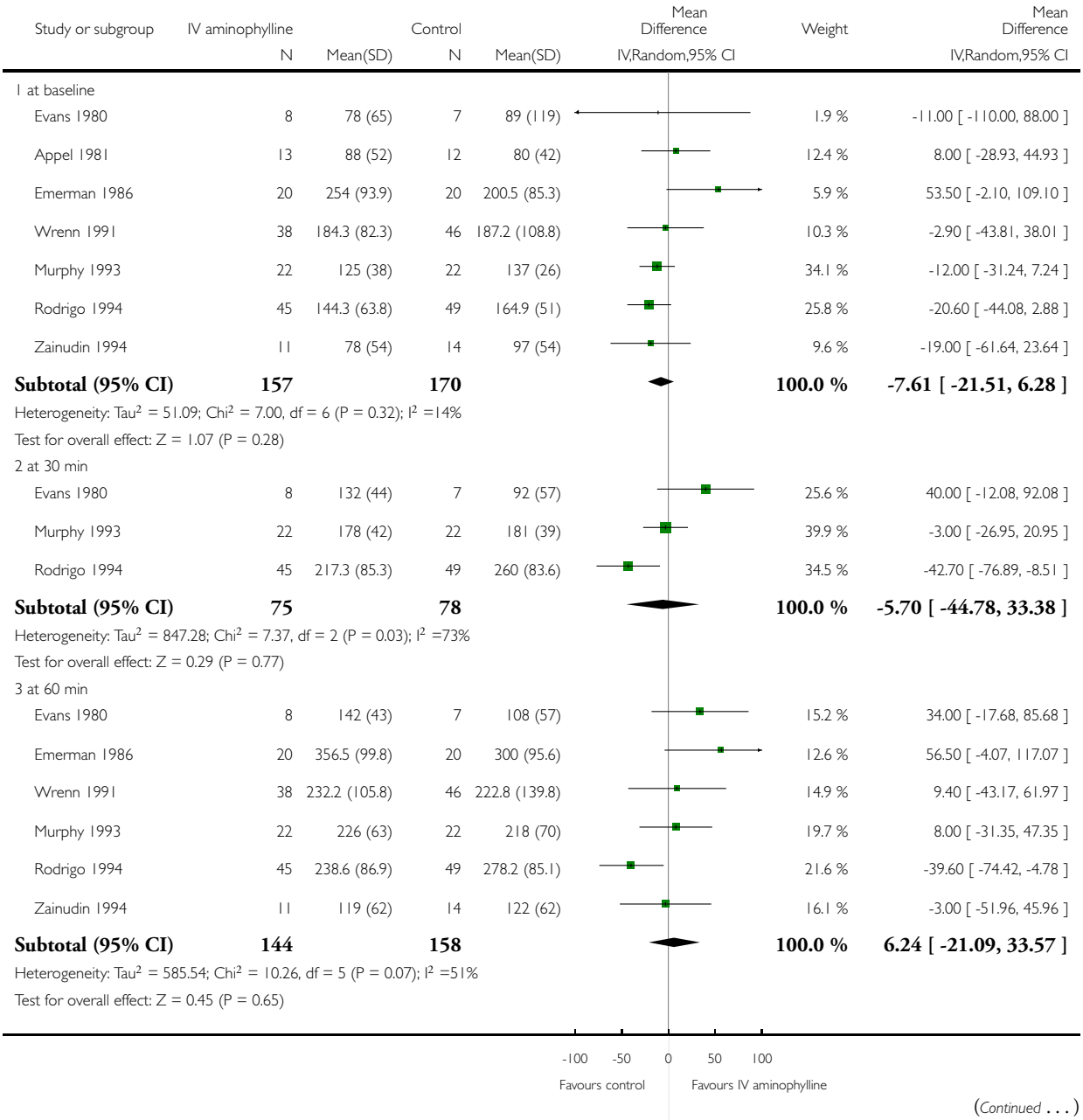


Analysis 1.2. Comparison 1 Aminophylline vs Placebo, Outcome 2 PEF (L/min).

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 1 Aminophylline vs Placebo

Outcome: 2 PEF (L/min)



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Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
4 at 12 h							
Evans 1980	8	175 (53)	7	155 (77)		18.3 %	20.00 [-47.84, 87.84]
Murphy 1993	22	358 (78)	22	355 (59)		50.3 %	3.00 [-37.87, 43.87]
Zainudin 1994	11	194 (65.5)	14	184 (65.5)		31.4 %	10.00 [-41.72, 61.72]
Subtotal (95% CI)	**41**		**43**			**100.0 %**	**8.30 [-20.69, 37.29]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.18$, df = 2 (P = 0.91); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.56 (P = 0.57)							
5 at 24 h							
Evans 1980	8	240 (121)	7	191 (136)		36.2 %	49.00 [-82.07, 180.07]
Zainudin 1994	11	216 (125)	14	209 (125)		63.8 %	7.00 [-91.71, 105.71]
Subtotal (95% CI)	**19**		**21**			**100.0 %**	**22.20 [-56.65, 101.05]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.25$, df = 1 (P = 0.62); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.55 (P = 0.58)							

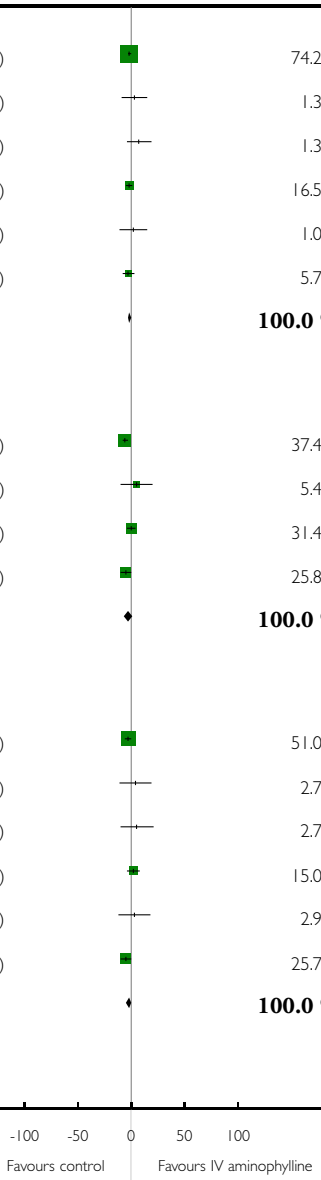
Analysis 1.3. Comparison 1 Aminophylline vs Placebo, Outcome 3 PEF (% predicted).

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 1 Aminophylline vs Placebo

Outcome: 3 PEF (% predicted)

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 at baseline							
Josephson 1979	24	22.8 (1.8)	27	24.4 (3.6)		74.2 %	-1.60 [-3.14, -0.06]
Appel 1981	13	32 (17)	12	29 (13)		1.3 %	3.00 [-8.81, 14.81]
Emerman 1986	20	53.5 (20.6)	20	46.1 (16.8)		1.3 %	7.40 [-4.25, 19.05]
Murphy 1993	22	21 (6)	22	23 (5)		16.5 %	-2.00 [-5.26, 1.26]
Coleridge 1993	16	46.4 (20.5)	15	44.2 (16.8)		1.0 %	2.20 [-10.96, 15.36]
Rodrigo 1994	45	30.4 (16)	49	33.3 (10.6)		5.7 %	-2.90 [-8.44, 2.64]
Subtotal (95% CI)	**140**		**145**			**100.0 %**	**-1.53 [-2.85, -0.20]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.45, df = 5 (P = 0.63); I^2 =0.0%							
Test for overall effect: Z = 2.26 (P = 0.024)							
2 at 30 min							
Josephson 1979	24	47.2 (4.2)	27	52.8 (4.6)		37.4 %	-5.60 [-8.02, -3.18]
Appel 1981	13	68 (14)	12	63 (22)		5.4 %	5.00 [-9.59, 19.59]
Murphy 1993	22	30 (6)	22	30 (6)		31.4 %	0.0 [-3.55, 3.55]
Rodrigo 1994	45	43 (11.2)	49	48 (11.8)		25.8 %	-5.00 [-9.65, -0.35]
Subtotal (95% CI)	**104**		**110**			**100.0 %**	**-3.11 [-6.74, 0.52]**
Heterogeneity: Tau^2 = 7.66; Chi^2 = 8.19, df = 3 (P = 0.04); I^2 =63%							
Test for overall effect: Z = 1.68 (P = 0.093)							
3 at 60 min							
Josephson 1979	24	56 (4.4)	27	59.2 (5.8)		51.0 %	-3.20 [-6.01, -0.39]
Appel 1981	13	72 (16)	12	68 (22.5)		2.7 %	4.00 [-11.42, 19.42]
Emerman 1986	20	75.7 (25.3)	20	70.4 (24.6)		2.7 %	5.30 [-10.17, 20.77]
Murphy 1993	22	38 (10)	22	36 (11)		15.0 %	2.00 [-4.21, 8.21]
Coleridge 1993	16	60 (24.8)	15	57 (16.8)		2.9 %	3.00 [-11.83, 17.83]
Rodrigo 1994	45	47 (10.6)	49	52 (11.8)		25.7 %	-5.00 [-9.53, -0.47]
Subtotal (95% CI)	**140**		**145**			**100.0 %**	**-2.28 [-4.84, 0.27]**
Heterogeneity: Tau^2 = 1.28; Chi^2 = 5.61, df = 5 (P = 0.35); I^2 =11%							
Test for overall effect: Z = 1.75 (P = 0.080)							



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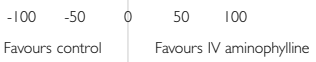
Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
4 at 12 h							
Murphy 1993	22	61 (15)	23	59 (13)		81.0 %	2.00 [-6.22, 10.22]
Coleridge 1993	16	84.2 (8.5)	15	99.1 (53.4)		19.0 %	-14.90 [-42.24, 12.44]
Subtotal (95% CI)	**38**		**38**			**100.0 %**	**-1.21 [-14.21, 11.78]**
Heterogeneity: Tau^2 = 36.71; Chi^2 = 1.35, df = 1 (P = 0.25); I^2 =26%							
Test for overall effect: Z = 0.18 (P = 0.85)							
5 at 24 h							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							

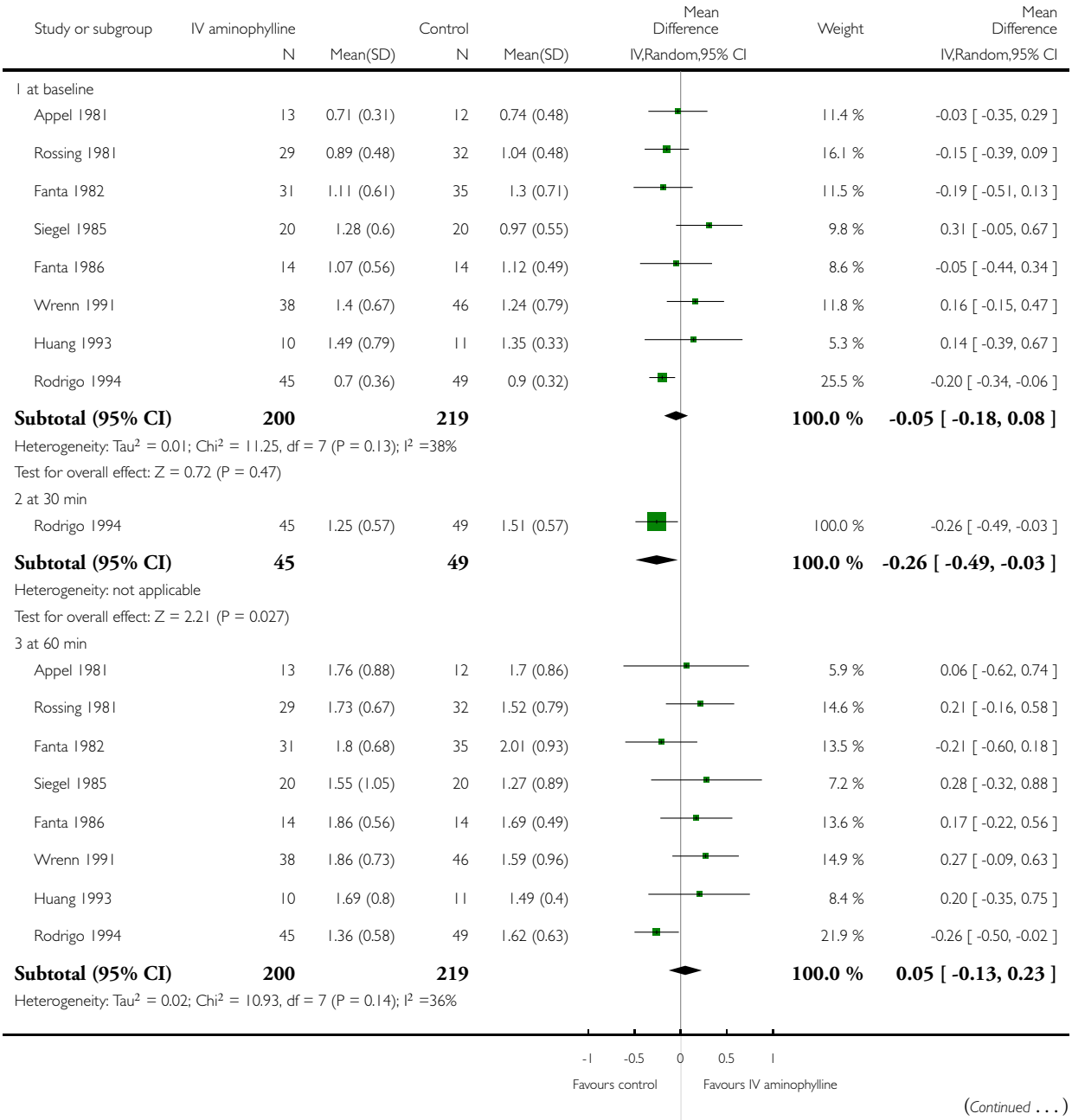


Analysis 1.4. Comparison 1 Aminophylline vs Placebo, Outcome 4 FEV_1 (L).

Review: Addition of intravenous aminophylline to inhaled $beta_2$-agonists in adults with acute asthma

Comparison: 1 Aminophylline vs Placebo

Outcome: 4 FEV_1 (L)



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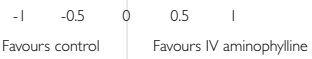
Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 0.53 (P = 0.60)							
4 at 12 h							
Huang 1993	10	2.03 (0.87)	11	1.62 (0.33)		100.0 %	0.41 [-0.16, 0.98]
Subtotal (95% CI)	**10**		**11**			**100.0 %**	**0.41 [-0.16, 0.98]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.40 (P = 0.16)							
5 at 24 h							
Huang 1993	10	2.17 (0.82)	11	1.75 (0.35)		100.0 %	0.42 [-0.13, 0.97]
Subtotal (95% CI)	**10**		**11**			**100.0 %**	**0.42 [-0.13, 0.97]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.50 (P = 0.13)							

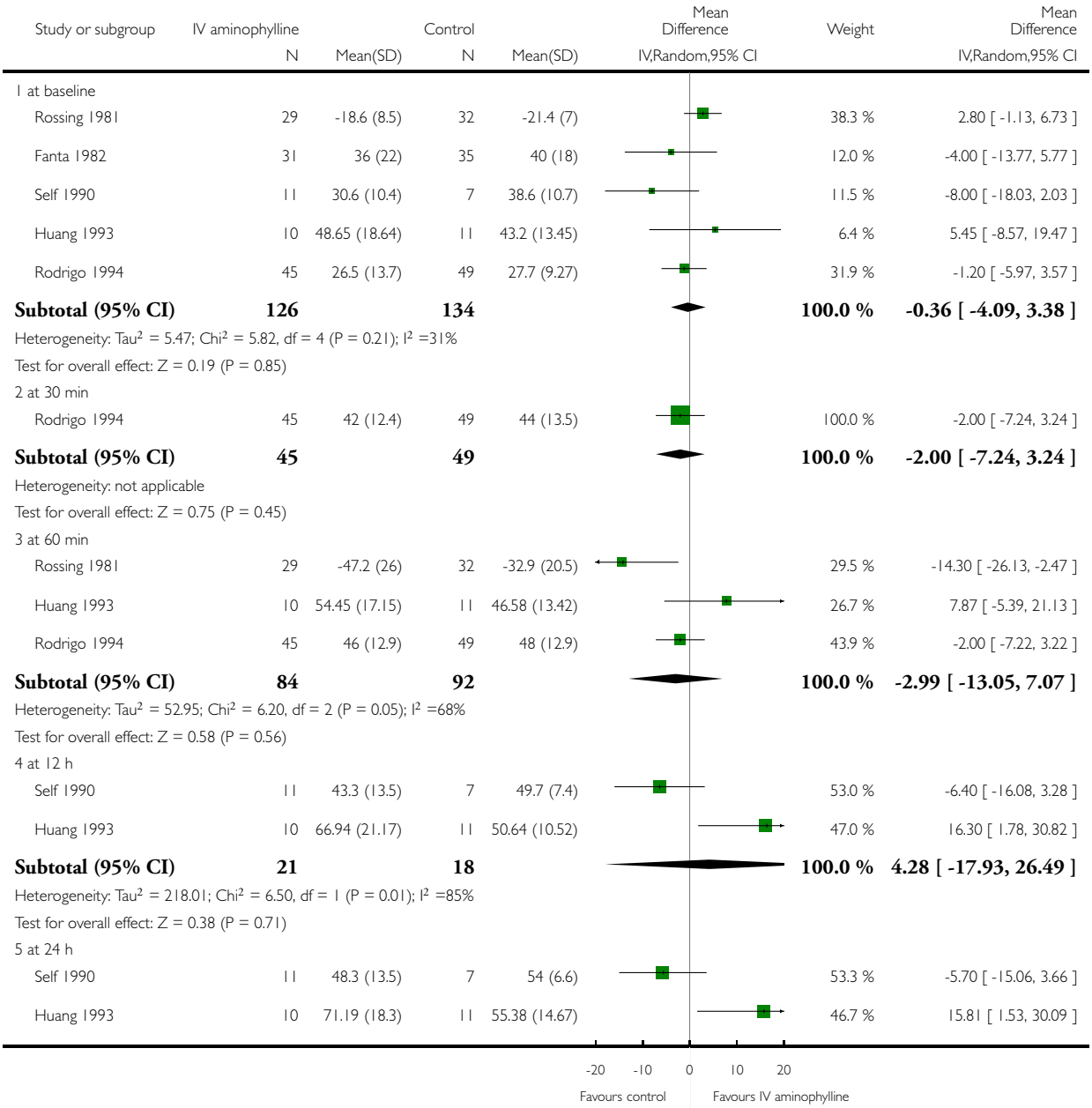


Analysis 1.5. Comparison 1 Aminophylline vs Placebo, Outcome 5 FEV_1 (% predicted).

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 1 Aminophylline vs Placebo

Outcome: 5 FEV_1 (% predicted)



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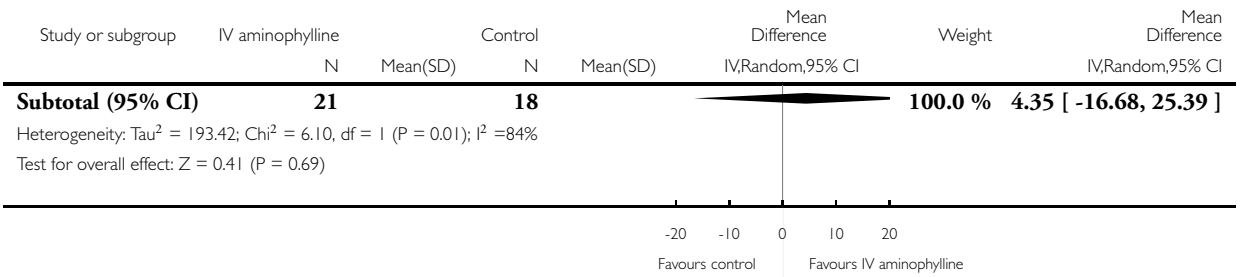
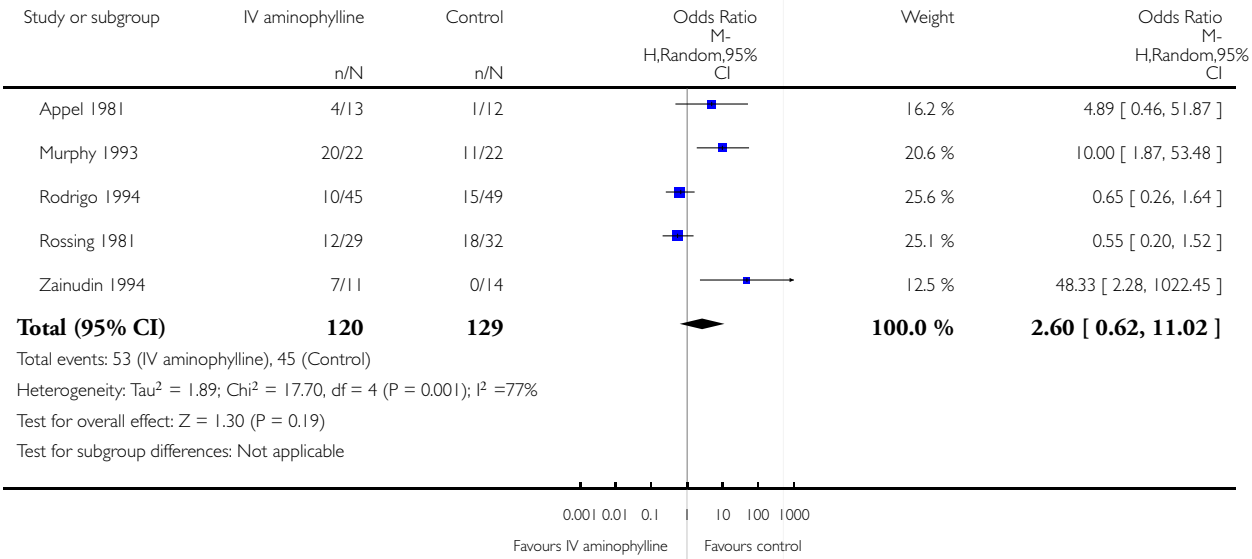


Analysis 1.6. Comparison 1 Aminophylline vs Placebo, Outcome 6 Tremor.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 1 Aminophylline vs Placebo

Outcome: 6 Tremor

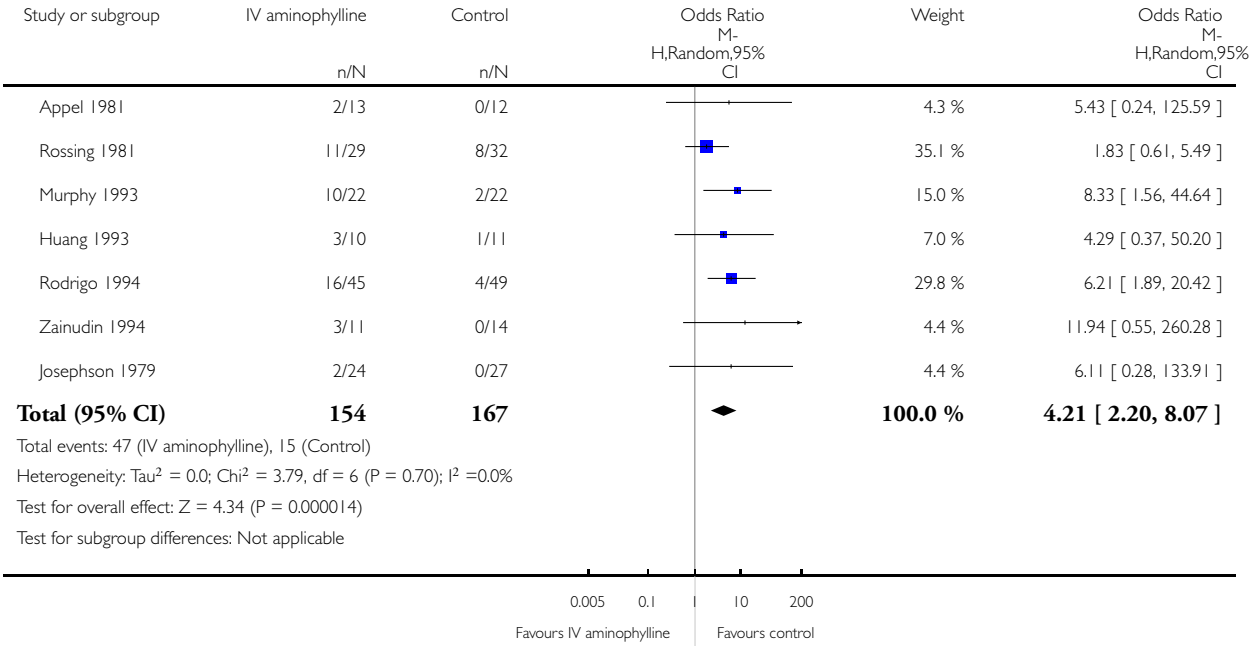


Analysis 1.7. Comparison 1 Aminophylline vs Placebo, Outcome 7 Vomiting.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 1 Aminophylline vs Placebo

Outcome: 7 Vomiting

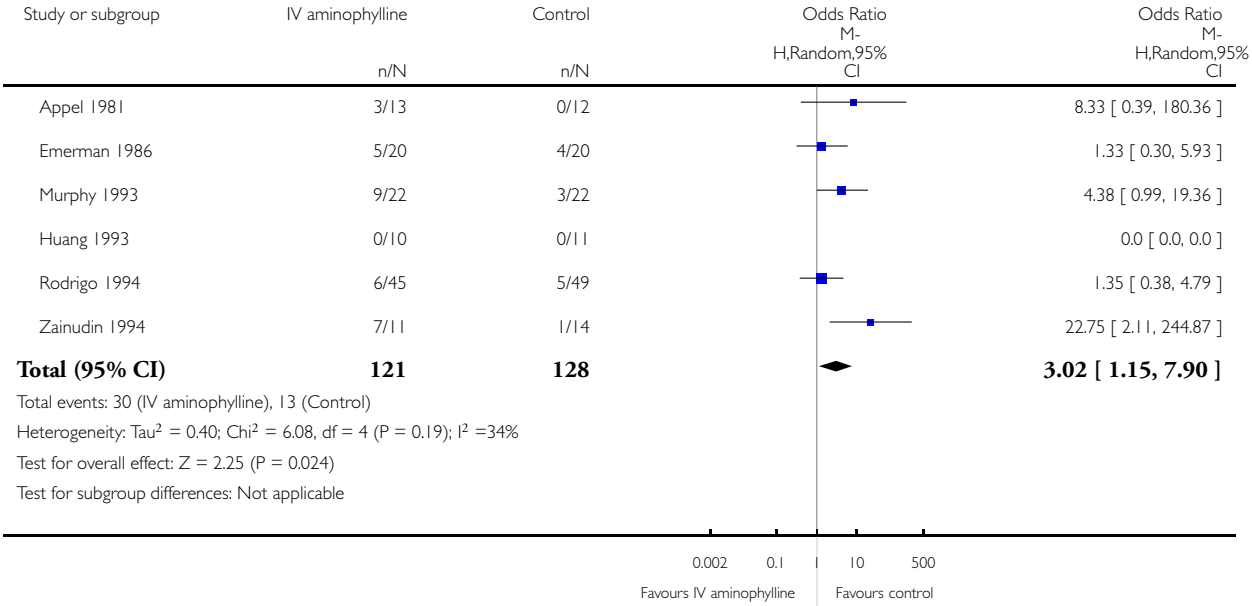


Analysis 1.8. Comparison 1 Aminophylline vs Placebo, Outcome 8 Arrythmia/palpitations.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 1 Aminophylline vs Placebo

Outcome: 8 Arrythmia/palpitations



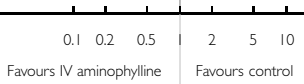
Analysis 1.9. Comparison 1 Aminophylline vs Placebo, Outcome 9 Convulsions.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 1 Aminophylline vs Placebo

Outcome: 9 Convulsions

Study or subgroup	IV aminophylline n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Huang 1993	0/10	0/11		0.0 [0.0, 0.0]
Total (95% CI)	**10**	**11**		**0.0 [0.0, 0.0]**
Total events: 0 (IV aminophylline), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

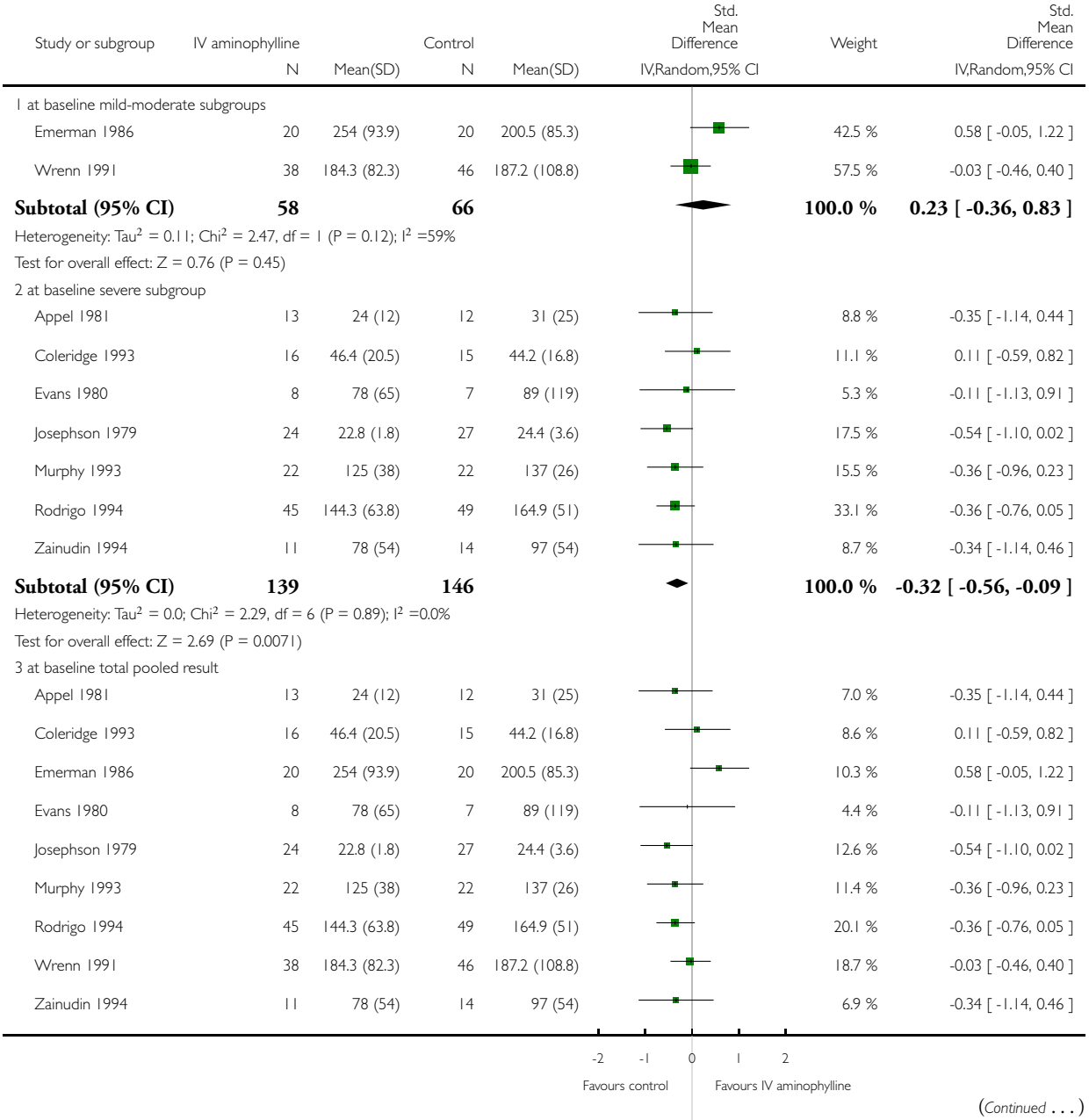


Analysis 2.1. Comparison 2 Aminophylline vs placebo (grouped by baseline severity), Outcome 1 PEF (L/min) or PEF (%) if missing at baseline.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 2 Aminophylline vs placebo (grouped by baseline severity)

Outcome: 1 PEF (L/min) or PEF (%) if missing at baseline



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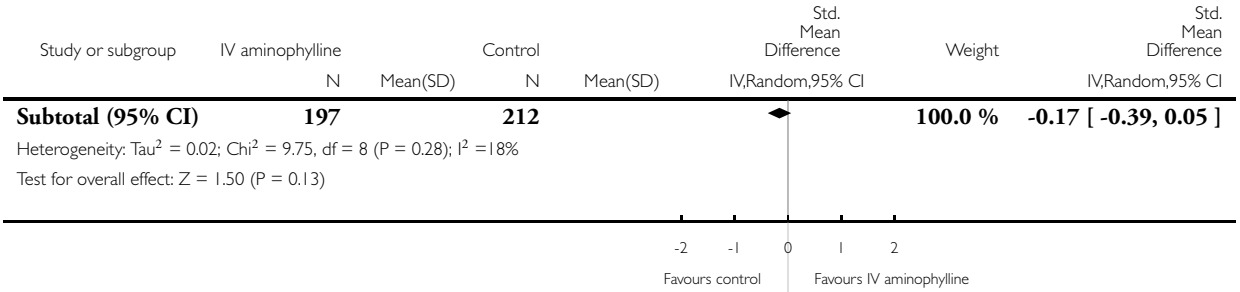
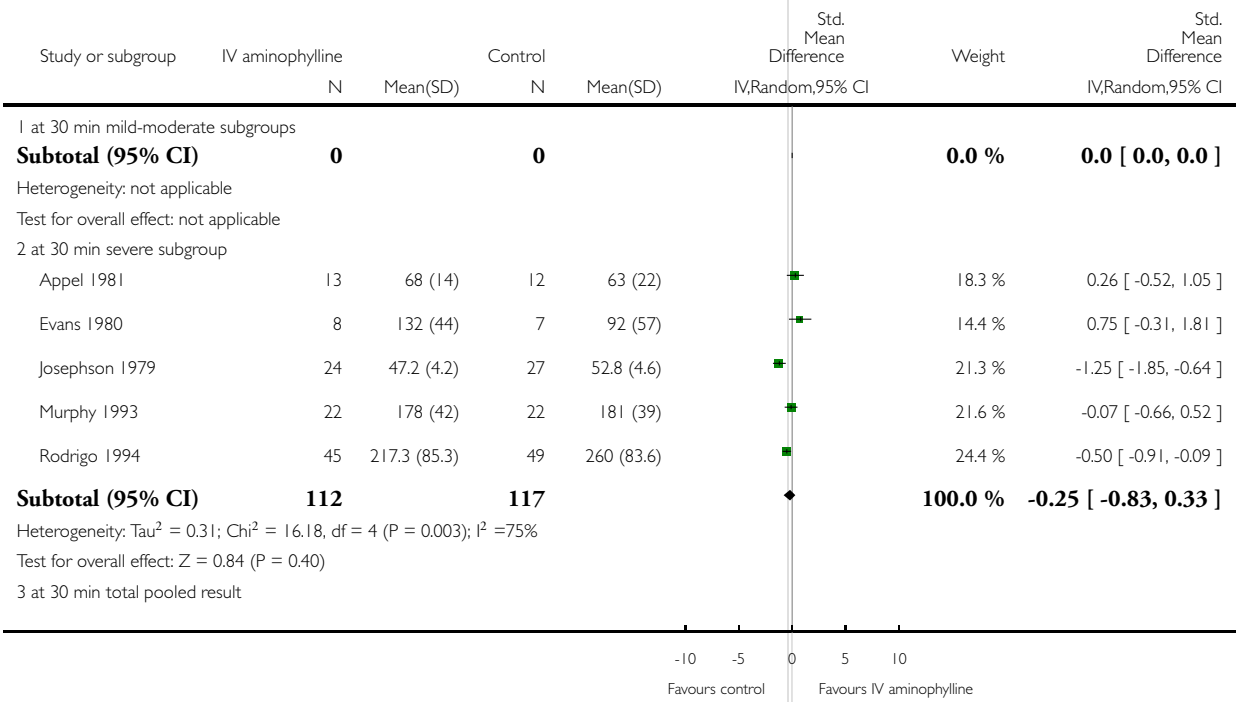


Analysis 2.2. Comparison 2 Aminophylline vs placebo (grouped by baseline severity), Outcome 2 PEF (L/min) or PEF (%) if missing at 30 min.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 2 Aminophylline vs placebo (grouped by baseline severity)

Outcome: 2 PEF (L/min) or PEF (%) if missing at 30 min



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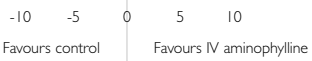
Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Appel 1981	13	68 (14)	12	63 (22)		18.3 %	0.26 [-0.52, 1.05]
Evans 1980	8	132 (44)	7	92 (57)		14.4 %	0.75 [-0.31, 1.81]
Josephson 1979	24	47.2 (4.2)	27	52.8 (4.6)		21.3 %	-1.25 [-1.85, -0.64]
Murphy 1993	22	178 (42)	22	181 (39)		21.6 %	-0.07 [-0.66, 0.52]
Rodrigo 1994	45	217.3 (85.3)	49	260 (83.6)		24.4 %	-0.50 [-0.91, -0.09]
Subtotal (95% CI)	**112**		**117**			**100.0 %**	**-0.25 [-0.83, 0.33]**

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 16.18$, df = 4 (P = 0.003); $I^2 = 75\%$

Test for overall effect: Z = 0.84 (P = 0.40)

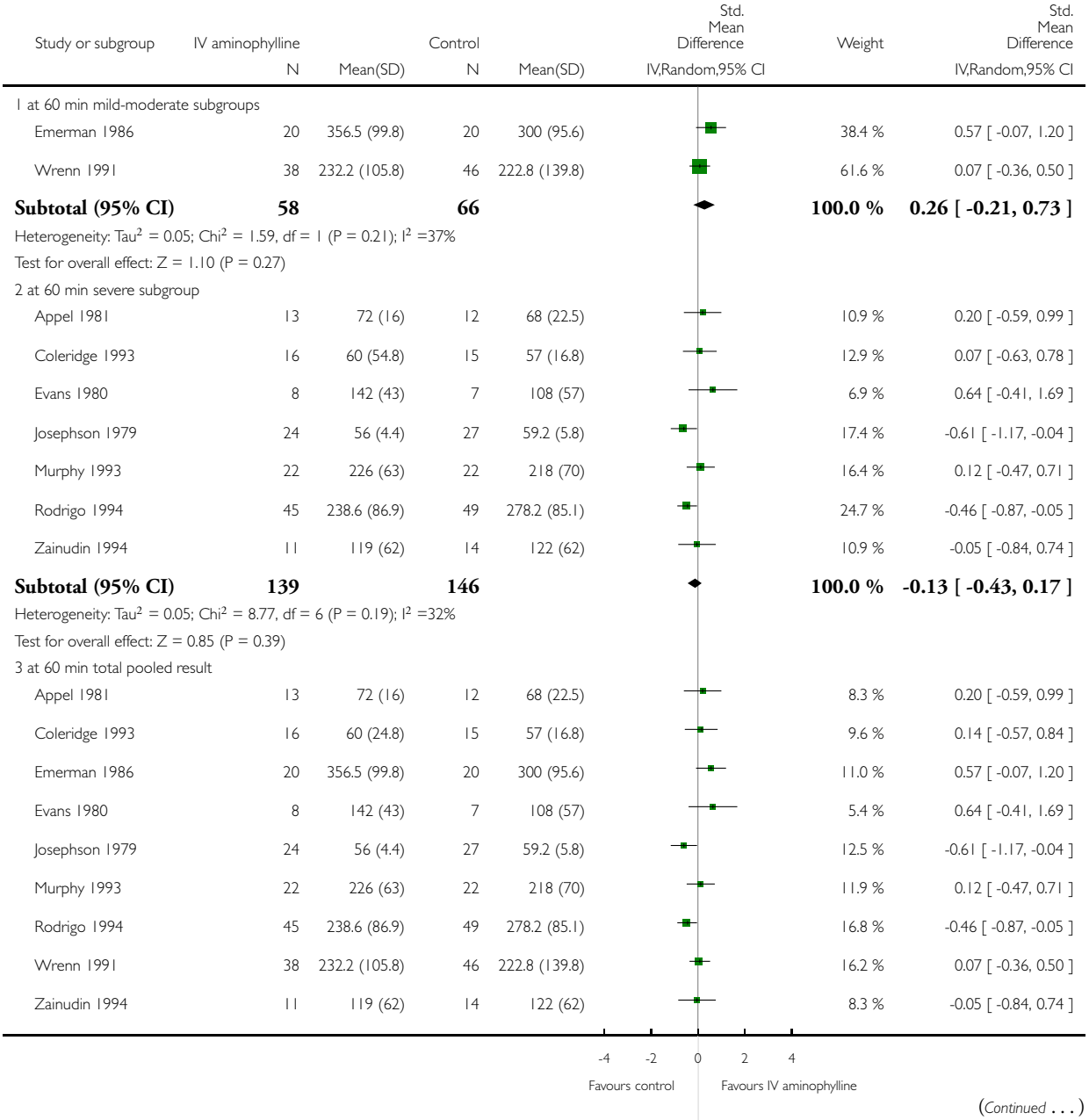


Analysis 2.3. Comparison 2 Aminophylline vs placebo (grouped by baseline severity), Outcome 3 PEF (L/min) or PEF (%) if missing at 60 min.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 2 Aminophylline vs placebo (grouped by baseline severity)

Outcome: 3 PEF (L/min) or PEF (%) if missing at 60 min



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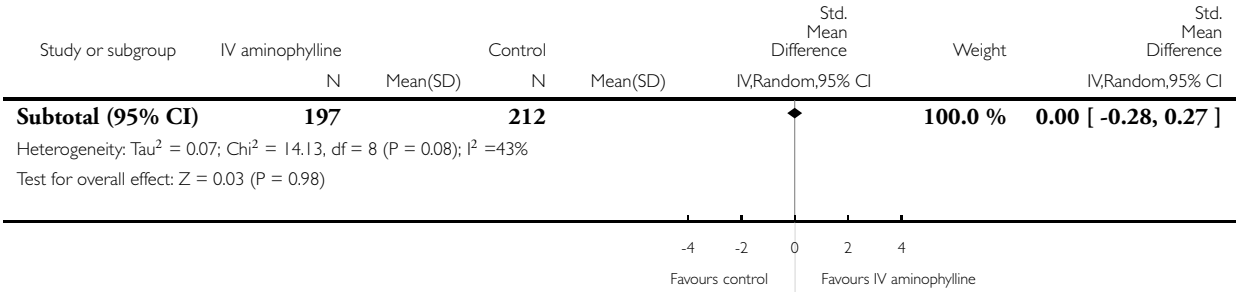
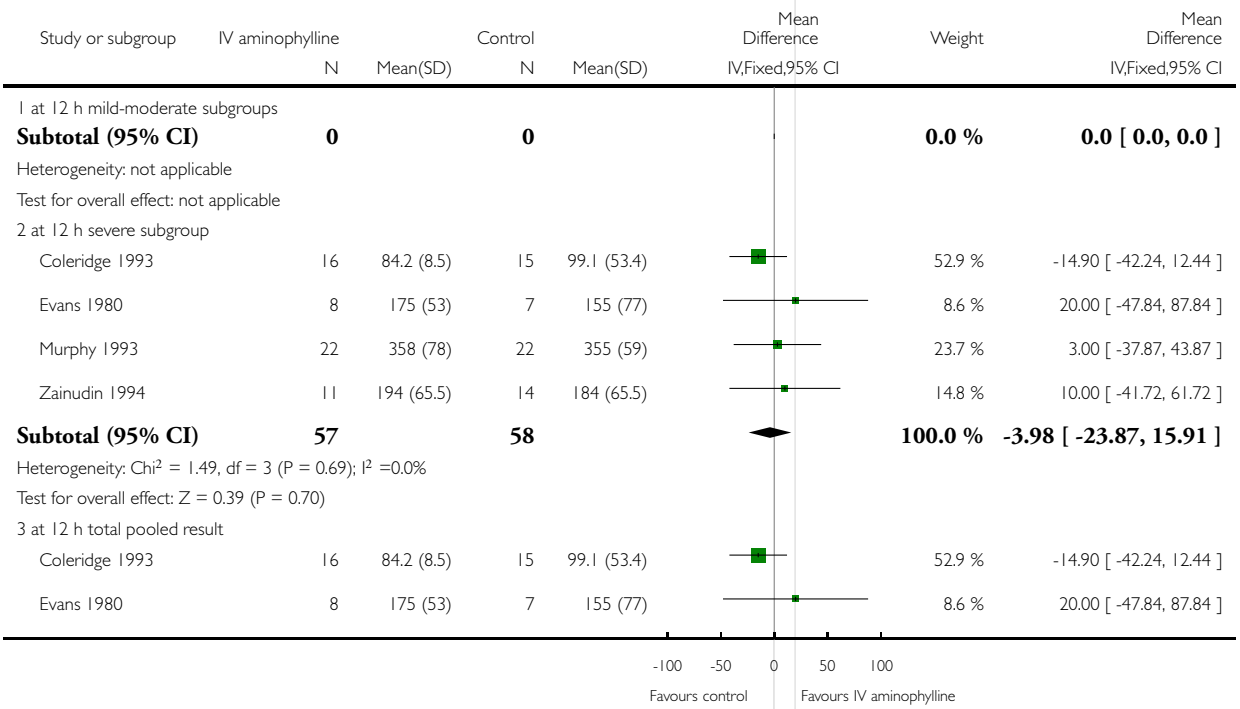


Analysis 2.4. Comparison 2 Aminophylline vs placebo (grouped by baseline severity), Outcome 4 PEF (L/m) or PEF (%) if missing at 12 h.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 2 Aminophylline vs placebo (grouped by baseline severity)

Outcome: 4 PEF (L/m) or PEF (%) if missing at 12 h



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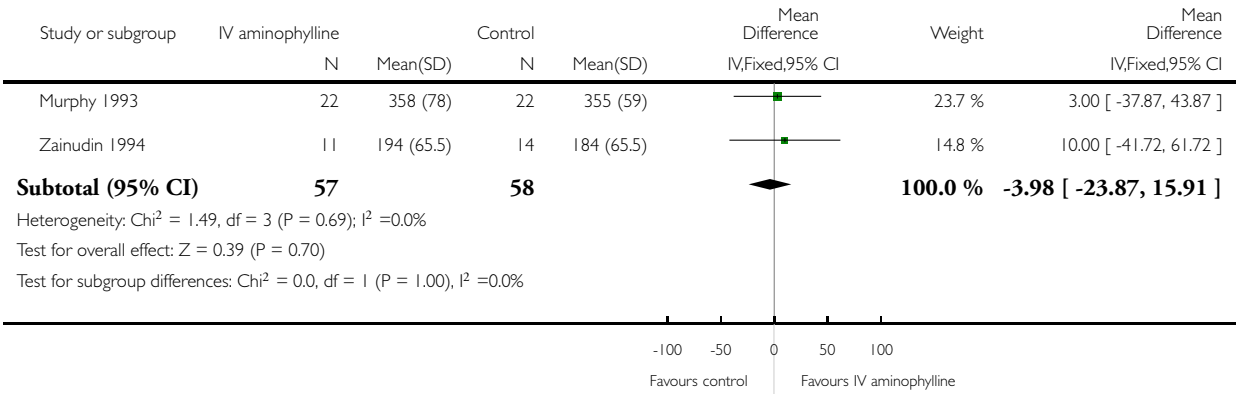
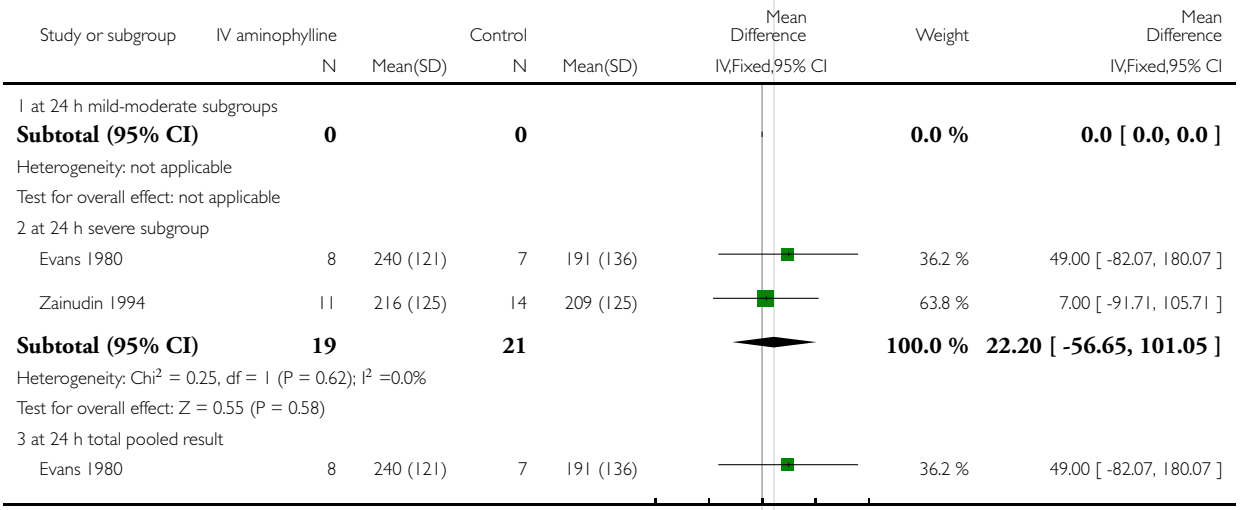


Analysis 2.5. Comparison 2 Aminophylline vs placebo (grouped by baseline severity), Outcome 5 PEF (L/min) or PEF (%) if missing at 24 h.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 2 Aminophylline vs placebo (grouped by baseline severity)

Outcome: 5 PEF (L/min) or PEF (%) if missing at 24 h



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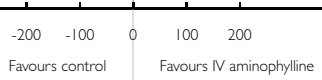
Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Zainudin 1994	11	216 (125)	14	209 (125)		63.8 %	7.00 [-91.71, 105.71]
Subtotal (95% CI)	**19**		**21**			**100.0 %**	**22.20 [-56.65, 101.05]**

Heterogeneity: Chi^2 = 0.25, df = 1 (P = 0.62); I^2 =0.0%

Test for overall effect: Z = 0.55 (P = 0.58)

Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%



Analysis 2.6. Comparison 2 Aminophylline vs placebo (grouped by baseline severity), Outcome 6 FEV_1 (L) or FEV_1 (%) if missing at baseline.

Review: Addition of intravenous aminophylline to inhaled $beta_2$-agonists in adults with acute asthma

Comparison: 2 Aminophylline vs placebo (grouped by baseline severity)

Outcome: 6 FEV_1 (L) or FEV_1 (%) if missing at baseline

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at baseline mild-moderate subgroups							
Fanta 1986	14	1.07 (0.56)	14	1.12 (0.49)		20.2 %	-0.09 [-0.83, 0.65]
Huang 1993	10	1.49 (0.79)	11	1.35 (0.33)		15.3 %	0.23 [-0.63, 1.09]
Self 1990	11	30.6 (10.4)	7	38.6 (10.7)		11.8 %	-0.72 [-1.71, 0.26]
Wrenn 1991	38	1.4 (0.67)	46	1.24 (0.79)		52.7 %	0.21 [-0.22, 0.65]
Subtotal (95% CI)	**73**		**78**			**100.0 %**	**0.04 [-0.30, 0.39]**

Heterogeneity: Tau^2 = 0.01; Chi^2 = 3.24, df = 3 (P = 0.36); I^2 =7%

Test for overall effect: Z = 0.25 (P = 0.80)

2 at baseline severe subgroup

Appel 1981	13	0.71 (0.31)	12	0.74 (0.48)		13.4 %	-0.07 [-0.86, 0.71]
Fanta 1982	31	1.11 (0.61)	35	1.3 (0.71)		22.4 %	-0.28 [-0.77, 0.20]
Rodrigo 1994	45	0.7 (0.36)	49	0.9 (0.32)		25.3 %	-0.58 [-1.00, -0.17]

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Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Rossing 1981	29	0.89 (0.48)	32	1.04 (0.48)		21.6 %	-0.31 [-0.81, 0.20]
Siegel 1985	20	1.28 (0.6)	20	0.97 (0.55)		17.4 %	0.53 [-0.10, 1.16]
Subtotal (95% CI)	**138**		**148**			**100.0 %**	**-0.20 [-0.55, 0.16]**
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 8.59$, df = 4 (P = 0.07); $I^2 = 53\%$							
Test for overall effect: Z = 1.08 (P = 0.28)							
3 at baseline total pooled result							
Appel 1981	13	0.71 (0.31)	12	0.74 (0.48)		8.0 %	-0.07 [-0.86, 0.71]
Fanta 1982	31	1.11 (0.61)	35	1.3 (0.71)		14.2 %	-0.28 [-0.77, 0.20]
Fanta 1986	14	1.07 (0.56)	14	1.12 (0.49)		8.7 %	-0.09 [-0.83, 0.65]
Huang 1993	10	1.49 (0.79)	11	1.35 (0.33)		7.0 %	0.23 [-0.63, 1.09]
Rodrigo 1994	45	0.7 (0.36)	49	0.9 (0.32)		16.3 %	-0.58 [-1.00, -0.17]
Rossing 1981	29	0.89 (0.48)	32	1.04 (0.48)		13.6 %	-0.31 [-0.81, 0.20]
Self 1990	11	30.6 (10.4)	7	38.6 (10.7)		5.7 %	-0.72 [-1.71, 0.26]
Siegel 1985	20	1.28 (0.6)	20	0.97 (0.55)		10.7 %	0.53 [-0.10, 1.16]
Wrenn 1991	38	1.4 (0.67)	46	1.24 (0.79)		15.8 %	0.21 [-0.22, 0.65]
Subtotal (95% CI)	**211**		**226**			**100.0 %**	**-0.13 [-0.39, 0.14]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 14.17$, df = 8 (P = 0.08); $I^2 = 44\%$							
Test for overall effect: Z = 0.93 (P = 0.35)							

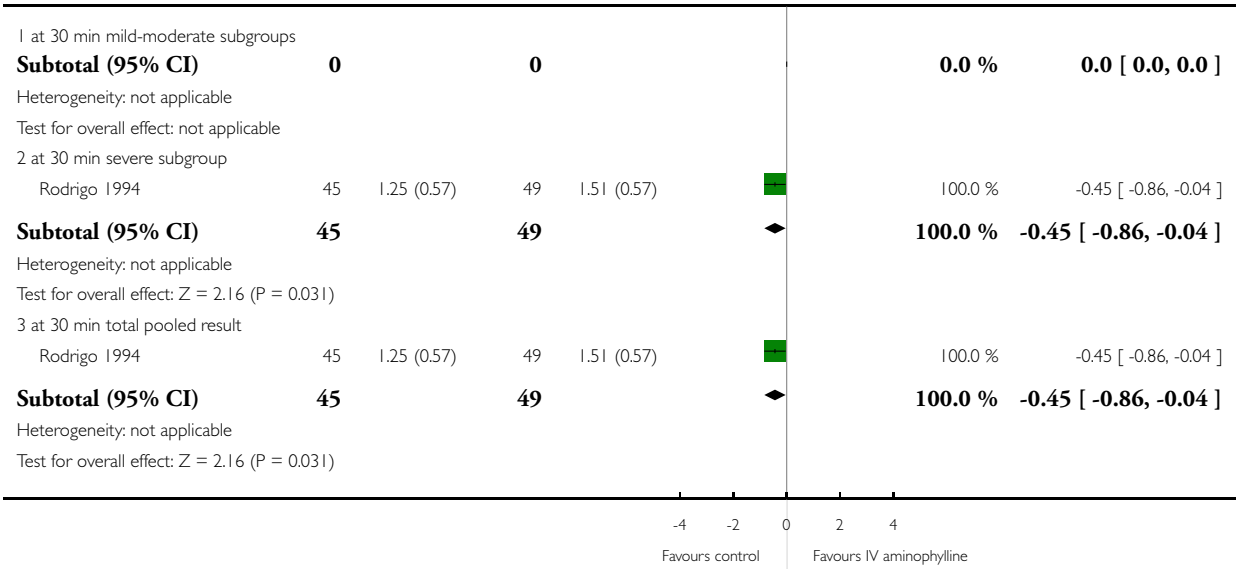
Analysis 2.7. Comparison 2 Aminophylline vs placebo (grouped by baseline severity), Outcome 7 FEV_1 (L) or FEV_1 (%) if missing at 30 min.

Review: Addition of intravenous aminophylline to inhaled $beta_2$-agonists in adults with acute asthma

Comparison: 2 Aminophylline vs placebo (grouped by baseline severity)

Outcome: 7 FEV_1 (L) or FEV_1 (%) if missing at 30 min

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at 30 min mild-moderate subgroups							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 at 30 min severe subgroup							
Rodrigo 1994	45	1.25 (0.57)	49	1.51 (0.57)		100.0 %	-0.45 [-0.86, -0.04]
Subtotal (95% CI)	**45**		**49**			**100.0 %**	**-0.45 [-0.86, -0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.16 (P = 0.031)							
3 at 30 min total pooled result							
Rodrigo 1994	45	1.25 (0.57)	49	1.51 (0.57)		100.0 %	-0.45 [-0.86, -0.04]
Subtotal (95% CI)	**45**		**49**			**100.0 %**	**-0.45 [-0.86, -0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.16 (P = 0.031)							



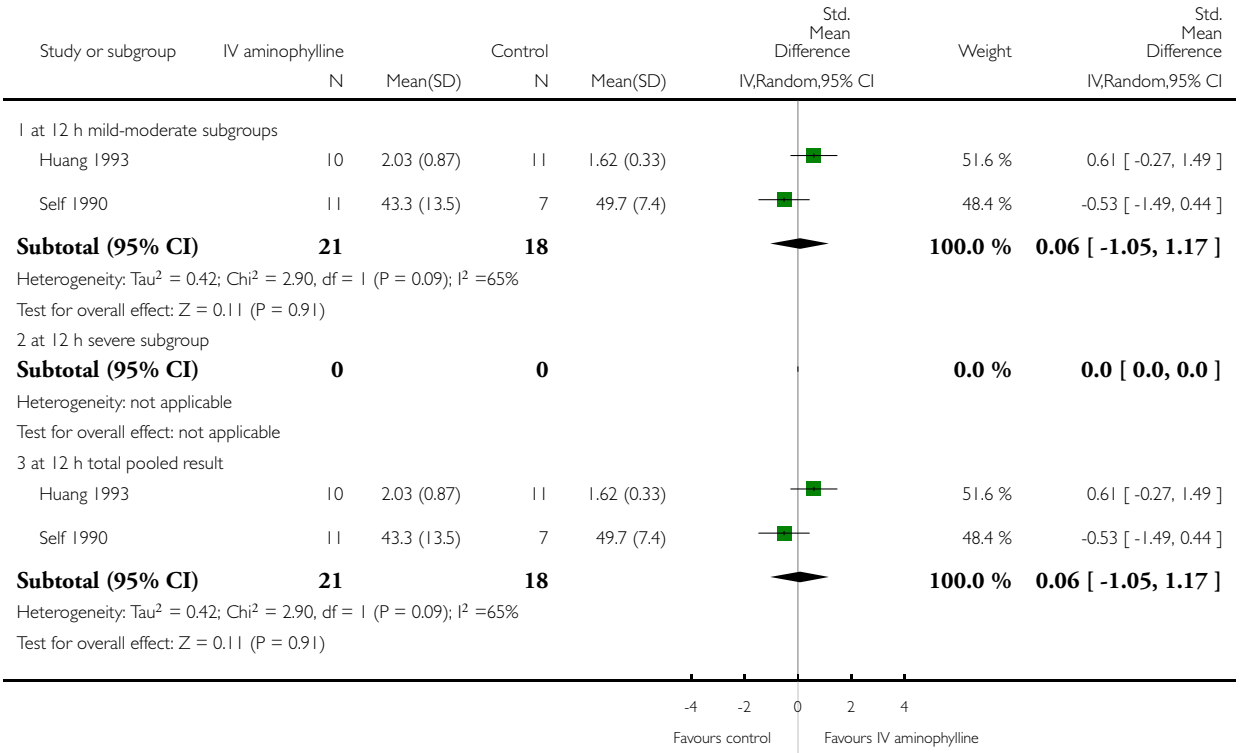
Analysis 2.8. Comparison 2 Aminophylline vs placebo (grouped by baseline severity), Outcome 8 FEV_1 (L) or FEV_1 (%) if missing at 12 h.

Review: Addition of intravenous aminophylline to inhaled $beta_2$-agonists in adults with acute asthma

Comparison: 2 Aminophylline vs placebo (grouped by baseline severity)

Outcome: 8 FEV_1 (L) or FEV_1 (%) if missing at 12 h

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at 12 h mild-moderate subgroups							
Huang 1993	10	2.03 (0.87)	11	1.62 (0.33)		51.6 %	0.61 [-0.27, 1.49]
Self 1990	11	43.3 (13.5)	7	49.7 (7.4)		48.4 %	-0.53 [-1.49, 0.44]
Subtotal (95% CI)	**21**		**18**			**100.0 %**	**0.06 [-1.05, 1.17]**
Heterogeneity: Tau^2 = 0.42; Chi^2 = 2.90, df = 1 (P = 0.09); I^2 =65%							
Test for overall effect: Z = 0.11 (P = 0.91)							
2 at 12 h severe subgroup							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 at 12 h total pooled result							
Huang 1993	10	2.03 (0.87)	11	1.62 (0.33)		51.6 %	0.61 [-0.27, 1.49]
Self 1990	11	43.3 (13.5)	7	49.7 (7.4)		48.4 %	-0.53 [-1.49, 0.44]
Subtotal (95% CI)	**21**		**18**			**100.0 %**	**0.06 [-1.05, 1.17]**
Heterogeneity: Tau^2 = 0.42; Chi^2 = 2.90, df = 1 (P = 0.09); I^2 =65%							
Test for overall effect: Z = 0.11 (P = 0.91)							

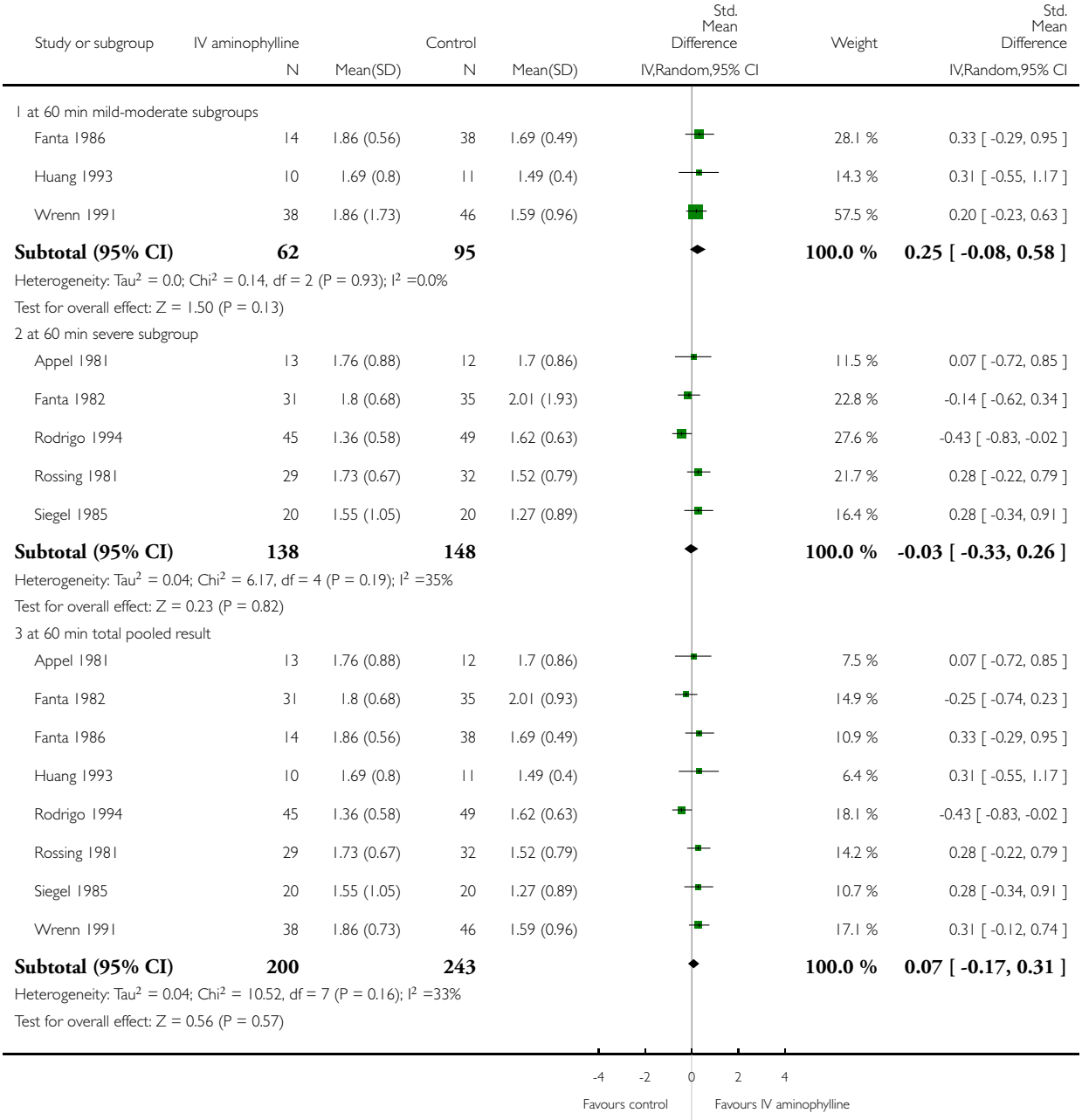


Analysis 2.9. Comparison 2 Aminophylline vs placebo (grouped by baseline severity), Outcome 9 FEV_1 (L) or FEV_1 (%) if missing at 60 min.

Review: Addition of intravenous aminophylline to inhaled $beta_2$-agonists in adults with acute asthma

Comparison: 2 Aminophylline vs placebo (grouped by baseline severity)

Outcome: 9 FEV_1 (L) or FEV_1 (%) if missing at 60 min



Analysis 2.10. Comparison 2 Aminophylline vs placebo (grouped by baseline severity), Outcome 10 FEV_1 (L) or FEV_1 (%) if missing at 24 h.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 2 Aminophylline vs placebo (grouped by baseline severity)

Outcome: 10 FEV_1 (L) or FEV_1 (%) if missing at 24 h

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at 24 h mild-moderate subgroups							
Huang 1993	10	2.17 (0.82)	11	1.75 (0.35)		51.5 %	0.65 [-0.23, 1.54]
Self 1990	11	48.3 (13.5)	7	54 (6.6)		48.5 %	-0.48 [-1.44, 0.49]
Subtotal (95% CI)	**21**		**18**			**100.0 %**	**0.10 [-1.00, 1.21]**
Heterogeneity: Tau^2 = 0.41; Chi^2 = 2.85, df = 1 (P = 0.09); I^2 =65%							
Test for overall effect: Z = 0.19 (P = 0.85)							
2 at 24 h severe subgroup							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 at 24 h total pooled result							
Huang 1993	10	2.17 (0.82)	11	1.75 (0.35)		51.5 %	0.65 [-0.23, 1.54]
Self 1990	11	48.3 (13.5)	7	54 (6.6)		48.5 %	-0.48 [-1.44, 0.49]
Subtotal (95% CI)	**21**		**18**			**100.0 %**	**0.10 [-1.00, 1.21]**
Heterogeneity: Tau^2 = 0.41; Chi^2 = 2.85, df = 1 (P = 0.09); I^2 =65%							
Test for overall effect: Z = 0.19 (P = 0.85)							

Analysis 3.1. Comparison 3 Aminophylline vs placebo (grouped by corticosteroid use), Outcome 1 PEF (L/min) or PEF (%) if missing at baseline.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 3 Aminophylline vs placebo (grouped by corticosteroid use)

Outcome: 1 PEF (L/min) or PEF (%) if missing at baseline

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at baseline subgroup with CS							
Coleridge 1993	16	46.4 (20.5)	15	44.2 (16.8)		10.7 %	0.11 [-0.59, 0.82]
Evans 1980	8	78 (65)	7	89 (119)		5.2 %	-0.11 [-1.13, 0.91]
Murphy 1993	22	125 (38)	22	137 (26)		15.0 %	-0.36 [-0.96, 0.23]
Rodrigo 1994	45	144.3 (63.8)	49	164.9 (51)		32.0 %	-0.36 [-0.76, 0.05]
Wrenn 1991	38	184.3 (82.3)	46	187.2 (108.8)		28.8 %	-0.03 [-0.46, 0.40]
Zainudin 1994	11	78 (54)	14	97 (54)		8.4 %	-0.34 [-1.14, 0.46]
Subtotal (95% CI)	**140**		**153**			**100.0 %**	**-0.20 [-0.43, 0.03]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.36, df = 5 (P = 0.80); I^2 =0.0%							
Test for overall effect: Z = 1.69 (P = 0.092)							
2 at baseline subgroup without CS							
Appel 1981	13	24 (12)	12	31 (25)		29.7 %	-0.35 [-1.14, 0.44]
Emerman 1986	20	254 (93.9)	20	200.5 (85.3)		34.1 %	0.58 [-0.05, 1.22]
Josephson 1979	24	22.8 (1.8)	27	24.4 (3.6)		36.2 %	-0.54 [-1.10, 0.02]
Subtotal (95% CI)	**57**		**59**			**100.0 %**	**-0.10 [-0.82, 0.62]**
Heterogeneity: Tau^2 = 0.29; Chi^2 = 7.26, df = 2 (P = 0.03); I^2 =72%							
Test for overall effect: Z = 0.28 (P = 0.78)							
3 at baseline total pooled result							
Appel 1981	13	24 (12)	12	31 (25)		7.0 %	-0.35 [-1.14, 0.44]
Coleridge 1993	16	46.4 (20.5)	15	44.2 (16.8)		8.6 %	0.11 [-0.59, 0.82]
Emerman 1986	20	254 (93.9)	20	200.5 (85.3)		10.3 %	0.58 [-0.05, 1.22]
Evans 1980	8	78 (65)	7	89 (119)		4.4 %	-0.11 [-1.13, 0.91]
Josephson 1979	24	22.8 (1.8)	27	24.4 (3.6)		12.6 %	-0.54 [-1.10, 0.02]
Murphy 1993	22	125 (38)	22	137 (26)		11.4 %	-0.36 [-0.96, 0.23]
Rodrigo 1994	45	144.3 (63.8)	49	164.9 (51)		20.1 %	-0.36 [-0.76, 0.05]
Wrenn 1991	38	184.3 (82.3)	46	187.2 (108.8)		18.7 %	-0.03 [-0.46, 0.40]
Zainudin 1994	11	78 (54)	14	97 (54)		6.9 %	-0.34 [-1.14, 0.46]

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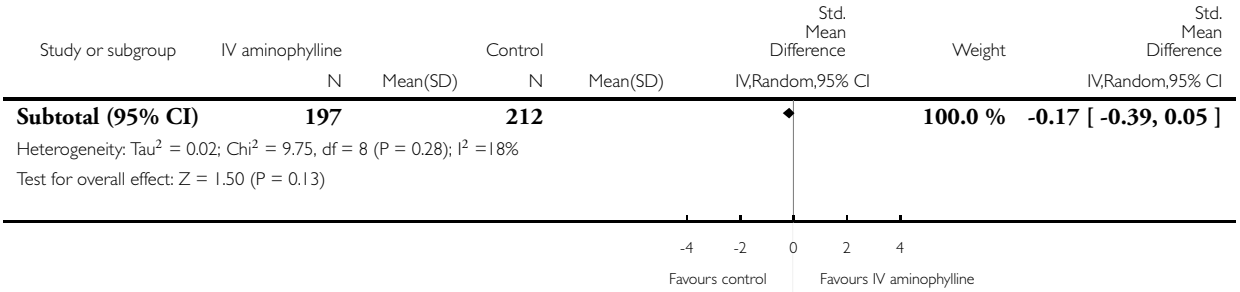
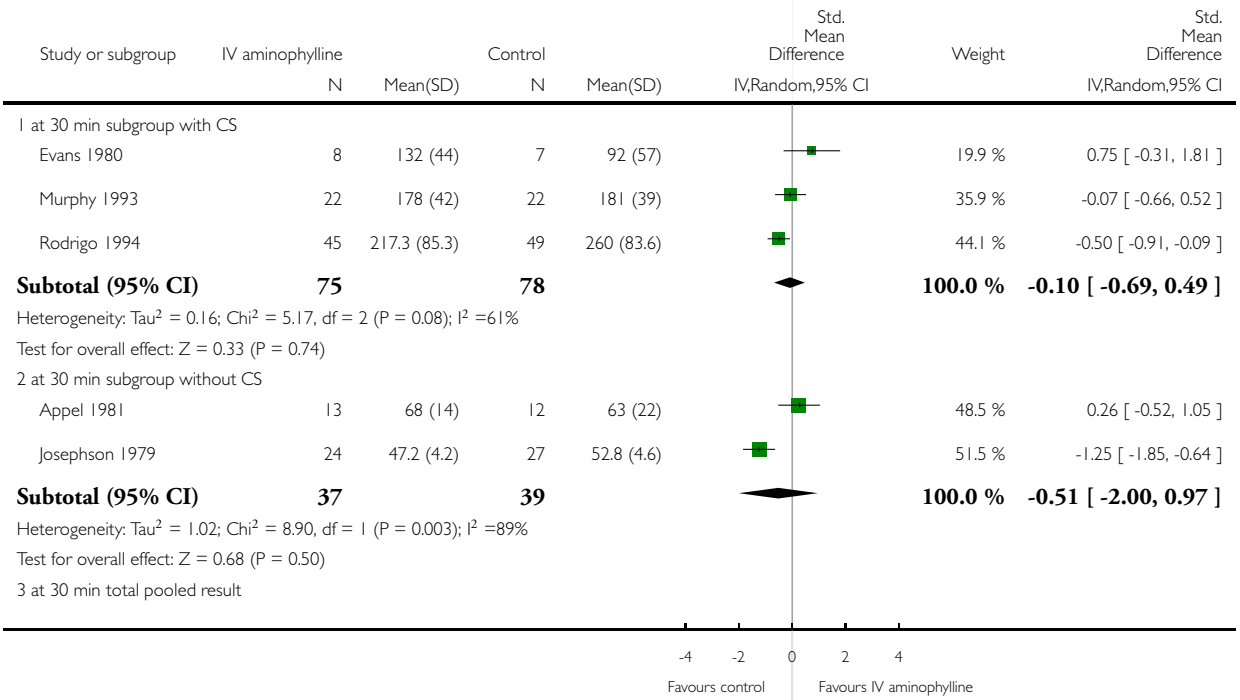


Analysis 3.2. Comparison 3 Aminophylline vs placebo (grouped by corticosteroid use), Outcome 2 PEF (L/min) or PEF (%) if missing at 30 min.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 3 Aminophylline vs placebo (grouped by corticosteroid use)

Outcome: 2 PEF (L/min) or PEF (%) if missing at 30 min



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Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Appel 1981	13	68 (14)	12	63 (22)		18.3 %	0.26 [-0.52, 1.05]
Evans 1980	8	132 (44)	7	92 (57)		14.4 %	0.75 [-0.31, 1.81]
Josephson 1979	24	47.2 (4.2)	27	52.8 (4.6)		21.3 %	-1.25 [-1.85, -0.64]
Murphy 1993	22	178 (42)	22	181 (39)		21.6 %	-0.07 [-0.66, 0.52]
Rodrigo 1994	45	217.3 (85.3)	49	260 (83.6)		24.4 %	-0.50 [-0.91, -0.09]
Subtotal (95% CI)	**112**		**117**			**100.0 %**	**-0.25 [-0.83, 0.33]**

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 16.18$, df = 4 (P = 0.003); $I^2 = 75\%$

Test for overall effect: Z = 0.84 (P = 0.40)

Analysis 3.3. Comparison 3 Aminophylline vs placebo (grouped by corticosteroid use), Outcome 3 PEF (L/min) or PEF (%) if missing at 60 min.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 3 Aminophylline vs placebo (grouped by corticosteroid use)

Outcome: 3 PEF (L/min) or PEF (%) if missing at 60 min

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at 60 min subgroup with CS							
Coleridge 1993	16	60 (24.8)	15	57 (16.8)		12.4 %	0.14 [-0.57, 0.84]
Evans 1980	8	142 (43)	7	108 (57)		6.1 %	0.64 [-0.41, 1.69]
Murphy 1993	22	226 (63)	22	218 (70)		16.6 %	0.12 [-0.47, 0.71]
Rodrigo 1994	45	238.6 (86.9)	49	278.2 (85.1)		28.1 %	-0.46 [-0.87, -0.05]
Wrenn 1991	38	232.2 (105.8)	46	222.8 (139.8)		26.5 %	0.07 [-0.36, 0.50]
Zainudin 1994	11	119 (62)	14	122 (62)		10.2 %	-0.05 [-0.84, 0.74]
Subtotal (95% CI)	**140**		**153**			**100.0 %**	**-0.04 [-0.31, 0.23]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 6.33, df = 5 (P = 0.28); I^2 =21%							
Test for overall effect: Z = 0.27 (P = 0.78)							
2 at 60 min subgroup without CS							
Appel 1981	13	72 (16)	12	68 (22.5)		30.0 %	0.20 [-0.59, 0.99]
Emerman 1986	20	356.5 (99.8)	20	300 (95.6)		34.1 %	0.57 [-0.07, 1.20]
Josephson 1979	24	56 (4.4)	27	59.2 (5.8)		35.9 %	-0.61 [-1.17, -0.04]
Subtotal (95% CI)	**57**		**59**			**100.0 %**	**0.04 [-0.71, 0.78]**
Heterogeneity: Tau^2 = 0.32; Chi^2 = 7.77, df = 2 (P = 0.02); I^2 =74%							
Test for overall effect: Z = 0.09 (P = 0.93)							
3 at 60 min total pooled result							
Appel 1981	13	72 (16)	12	68 (22.5)		8.3 %	0.20 [-0.59, 0.99]
Coleridge 1993	16	60 (24.8)	15	57 (16.8)		9.6 %	0.14 [-0.57, 0.84]
Emerman 1986	20	356.5 (99.8)	20	300 (95.6)		11.0 %	0.57 [-0.07, 1.20]
Evans 1980	8	142 (43)	7	108 (57)		5.4 %	0.64 [-0.41, 1.69]
Josephson 1979	24	56 (4.4)	27	59.2 (5.8)		12.5 %	-0.61 [-1.17, -0.04]
Murphy 1993	22	226 (63)	22	218 (70)		11.9 %	0.12 [-0.47, 0.71]
Rodrigo 1994	45	238.6 (86.9)	49	278.2 (85.1)		16.8 %	-0.46 [-0.87, -0.05]
Wrenn 1991	38	232.2 (105.8)	46	222.8 (139.8)		16.2 %	0.07 [-0.36, 0.50]
Zainudin 1994	11	119 (62)	14	122 (62)		8.3 %	-0.05 [-0.84, 0.74]

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Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**197**		**212**			**100.0 %**	**0.00 [-0.28, 0.27]**
Heterogeneity: Tau² = 0.07; Chi² = 14.13, df = 8 (P = 0.08); I² =43%							
Test for overall effect: Z = 0.03 (P = 0.98)							

Analysis 3.4. Comparison 3 Aminophylline vs placebo (grouped by corticosteroid use), Outcome 4 PEF (L/min) or PEF (%) if missing at 12 h.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 3 Aminophylline vs placebo (grouped by corticosteroid use)

Outcome: 4 PEF (L/min) or PEF (%) if missing at 12 h

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at 12 h subgroup with CS							
Coleridge 1993	16	84.2 (8.5)	15	99.1 (53.4)		26.7 %	-0.39 [-1.10, 0.33]
Evans 1980	8	175 (53)	7	155 (77)		13.0 %	0.29 [-0.73, 1.31]
Murphy 1993	22	358 (78)	22	355 (59)		38.7 %	0.04 [-0.55, 0.63]
Zainudin 1994	11	194 (65.5)	14	184 (65.5)		21.6 %	0.15 [-0.64, 0.94]
Subtotal (95% CI)	**57**		**58**			**100.0 %**	**-0.02 [-0.38, 0.35]**
Heterogeneity: Tau² = 0.0; Chi² = 1.58, df = 3 (P = 0.66); I² =0.0%							
Test for overall effect: Z = 0.09 (P = 0.93)							
2 at 12 h subgroup without CS							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 at 12 h total pooled result							
Coleridge 1993	16	84.2 (8.5)	15	99.1 (53.4)		26.7 %	-0.39 [-1.10, 0.33]

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Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Evans 1980	8	175 (53)	7	155 (77)		13.0 %	0.29 [-0.73, 1.31]
Murphy 1993	22	358 (78)	22	355 (59)		38.7 %	0.04 [-0.55, 0.63]
Zainudin 1994	11	194 (65.5)	14	184 (65.5)		21.6 %	0.15 [-0.64, 0.94]
Subtotal (95% CI)	**57**		**58**			**100.0 %**	**-0.02 [-0.38, 0.35]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.58$, df = 3 (P = 0.66); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.09 (P = 0.93)							

Analysis 3.5. Comparison 3 Aminophylline vs placebo (grouped by corticosteroid use), Outcome 5 PEF (L/min) or PEF (%) if missing at 24 h.

Review: Addition of intravenous aminophylline to inhaled beta2-agonists in adults with acute asthma

Comparison: 3 Aminophylline vs placebo (grouped by corticosteroid use)

Outcome: 5 PEF (L/min) or PEF (%) if missing at 24 h

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at 24 h subgroup with CS							
Evans 1980	8	240 (121)	7	191 (136)		37.2 %	0.36 [-0.67, 1.39]
Zainudin 1994	11	216 (125)	14	209 (125)		62.8 %	0.05 [-0.74, 0.84]
Subtotal (95% CI)	**19**		**21**			**100.0 %**	**0.17 [-0.46, 0.79]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.21$, df = 1 (P = 0.64); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.53 (P = 0.60)							
2 at 24 h subgroup without CS							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 at 24 h total pooled result							

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Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Evans 1980	8	240 (121)	7	191 (136)		37.2 %	0.36 [-0.67, 1.39]
Zainudin 1994	11	216 (125)	14	209 (125)		62.8 %	0.05 [-0.74, 0.84]
Subtotal (95% CI)	**19**		**21**			**100.0 %**	**0.17 [-0.46, 0.79]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.21$, df = 1 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 0.53 (P = 0.60)

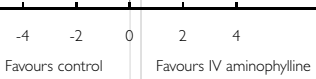
Analysis 3.6. Comparison 3 Aminophylline vs placebo (grouped by corticosteroid use), Outcome 6 FEV_1 (L) or FEV_1 (%) if missing at baseline.

Review: Addition of intravenous aminophylline to inhaled $beta_2$-agonists in adults with acute asthma

Comparison: 3 Aminophylline vs placebo (grouped by corticosteroid use)

Outcome: 6 FEV_1 (L) or FEV_1 (%) if missing at baseline

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at baseline subgroup with CS							
Huang 1993	10	1.49 (0.79)	11	1.35 (0.33)		19.3 %	0.23 [-0.63, 1.09]
Rodrigo 1994	45	1.7 (0.36)	49	1.9 (0.32)		32.3 %	-0.58 [-1.00, -0.17]
Self 1990	11	30.6 (10.4)	7	38.6 (10.7)		16.6 %	-0.72 [-1.71, 0.26]
Wrenn 1991	38	1.4 (0.67)	46	1.24 (0.79)		31.8 %	0.21 [-0.22, 0.65]
Subtotal (95% CI)	**104**		**113**			**100.0 %**	**-0.20 [-0.72, 0.33]**
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 8.90$, df = 3 (P = 0.03); $I^2 = 66\%$							
Test for overall effect: Z = 0.74 (P = 0.46)							
2 at baseline subgroup without CS							
Appel 1981	13	0.71 (0.31)	12	0.74 (0.48)		11.5 %	-0.07 [-0.86, 0.71]
Fanta 1982	31	1.11 (0.61)	35	1.3 (0.71)		30.1 %	-0.28 [-0.77, 0.20]



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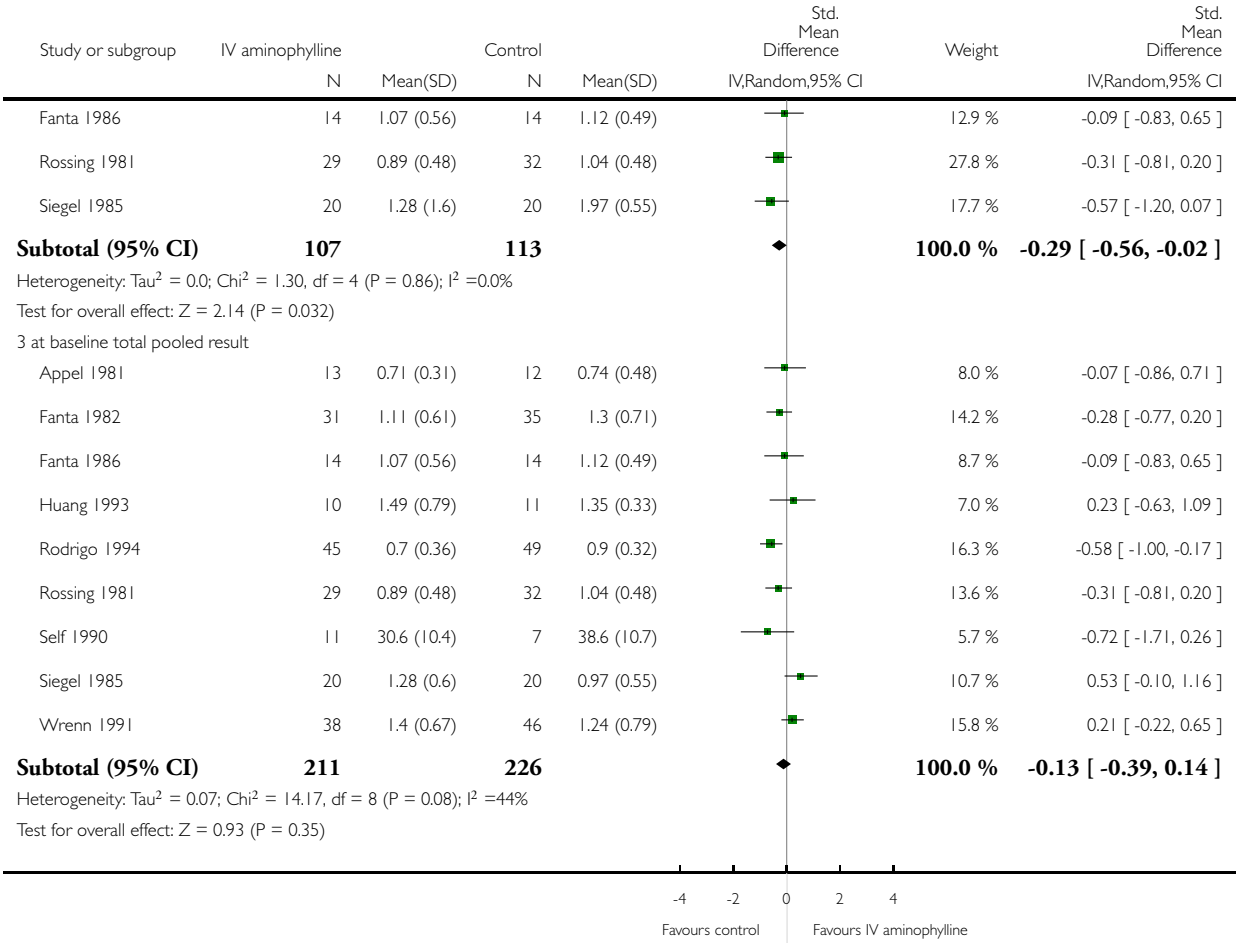


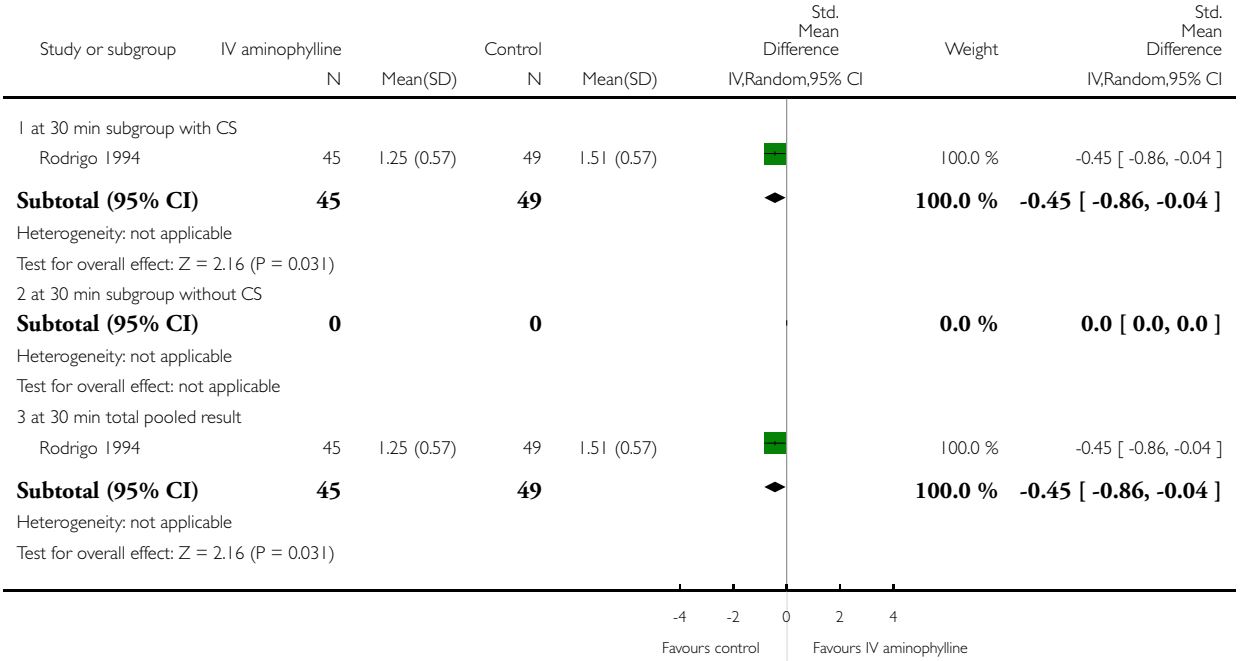
Analysis 3.7. Comparison 3 Aminophylline vs placebo (grouped by corticosteroid use), Outcome 7 FEV_1 (L) or FEV_1 (%) if missing at 30 min.

Review: Addition of intravenous aminophylline to inhaled $beta_2$-agonists in adults with acute asthma

Comparison: 3 Aminophylline vs placebo (grouped by corticosteroid use)

Outcome: 7 FEV_1 (L) or FEV_1 (%) if missing at 30 min

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at 30 min subgroup with CS							
Rodrigo 1994	45	1.25 (0.57)	49	1.51 (0.57)		100.0 %	-0.45 [-0.86, -0.04]
Subtotal (95% CI)	**45**		**49**			**100.0 %**	**-0.45 [-0.86, -0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.16 (P = 0.031)							
2 at 30 min subgroup without CS							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 at 30 min total pooled result							
Rodrigo 1994	45	1.25 (0.57)	49	1.51 (0.57)		100.0 %	-0.45 [-0.86, -0.04]
Subtotal (95% CI)	**45**		**49**			**100.0 %**	**-0.45 [-0.86, -0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.16 (P = 0.031)							

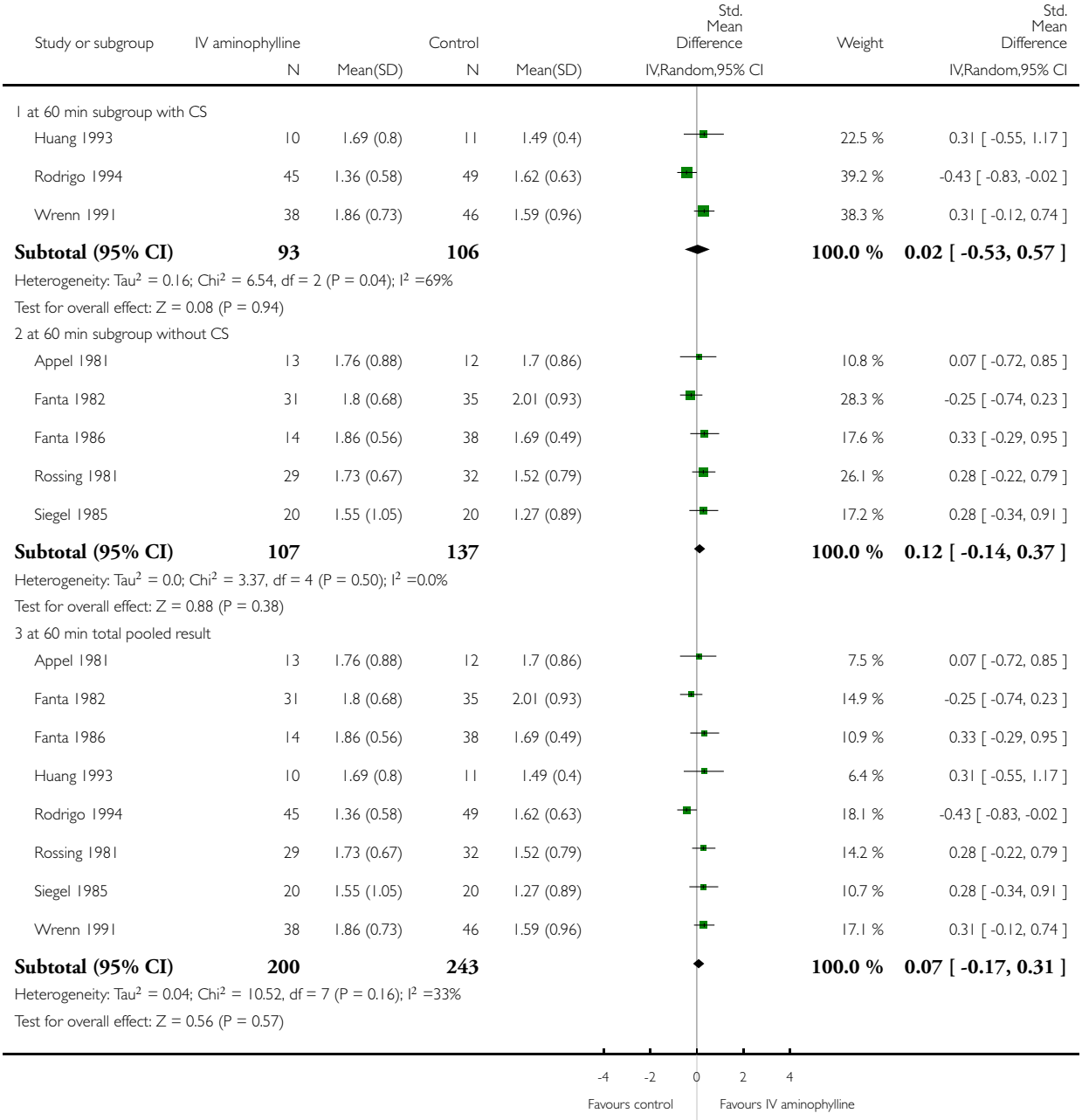


Analysis 3.8. Comparison 3 Aminophylline vs placebo (grouped by corticosteroid use), Outcome 8 FEV_1 (L) or FEV_1 (%) if missing at 60 min.

Review: Addition of intravenous aminophylline to inhaled $beta_2$-agonists in adults with acute asthma

Comparison: 3 Aminophylline vs placebo (grouped by corticosteroid use)

Outcome: 8 FEV_1 (L) or FEV_1 (%) if missing at 60 min

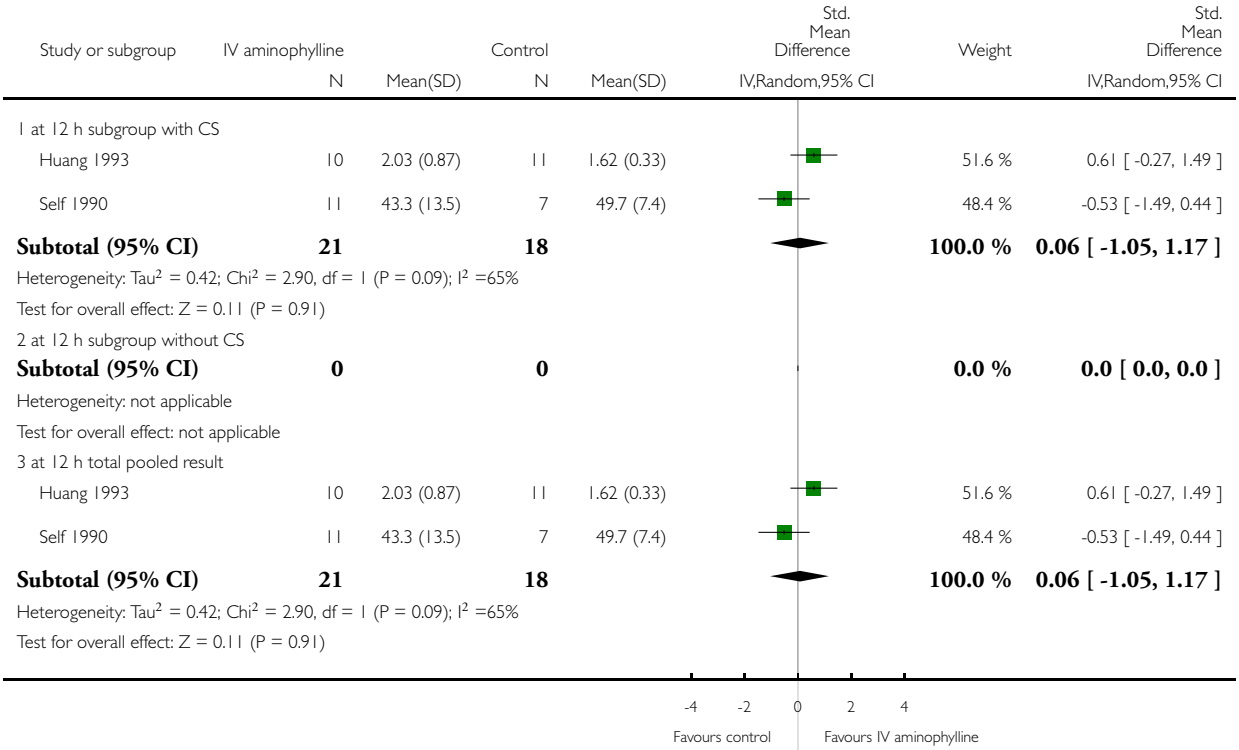


Analysis 3.9. Comparison 3 Aminophylline vs placebo (grouped by corticosteroid use), Outcome 9 FEV_1 (L) or FEV_1 (%) if missing at 12 h.

Review: Addition of intravenous aminophylline to inhaled beta$_2$-agonists in adults with acute asthma

Comparison: 3 Aminophylline vs placebo (grouped by corticosteroid use)

Outcome: 9 FEV_1 (L) or FEV_1 (%) if missing at 12 h



Analysis 3.10. Comparison 3 Aminophylline vs placebo (grouped by corticosteroid use), Outcome 10 FEV_1 (L) or FEV_1 (%) if missing at 24 h.

Review: Addition of intravenous aminophylline to inhaled $beta_2$-agonists in adults with acute asthma

Comparison: 3 Aminophylline vs placebo (grouped by corticosteroid use)

Outcome: 10 FEV_1 (L) or FEV_1 (%) if missing at 24 h

Study or subgroup	IV aminophylline N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 at 24 h subgroup with CS							
Huang 1993	10	2.17 (0.82)	11	1.75 (0.35)		51.5 %	0.65 [-0.23, 1.54]
Self 1990	11	48.3 (13.5)	7	54 (6.6)		48.5 %	-0.48 [-1.44, 0.49]
Subtotal (95% CI)	**21**		**18**			**100.0 %**	**0.10 [-1.00, 1.21]**
Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 2.85$, df = 1 (P = 0.09); $I^2 = 65\%$							
Test for overall effect: Z = 0.19 (P = 0.85)							
2 at 24 h subgroup without CS							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 at 24 h total pooled result							
Huang 1993	10	2.17 (0.82)	11	1.75 (0.35)		51.5 %	0.65 [-0.23, 1.54]
Self 1990	11	48.3 (13.5)	7	54 (6.6)		48.5 %	-0.48 [-1.44, 0.49]
Subtotal (95% CI)	**21**		**18**			**100.0 %**	**0.10 [-1.00, 1.21]**
Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 2.85$, df = 1 (P = 0.09); $I^2 = 65\%$							
Test for overall effect: Z = 0.19 (P = 0.85)							

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (*the Cochrane Library*)	Monthly
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 trials for the CAGR

Asthma 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

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 trials in other electronic databases

Appendix 2. Clinicaltrials.gov search

Search terms: aminophyllline or theophylline
Study type: Interventional Studies
Conditions: asthma

Appendix 3. Search methods for previous version of review (2000)

The Cochrane Airways Review Group Register was searched using the following terms:
[emerg* OR acute OR status OR severe] AND [infusion OR multi-dose OR bolus OR intravenous OR IV OR administration OR dosage AND [[methyl-xanthine* OR theophylline* OR aminophylline*]
The search covered publication years up to 1999.

WHAT'S NEW

Last assessed as up-to-date: 28 September 2012.

Date	Event	Description
28 September 2012	New search has been performed	New literature search run
28 September 2012	New citation required but conclusions have not changed	in this update, the question on aminophylline versus intravenous beta$_2$-agonists was removed and now appears in a new review called "Intravenous beta$_2$-agonists versus intravenous aminophylline for acute asthma" (Travers 2012). We added two new trials to the review, narratively (Pavalakou 2006; Whig 2001). Conclusions of original review were unchallenged by these studies

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 4, 2000

Date	Event	Description
21 May 2008	Amended	Converted to new review format.
19 June 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

In 2000 the contributions of authors were as follows:

Belda J: lead investigator, protocol development, search review, assessment of inclusion criteria, assessment of quality, data extraction/ analysis/interpretation and write-up.

Nair P: involved in protocol development, assessment of inclusion criteria, assessment of quality, data extraction and write-up.

Rowe BH: assigned CAGR Co-editor. Involved in protocol development, search review, adjudication, data analysis, interpretation and write-up.

In the 2012 revision of this review:

Milan SJ, Melissa Bota and Lindsay Lovstrom independently selected trials for inclusion from initial searches.

Nair P and Milan SJ independently selected trials for inclusion from full trial reports.

Milan SJ and Nair P updated the 'Risk of bias' tables for trials already included in the review and similarly for any new trials identified in the update.

Milan SJ, Nair P and Rowe BH updated the text of the review

DECLARATIONS OF INTEREST

The authors who have been involved in this review have done so without any known conflicts of interest. They are not involved with the primary studies. Moreover, none of the authors are considered paid consultants by any pharmaceutical companies that produce aminophylline agents.

SOURCES OF SUPPORT

Internal sources

- National Institute for Health Research, UK.
- Department of Emergency Medicine, University of Alberta (BHR), Canada.

External sources

- Canadian Institutes of Health Research (CIHR); Ottawa, Ontario (BHR), Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2012 update of this review heterogeneity was assessed mainly in relation to I^2. Risk of bias is assessed in accordance with Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [administration & dosage]; Adrenergic beta-Agonists [*administration & dosage]; Aminophylline [*administration & dosage]; Asthma [*drug therapy]; Bronchodilator Agents [*administration & dosage]; Drug Therapy, Combination; Injections, Intravenous; Meta-Analysis as Topic; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans