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Intravenous beta2-agonists for acute asthma in the emergency department (Review)

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TABLE OF CONTENTS

[Intervention Review]

Intravenous beta2-agonists for acute asthma in the emergency department

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ABSTRACT

Background

Inhaled beta-agonist therapy is central to the management of acute asthma. The use of intravenous beta-agonist agents may also be beneficial in this setting.

Objectives

To determine the benefit of intravenous (IV) beta2-agonists for severe acute asthma treated in the emergency department.

Search methods

Randomised controlled trials (RCT) were identified using the Cochrane Airways Group Register which is a compilation of systematic searches of MEDLINE, EMBASE, CINAHL, and CENTRAL as well as hand searching of 20 respiratory journals. Bibliographies from included studies and known reviews were also searched. Primary authors and content experts were contacted to identify eligible studies.

Selection criteria

Only RCTs were considered for inclusion. Studies were included if patients presented to the emergency department with acute asthma and were treated with IV selective or nonselective beta2-agonists versus placebo, inhaled beta2-agonists, or other standard of care. Pulmonary function, vital signs, arterial gasses, adverse effects, and/or clinical success could be reported as outcome measures. Two reviewers independently selected potentially relevant articles and selected articles for inclusion. Methodological quality was independently assessed using two scoring systems and two reviewers.

Data collection and analysis

Data were extracted independently by two reviewers, and confirmed with corresponding authors. Missing data were obtained from authors or calculated from data present in the papers. Trials were combined using a random effects model for odds ratios (OR) or weighted mean differences (WMD) and reported with 95% confidence intervals (95% CI).

Main results

From 746 identified references, 55 potentially relevant articles were identified and 15 were included. The trials included 584 patients. Overall, selective IV beta2-agonist use conferred no advantage over the comparator regimes. For example, it was associated with a lower PEFR after 60 minutes compared to inhaled beta2-agonist, although the difference was not statistically significant (-24.7 l/min; 95%CI 2.9,

-52.3). There was no difference in heart rate (4.5 bpm; 95% CI -4.9, 14.0). In the well performed blinded studies there was no difference in autonomic side effects between treatments (Odds Ratio 2.2 (95%CI 0.9, 5.7).

Authors' conclusions

There is no evidence to support the use of IV beta2-agonists in patients with severe acute asthma. These drugs should be given by inhalation. No subgroups were identified in which the IV route should be considered.

PLAIN LANGUAGE SUMMARY

Intravenous beta2-agonists for acute asthma in the emergency department

Beta2-agonist drugs form one of the mainstays of the treatment of acute severe asthma. They may be given by the inhaled or intravenous route. This review examined all the randomised controlled trials of the use of intravenous beta2-agonists in acute asthma and found no evidence to support its use.

BACKGROUND

The general approach to treating patients with severe acute asthma is to use beta2-agonist bronchodilators and corticosteroids. For rapid bronchodilatation, penetration of inhaled drug to the affected small conducting airways may be impeded, and consequently responses may be a result of drug reaching the receptors via the systemic circulation. In these circumstances, if bronchodilatation occurs predominantly in response to the systemic distribution of the drug, intravenous (IV) rather than inhaled administration of bronchodilators may provide an earlier clinical response (Browne 1997). The research investigating the role of IV beta2-agonists in the emergent treatment of asthma has spanned more than 25 years. At present, each of the guidelines in North America and Europe recommend inhaled beta2-agonist therapy for all cases of asthma that present to the emergency department (Lipworth 1997; Beveridge 1996; Ernst 1996; NAEPP 1997). IV and subcutaneous (SC) beta2-agonists are described as second line therapy for use in patients unresponsive to inhaled bronchodilator and systemic corticosteroid therapy, or if the inhaled route is not practical for the patient (Lipworth 1997; Beveridge 1996; Ernst 1996; NAEPP 1997). However, debate regarding the benefit of this route of delivery remains. No systematic review of the IV beta2-agonist literature for the treatment of asthmatic exacerbations has been published to date.

OBJECTIVES

The objective of this review was to determine if the evidence from randomised trials supports the use of IV beta2-agonists in the treatment of patients with severe acute asthma who present to the emergency department (ED). The questions specifically addressed are:
1. What is the clinical effect of administration of IV beta2-agonists on pulmonary function tests, laboratory parameters, vital signs, adverse effects, and clinical improvement/failure?
2. Does the age of the patient, beta2-agonist type (selective, nonselective), treatment strategy (Strategy I: IV vs. inhaled beta2-agonist; Strategy II: IV with inhaled vs. inhaled beta2-agonist, Strategy III: IV beta2-agonist vs. IV methylxanthine) or rate of administration influence the magnitude of effect?
3. Is the magnitude of effect influenced by the methodological quality of the included studies or the statistical model used for analysis?

METHODS

Criteria for considering studies for this review

Types of studies

To be considered for review, studies had to be randomised controlled trials (RCTs) or quasi RCTs (allocation on days of the week, or some other method).

Types of participants

Studies of adult or pediatric patients with severe acute asthma presenting to an emergency room (or its equivalent) were considered.

Types of interventions

The target intervention was the administration of IV selective or non-selective beta2-agonists. The control intervention was the administration of placebo, other intravenous bronchodilators (i.e. methylxanthines), or other inhaled selective or nonselective beta2-agonists. Included studies could also use other recognised standards of care (i.e. corticosteroids).

Types of outcome measures

Pulmonary functions, vital signs, adverse effects and clinical scores.

Search methods for identification of studies

Electronic searches

Randomised controlled trials were identified in the both the Cochrane Airways Review Group database and Cochrane Controlled Trials Register (CCTR) using the following search strategy: (placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study). An advanced search of this database, and the Cochrane Controlled Trials Register, was completed using the following terms:

(1) Asthma OR Wheez* AND
(2) Emerg* OR acute* OR status* AND
(3) Discharge* OR admi* OR hospit* AND
(4) beta-agonist OR betaagonist OR beta agonist OR bronchodilat* OR adrenaline OR albuterol OR bricanyl OR epinephrine OR isoprenaline OR isoproterenol OR hexoprenaline OR reproterol OR salbutamol OR terbutaline OR ventolin OR *erol. Several other databases were also searched separately using the same search terms, including: MEDLINE, EMBASE, CINAHL, and Current Contents. Reference lists of all available primary studies and review articles were reviewed to identify potential relevant citations. Trials were not excluded on the basis of language.

Searching other resources

Inquiries regarding other published or unpublished studies known and/or supported by the authors of the primary studies were made so that these results could be included in this review. Several pathways were used to locate authors including letters to an address presented in the article, Internet 'People and Hospital Searches', electronic author searches in library databases for the address on the most recent article published by the author, and contact with other reviewers on the ARG. Scientific advisors of the various pharmaceutical companies (Glaxo) that manufacture beta2-agonists were contacted for any unpublished, published, or interim results on beta2-agonist research. Personal contact with colleagues, collaborators and other trialists working in the field of asthma was made to identify potentially relevant studies.

Data collection and analysis

Selection of studies

The reference lists from the search strategy was independently reviewed by two researchers (AHT, BHR), and clearly irrelevant articles were discarded. If the title, abstract, or descriptors suggested any potential relevance, the full text article was retrieved. Agreement for relevance was measured using kappa statistics. Each relevant paper was then assessed by two independent reviewers (BHR, AJ) for inclusion in this review. The reviewers were not blinded to the authors, journal of publication, or results of the studies as investigator bias was deemed unlikely. Agreement for final inclusion was measured using

kappa statistics. Disagreement was resolved by consensus or third party adjudication (AHT).

Data extraction and management

Data for the trials were independently extracted by two reviewers (AHT, CS) and entered (SJB) into the Cochrane Collaboration software program (Review Manager Version 4.0.4). Primary study authors were requested to confirm data extraction and provide additional clarification or information for the review. In cases where tables were unavailable, graphs were enlarged and values were approximated. This technique was required for seven studies (Hambleton 1979; Hussein 1986; Johnson 1978; Swedish Society 1990; Tribe 1976; Van Renterghem 1987; Williams 1981).

Assessment of risk of bias in included studies

Assessment of Methodological Quality: The methodological quality of each included paper was assessed independently by two reviewers, using two methods of quality assessment. In the first method, two reviewers (CC and AJ) used the Cochrane approach to assessment of allocation concealment:

- Grade A: Adequate concealment
- Grade B: Uncertain
- Grade C: Clearly inadequate concealment

In the second method, two reviewers (AHT, CS) used the Jadad Criteria for methodological quality (Jadad 1996). Using this tool, one point is allocated each for randomisation, blinding, and description of withdrawals and dropouts. An extra point is added for both methods of randomisation and blinding that are well described and adequate, whereas a point is deducted if the methods are considered inadequate. The maximum score is five points and studies scoring 3 or more are regarded as being of high methodological quality. Using either method, inter-rater reliability was measured by using simple agreement, kappa, and weighted kappa statistics, and disagreement was resolved by third party adjudication (BHR).

Data synthesis

All trials were combined using the Review Manager 4.0.4. For continuous variables, a random effects weighted mean difference (WMD) and 95% confidence interval (CI) were calculated for each study. For dichotomous variables, a random effects odds ratio (OR, 95% CI) was calculated for individual studies. All similar studies were pooled using random effects OR or WMD and 95% CIs.

Subgroup analysis and investigation of heterogeneity

For pooled effects, heterogeneity was tested using the Breslow-Day test; $p < 0.05$ was considered statistically significant. For those main outcome measures with statistical heterogeneity, a priori subgroup analyses were divided on the following basis:

(a) Population: adult vs. pediatric
(b) Population: severity of illness based on PFTs
(c) Intervention: selective vs. nonselective beta2-agonists
(d) Intervention: IV vs. inhaled beta2-agonists
(e) Intervention: IV with inhaled vs. inhaled beta2-agonists
(f) Intervention: IV beta2-agonists vs. IV methylxanthines
(g) Intervention: infusion vs. bolus beta2-agonists

Sensitivity analysis

Sensitivity analyses were completed on the strength of methodological quality (high vs. low) and statistical method of analysis (random versus fixed effects).

RESULTS

Description of studies

Results of the search

The ARG database search revealed 976 references which represented 740 (76%) original publications: 258 (35%) in EMBASE; 250 (34%) in MEDLINE; 2 (0.3%) from CINAHL; 224 (30%) from both MEDLINE and EMBASE; and 6 references (0.7%) were cited in all three. Independent review of the abstracts and titles of these publications identified 31 potentially relevant studies. The agreement for relevance was high (kappa: 0.83). Twenty-four additional references were added from bibliographic searching of relevant articles and overviews; a total of 55 papers were reviewed for inclusion. Unpublished literature was requested from pharmaceutical companies and the authors of all included studies, but none were identified. Of these 55 articles, a total of fifteen studies (27%) were included in the overview (k = 0.87).

Included studies

The evidence for intervention with IV beta2-agonists spans a period of twenty-five years: 7 (47%) articles published in the 1970s, 5 (33%) papers in the 1980s, and 3 (20%) trials in the 1990s. Twelve (80%) of the studies were conducted in Europe, 1 (7%) in Asia, and 2 (13%) in Australia. No trials meeting our inclusion criteria were conducted in North America.

Study Design

Thirteen (87%) of the studies followed a parallel protocol, whereas 2 (13%) of the studies followed a crossover model (Bloomfield 1979; Tribe 1976). Eleven (73%) studies introduced IV beta2-agonists immediately upon entry into the study. The remaining 4 papers introduced IV beta2-agonists 30 to 75 minutes after entry into the study, during which time the patients received either inhaled beta2-agonists (Browne 1997; Cheong 1988; Van Renterghem 1987) or IV aminophylline (Johnson 1978).

There were three main treatment strategies utilized in the studies under review. Three papers utilized Strategy I in which IV beta2-agonists were compared to inhaled beta2-agonist, where both groups of patients received a run in of inhaled beta2-agonist therapy (Browne 1997; Cheong 1988; Van Renterghem 1987). Essentially, this was equivalent to comparing IV beta2-agonists and standard of care with standard of care alone. Six papers utilised Strategy II, where IV beta2-agonists were compared with inhaled agents, with no inhalational therapy in the IV beta2-agonist arm (Bloomfield 1979; Hussein 1986; Lawford 1978; Salmeron 1994; Swedish Society 1990; Williams 1981) . Essentially this approach compared IV to inhaled beta2-agonist delivery. The remaining six papers utilised Strategy III, where IV beta2-agonists were compared with IV methylxanthines, where neither group received inhaled beta2-agonist therapy (Femi-Pearse 1 1977; Hambleton 1979; Johnson 1978; Sharma 1 1984; Tribe 1976; Williams 1975).

Populations

Participants were selected from a sample of patients who presented to the emergency department or its equivalent with severe acute asthma; all patients were admitted to hospital. The majority of studies focused on adult patients only (age range: 15 to 65 years), with only three papers enrolling children (age range: 0.8 to 14.7 years; Browne 1997; Hambleton 1979; Hussein 1986). The pre-hospital asthma medication profile, and asthma history of the patients could not be easily determined from these studies. The median sample size across the studies was 23 with a range of 13 to 176 patients. All papers enrolled 'severe asthmatics'; however, there was variety in the parameters and definitions used for inclusion criteria. Nine papers used vital signs (heart rate greater than 100) and pulmonary function tests (PFT less than 20% expected) as primary inclusion criteria (Bloomfield 1979; Cheong 1988; Femi-Pearse 1 1977; Lawford 1978; Salmeron 1994; Swedish Society 1990; Van Renterghem 1987; Williams 1975; Williams 1981). Five papers required abnormalities in arterial blood gas (ABG) measurements (Hambleton 1979; Salmeron 1994; Van Renterghem 1987; Williams 1975; Williams 1981). Four papers listed simple clinical symptoms and signs of "severe shortness of breath or wheezing" as inclusion criteria (Johnson 1978; Hambleton 1979; Sharma 1 1984; Tribe 1976). Two papers described standardized clinical assessment scales or definitions for severe asthma as inclusion criteria. One author utilized national guidelines (National Asthma Campaign, 1993) of any 4 features of respiratory distress (wheeze, sternal retraction, accessory muscle use, dyspnea) or any absolute criteria (cyanosis, pulsus paradox, altered level of consciousness, silent chest) (Browne 1997). Another author (Salmeron 1994), enrolled only those patients who met the definition for severe asthma as defined by the American Thoracic Society (ATS 1962).

In summary, despite the variability of definitions, based on review, all patients entered into these studies could be considered to be suffering "severe acute asthma" requiring admission to hospital as defined by the organizations involved in asthma care (Beveridge 1996; Ernst 1996; Lipworth 1997; NAEPP 1997).

Interventions

A variety of co-interventions were administered across studies; however, all patients received supplemental oxygen by face mask and systemic corticosteroids. Most of the trials introduced the corticosteroids to all patients on entry into the study, however in one study an unspecified dose of steroids was withheld until two hours into the study in only a selected subgroups of patients (Swedish Society 1990). No patients received inhaled steroids, or inhaled anticholinergic agents in any of the studies. All studies used selective beta2-agonists. Nine papers (Bloomfield 1979; Browne 1997; Femi-Pearse 1 1977; Hambleton 1979; Sharma 1 1984; Swedish Society 1990; Tribe 1976; Van Renterghem 1987; Williams 1981) gave IV beta2-agonists as a bolus (range 100 - 500 ug, or 4 - 15 ug/kg) , whereas 6 studies (Cheong 1988; Johnson 1978; Hambleton 1979; Lawford 1978; Salmeron 1994) administered the IV beta2-agonist as an infusion (range: 8.3 - 20 ug/min to total doses of 500 ug - 3000 ug). Most studies (73%) used salbutamol as the beta-agonist, except for 3 studies in which terbutaline was evaluated (Sharma 1 1984; Van Renterghem 1987; Williams 1975), and 1 study where reproterol was used (Hussein 1986). One study ran a triple parallel protocol comparing IV salbutamol versus IV terbutaline versus IV aminophylline (Sharma 1 1984). For this review, only the comparison of IV salbutamol versus aminophylline was included.

Outcomes

Each paper evaluated their primary outcomes within a two hour period. However, six papers extended the observation interval longer: 3 hours (Sharma 1 1984), 5 hours (Cheong 1988), 6 hours (Salmeron 1994), 24 hours (Browne 1997; Hambleton 1979), and 36 hours (Hussein 1986; Johnson 1978). Multiple statistical tests were performed in each study, with a mean of 24 (varying from 0 to 80). No mention of adjustments for multiple testing were identified in these papers, and 11 (73%) made no mention of possible type I errors.

Over 240 individual outcome measurements were abstracted from the studies. Scores from a variety of symptom scales were occasionally used to describe outcomes; however, due to the different scores used, no pooled analyses were conducted. In addition, a number of PFT results were employed (including PEFR, FEV1, FVC, % predicted PEFR, % predicted FEV1), however variability in the type of PFT employed limited comparisons between studies. There were no descriptions of any patients who were intubated or died during any of the study observation periods. Five trials used improvements in PFTs (namely PEFR) as the primary outcome (Bloomfield 1979; Cheong 1988; Johnson 1978; Williams 1975; Williams 1981). Five papers described a primary outcome variable of "Clinical Improvement"; however, the definition varied widely between papers. Three of these relied on the 'impression by the patient or physician of improvement in symptoms' (Lawford 1978; Swedish Society 1990; Tribe 1976). The remaining two papers used predefined clinical determinants of success (Browne 1997; Salmeron 1994). The first defined three unique primary clinical measures of success: earlier ED discharge time (defined as the start of hourly inhaled salbutamol therapy), faster recovery time (to cessation of nebulised beta2-agonists every thirty minutes, and sixty minutes), and less oxygen dependence (defined at the two hour window as the requirement for medical oxygen to maintain oxygen saturations above 93%) (Browne 1997). The second paper defined 'Clinical Success' as the presence of at least two of the following points at 60 minutes: (1) a decrease in a "clinical index rating" of at least three points; (2) a decrease in PaCO2 of at least three mm Hg; (3) an increase in PEFR of at least 50 L/min (Salmeron 1994).

Consequent to the variety of outcomes, only seven domains were analysed where data were sufficiently available and similarly derived:
(a) serial PEFR
(b) serial % predicted PEFR
(c) serial FEV1
(d) serial HR
(e) autonomic side effects
(f) Clinical Success
(g) arterial gas values

Excluded studies

Of the 40 studies which were excluded, 30 (55%) were non-randomised, 7 (13%) included treatment of non-acute asthmatics or non-asthmatics, 3 (5%) examined non-IV routes of administration. The ARG database identified 12 (80%) of the included articles: six were from MEDLINE (Bloomfield 1979; Johnson 1978; Tribe 1976; Williams 1975; Williams 1981; Sharma

1 1984), two from EMBASE (Van Renterghem 1987; Hussein 1986), and four from both (Browne 1997; Cheong 1988; Salmeron 1994; Swedish Society 1990). The remaining three papers were found from separate MEDLINE searches (Lawford 1978; Femi-Pearse 1 1977; Hambleton 1979).

Risk of bias in included studies

Many of the included papers were double-blind, placebo controlled trials, however the methodological quality varied across studies. Using the Jadad method, 7 studies were rated as "strong" (47%) and 8 (53%) were rated as "weak" (Jadad 1996). Agreement between the two independent assessments of study quality was high (kappa ranged from 0.59 to 1.0 for each domain). There was no significant correlation between quality scores and the year of publication of the trial (Pearson r = 0.38, p=0.17). Using the Cochrane methodology, 5 papers (33%) were rated as having clearly blinded allocation and 10 (67%) were rated as having unclear allocation blinding (kappa = 1.0). There was no statistically significant association between those papers that were rated as strong methodologically and those that had blinded allocation (Chi square 2.04; df=1; p>0.05).

Effects of interventions

NOTE: data are entered into the graphs as negative values, to allow the graphs to conform to the 'Cochrane convention' that beneficial changes associated with the treatment under review go to the left of the no difference line.

OBJECTIVE ONE: COMBINED RESULTS FOR ALL TREATMENT OPTIONS

Pulmonary Function

Across the six hours observation in the seven papers reporting PEFR, no statistical differences in PEFR were identified between those patients who received IV beta2-agonists versus inhaled beta2-agonists or IV methylxanthines. Moreover, differences between the summary outcome measures in each time point were also of questionable clinical significance with pooled estimates of treatment effect ranging from -0.42 L/min to 19.42 L/min. The heterogeneity present in the 60 and 120 minute time points is addressed in the sensitivity analysis later in this section. It should be noted that in the comparisons with inhaled therapy, this treatment produced a significantly greater increase in PEFR at 60 minutes compared to the IV route, when a random effects model was used, although there was heterogeneity in size of effect between trials.

Three papers reported serial changes in percent predicted peak expiratory flow rates. Although there was no statistically significant difference between treatments over six hours, the results demonstrated an increasing treatment effect over a six hour period favouring IV beta2-agonists (compare -1.42% at one hour versus -8.75% at six hours). However, such marginal differences in percent predicted PEFR are of questionable clinical importance. There was no visual or statistical heterogeneity across the time points in this analysis. Two papers reported serial changes in forced expiratory volume in one second. Over six hours there were no statistically or clinically significant differences with respect to FEV1.

Serial Heart Rates

Nine papers described heart rate results over a six hour period. Over this time there were lower heart rates in those patients who received the comparison treatment (range 3.95 to 12.26 beats per minute). These differences were statistically significant in the 15 and 45 minute period, and the 2-6 hour time points, each of which were homogeneous pooled estimates. However, the differences in heart rates are of questionable clinical significance.

Arterial Blood Gas Measurements

Six papers described arterial blood gas measurements for oxygen tensions, and five papers described carbon dioxide tensions all within a two hour period. There was no statistical difference in either the arterial oxygen tension, or carbon dioxide tension between IV beta2-agonists and comparison treatments. Furthermore, there was no heterogeneity across any time point.

Autonomic Side Effects

Despite concern regarding the potential side effects of IV beta2-agonists, only 10 (67%) studies reported this information. Autonomic effects included: cardiovascular (palpitations, tachycardia, hypertension), neurological (tremor, headache), and/or gastrointestinal (nausea, vomiting). The pooled OR suggests that the proportion of patients who experienced adverse effects from IV treatment were approximately twice as frequent as those who received the comparison treatment. However, this result was not statistically significant and significant heterogeneity was present in the pooled estimate (Chi square 36.8; df=8; $p < 0.05$).

Clinical Failure

Five papers reported a primary outcome variable of "Clinical Improvement", however there was variability in the subjective and objective measures used. The pooled OR suggests that the proportion of patients who failed to improve with IV therapy was the same as the proportion who received the comparison treatment. However, significant heterogeneity was present in the pooled estimate (Chi square 24.48; df=4; $p < 0.05$).

OBJECTIVE TWO: SUBGROUP & SENSITIVITY ANALYSES

SUBGROUP ANALYSIS

Population

An insufficient number of pediatric papers with similar outcome measures were identified and this precluded any subgroup comparison on the basis of age. Only three of the fifteen included papers (20%) evaluated the pediatric population (Browne 1997; Hussein 1986; Hambleton 1979).

Intervention

Three types of beta2-agonists were evaluated - the majority examined salbutamol; however, terbutaline was reviewed in three papers (Sharma 1 1984; Van Renterghem 1987; Williams 1981), and reproterol in one paper (Hussein 1986). An insufficient number of similar outcomes prevented any formal comparison of results based on drug type. There was no statistical difference in any of the outcome domains when comparing beta2-agonists administered as an IV bolus versus infusion. Three of the 15 papers evaluated the question of whether IV beta2-agonists improve the initial bronchodilator response when given in addition to nebulised beta2-agonist therapy (Strategy I). Amongst these studies, the only

domain where sufficient similar outcomes were reported, were in two papers in the time point of %predicted PEFR (Cheong 1988; Van Renterghem 1987). In this time point there was no significant improvement at each point in time, and the changes that were identified would be clinically insignificant. In the remaining paper utilizing treatment Strategy I, there were no reports of pulmonary function data thereby limiting comparisons with the other two papers (Browne 1997). There was no change in the trends of the summary statistics for any of the outcome domains when Strategy II was compared to Strategy III. Too few studies with sufficient similar outcomes limited any meaningful comparison of Strategy I versus Strategy III.

SENSITIVITY ANALYSIS

Methodological Quality

Using Jadad's methods a strong methodological paper was defined as having a Jadad score of 3 to 5, and a weak paper as having a Jadad score of 0 to 2. This sensitivity analysis helps to explain much of the heterogeneity observed above. It is evident that the methodologically stronger papers fail to demonstrate a clinical or statistical difference between IV agents or the comparison treatment arm in terms of PEFR and clinical success. Moreover, although not statistically significant, IV beta2-agonists appear to have an increased risk of adverse effects and increased heart rate compared to the control treatment in this analysis. By comparing the two groups it is clear that the weak methodological papers had larger effects, favouring the comparison treatment. Sensitivity analysis by fixed effects modelling demonstrated no differences in results except for more time points with statistically significant lower serial heart rates for the non-IV groups (range: 0.1 to 14.1 beats/min).

DISCUSSION

The literature is conflicting regarding the use of IV agents, and this systematic overview is the first to examine evidence of the effect of treating asthmatics with IV beta2-agonists following diagnosis in the ED. The review included fifteen randomised parallel and crossover trials over twenty-five years that included 584 adults and children across nine countries. Several important points arise. First, there was no statistically significant difference in effect between IV beta2-agonists and all other treatments combined (inhaled beta2-agonists, or IV methylxanthines). Second, intravenous beta2-agonists administered either by bolus or infusion did not lead to significant improvements in any of the outcome measures of clinical success. Third, the use of IV beta2-agonists was associated with an non-significant increase in risk of autonomic side effects (2-12 times), and higher heart rates (4-10 beats per minute). Finally, there were no sub-groups in which this agent was shown to be effective.

It should be noted that when using a fixed effects model, inhaled beta2-agonist produced a significantly greater mean improvement at 60 mins than the IV route, but there was significant heterogeneity between studies, and the trials of poorer quality had a larger effect of inhaled therapy than IV therapy.

When examining the quality of papers involving IV agents in acute asthmatic presentations, it is obvious that greater care must be incorporated into further work if clarity is to emerge. There were broad discrepancies among outcomes from studies where methodological quality was scored using two accepted methods (Jadad 1996; Mulrow 1999). Moreover, statistical planning and sample size calculations were not carefully considered in most studies. No papers were large enough to protect against type II error, and sample size calculations were rarely reported. Furthermore, multiple statistical testing was performed in many studies, increasing the risk of type I error. Factors confounding the relationship of IV beta2-agonists use and outcome measures are the weak methodologies of the studies included in the summary measures. When analysed by methodological quality, the treatment effects were less pronounced in the methodologically stronger studies.

Trials involving IV beta2-agonists could be grouped into three categories. Historically, the first studies compared IV beta2-agonists with IV aminophylline (40% of the included papers in this review). However, as practice has changed, the routine use of aminophylline has diminished, and inhaled IV beta2-agonists have been increasingly used. Consequently, a shift in focus to compare IV versus nebulised beta2-agonists (40% of the included papers) occurred. However, the question whether IV beta2-agonists improve bronchodilator response when given in addition to nebulised bronchodilators was only addressed in 20% (3/15) of the studies under review. These trials evaluated differing age groups (two adult and one pediatric population) using different primary outcomes. This limited the conclusions that could be drawn from pooling of results. Consequently, although the evidence suggests that IV beta2-agonists alone are no better than the inhaled route of delivery, the role of IV beta2-agonists in addition to inhaled beta2-agonists remains unclear.

Methodological limitations

One potential concern in this systematic review is the pooling of results. The review identified 15 RCTs dealing with the use of IV beta2-agonists in severe acute asthma. The review authors evaluated the studies and concluded it would be sensible and efficient to combine these studies, since the sample sizes of the individual studies were insufficient to reach a firm conclusion on their own. In addition, the decision to combine results was based on demonstration of similarities in populations, interventions, and outcome measurements between studies. By dividing the papers into their respective categories, the issue of similarity was addressed. As a result of these steps, we feel the pooling of data was reasonable. Despite these features, statistically significant heterogeneity was still found in some of the analyses.

Due to the small number of trials included in this meta-analysis, and the overall small number of patients upon which the results are based, no firm conclusions regarding subgroups by treatment (i.e. IV with nebuliser versus IV without nebuliser) or age could be made. Also, this review analysed only the IV route of administration, and did not evaluate trials of subcutaneous routes of administration. While there was significant heterogeneity in pooled estimates for many of the outcome time points, upon further sensitivity analysis it appeared that papers of low methodological quality accounted for most of this heterogeneity. In particular, one paper (Swedish Society 1990) was responsible for the majority of the heterogeneity based on the following points: (1) Differential Methodological Quality: The Swedish Society paper was rated as the weakest paper amongst those in the review (Jadad score = 1); (2) Different Populations: All papers studied extremely severe asthmatic patients, however the majority of papers enrolled patients with mean PEFRs in the range of 50 to 100 L/min, whereas

the Swedish study evaluated patients with mean PEFRs in the 160 to 170 l/min range (still defined as "severe < 200 L/min" by international guidelines). (3) Different co-interventions: The Swedish study did not administer any steroid therapy until two hours into the study protocol, whereas all other papers introduced steroid therapy at time of enrolment into the study. The effects of each of these factors on the homogeneity of the outcome domains were confounding in isolation and in whole by the very large sample size of the Swedish study (n=176) in relation to the relatively smaller studies (range n=14 to 71).

Despite the intensive search strategy employed, there still exists a possibility of study selection bias or publication bias in this meta-analysis. For example, through missing unpublished negative or positive trials we may be erroneously estimating the non-significant effects of IV beta2-agonists. However, a comprehensive search of the published English and non-English literature for potentially relevant studies was conducted, using a systematic search strategy to avoid bias. In addition, attempts were made to contact first and corresponding authors. Despite these endeavours, no unpublished or non-English papers were uncovered; however, we recognize that they may exist.

Finally, the outcome measure for "success" in treating acute asthma was measured variably between studies, and perhaps also within studies (particularly in those studies relying on the subjective impression of improvement by the patient or physician). Better standardization of this outcome would improve study comparability. Most studies included PFT outcome measures, namely: absolute PEFR, percent change in predicted PEFR, FEV1, or percent change in predicted FEV1. Here again standardisation of reporting would allow better comparisons between trials. Evaluation of adverse side effects was complicated by a lack of standardized reporting.

AUTHORS' CONCLUSIONS

Implications for practice

[1] Intravenous beta2-agonist used either as an adjunct to, or replacement of, inhaled bronchodilator therapy appears to offer no clinical benefit in acute asthma.
[2] The benefit of IV therapy in ventilated patients has not been examined.
[3] Efficacy in the pediatric population remains unclear since too few pediatric clinical trials were identified.
[4] The only recommendations for IV beta2-agonists use should be for those patients in whom inhaled therapy cannot be used, however there have been no tests of its efficacy in such situations.

Implications for research

Population

[1] The effectiveness of IV beta2-agonists in pediatric patients with severe acute asthma exacerbation's that present to the ED remains to be determined.

Interventions

1. Future methodologically sound clinical trials could be justifiable to clarify whether IV beta2-agonists improve the initial bronchodilator response when given in addition to nebulised bronchodilator (beta2-agonists and anticholinergics) and corticosteroid therapy (intravenous, oral, or inhaled).
2. The evidence for subcutaneous routes of beta2-agonists (both selective and non-selective) must be formally evaluated via a systematic review.

Outcomes

Future research on acute asthma must concentrate on well defined outcomes which may lead to more informative overviews in the future. More specifically the following areas must be refined:

1. Statistical planning and sample size calculations must be more carefully considered. Trials should be large enough to protect against type II error, and when multiple statistical tests are performed the increased risk of type I error should be addressed.
2. Complete reporting of PFT data in a systematic and standardised fashion would assist in further work (i.e. reporting of % predicted PEFR and changes in %PEFR).
3. The inherent variability of these PFTs, particularly in acute asthma, emphasizes the need for further research into alternative measures, particularly assessment of factors that are important to the patient.
4. Standardization and complete reporting of symptom data and universal descriptions of what defines a "clinical success".
5. Standardization and complete reporting of adverse reactions and side effects.

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CHARACTERISTICS OF STUDIES

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

Bloomfield 1979

Methods	Randomisation: yes (of order of treatment) Blinding: double-blind Number excluded: no details Withdrawals: 2 due to worsening clinical condition Baseline characteristics: PEFR 103 (< 20% predicted); HR 138; RR 27.5; PaO2 87 (38, 124); pulsus paradoxus 33.8 Jadad score: "strong", score >/= 3
Participants	Location: Edinburgh, Scotland

Bloomfield 1979 *(Continued)*

	Participants: initially 19 (2 had contaminated neb Rx and were excluded), 20 eligible (of the 17 pts, 1 presented twice, and 1 thrice), 17-54 yrs (mean 27.35) Asthma definition and severity: all patients with severe acute asthma with HR > 120 beats/min and PEFR < 20% of predicted Exclusion criteria: none stated Inhaled corticosteroid use: 12 patients
Interventions	Crossover design one hour apart Standard care: O2 NPV 35 %, hydrocortisone 500 mg iv Treatment group: salbutamol 5mg IPPB at 0 min or at 60 min vs. salbutamol 500 ug iv over 3 minutes at 0 min or at 60 min Placebo: saline neb or injection
Outcomes	PFTs: PEFR iv pos 34, pos 25, pos 21, pos 24, pos 54; neb pos 20, pos 29, pos 26, pos 22, pos 74; summary PEFR pos 74.1 at 120 min (iv then neb) Timing: 15, 30, 45, 60, 120 min Admissions: Side effects 4 tremor, 2 palp Complications:
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Browne 1997

Methods	Randomization: yes (table of random numbers) Blinding: double-blind Number excluded: 13 Withdrawals: none Baseline characteristics: HR 127.8 (15.4) iv, 146.2 (13.6) neb; RR 38.9 (11.9) iv, 45.8 (9.9) neb; glucose 7.5 (2.7) iv, 8.5 (3.1) neb; potassium 3.9 (0.5) iv, 4.2 (0.6) neb; pulm index 12 iv, 15 neb; acc muscle use 12 iv, 15 neb; SOB 12 iv, 13 neb; wheeze 13 iv, 14 neb; fatigue 7 iv, 9 neb Jadad score: "strong", score > 3
Participants	Location: Westmead, Australia Participants: initially 50, 37 eligible, 29 final (8 gave no consent), 1-12 yrs (mean 8.4 iv, 6.3 neb); males 7 iv, 12 neb; females 7 iv, 3 neb; height 1.3m (0.2) iv, 1.2m (0.2) neb; weight 29.2 kg (10.1) iv, 22.5 kg (8.1) neb Asthma definition and severity: severe acute asthma as per NAAC guidelines Exclusion criteria: mild, moderate or life-threatening asthma, CHD, SVT, respiratory illness, DM, <10kg, >50kg, <12mos, >12yrs, max iv dose already Inhaled corticosteroid use: no details
Interventions	Standard care: Coincident with iv drugs, O2 NPV 30%, continuous salbutamol 2.5 mg (< 2 yrs) or 5 mg (> 2 yrs), hydrocortisone 5 mg/kg iv, then from 2 hrs onwards continuous salbutamol, then q30 min, q60 min, q2h, q3h, q4h prn Treatment group: placebo vs. salbutamol iv 15 ug/kg over 10 min at 0 min Placebo: saline
Outcomes	PFTs: not done Timing: not done

Browne 1997 *(Continued)*

	Admissions: all patients admitted to high-dependency ward Side effects: higher proportion with tremor at 2 hr (specifics unknown) Complications:
Notes	Run in period of 30 min where pts given salb neb of 2.5 or 5 mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Investigators unaware as to order of randomisation sequence

Cheong 1988

Methods	Randomization: yes (unknown, sealed envelope) Blinding: no Number excluded: no details Withdrawals: 5 (2 iv due to side effects and 3 neb due to non-response) Baseline characteristics: HR 114 (SD 14) iv, 110 (SD 14) neb; PaO2 8.8 (1.1) kpa iv, 9.1 (1.2) kpa neb; PaCO2 4.9 (1.0) kpa iv, 4.7 (0.7) kpa neb; PEFR 91 (37.2) iv, 111 (53.4) neb (predicted PEFR 20.4 (6.9) iv, 24 (9.1) neb) Jadad score: "strong", score >/= 3
Participants	Location: Penarth, South Glamorgan Participants: 76 eligible, 71 final (5 removed b/c adverse effects, or non-response to Rx); 16-70 yrs (mean 37 yrs (16-69) iv, 35 yrs (16-66) neb); males 26 iv, 23 neb; females 11 iv, 12 neb Asthma definition and severity: initially PEF < 20% predicted, run in phase selecting those with expected PEFR < 50% 30 min after first nebulized treatment of salbutamol Exclusion criteria: history of CV disease, prehospital steroid use, previous iv bronchodilator use Inhaled corticosteroid use: no details
Interventions	Standard care: For first 30 min O2 NP35%, salbutamol 5 mg neb X 1, hydrocortisone 200 mg iv Treatment group: salbutamol 5 mg neb at 30 min and at 120 min vs. salbutamol iv infusion 12.5 ug/min for four hrs at 30 min Placebo: ?
Outcomes	PFTs: % PEFR response iv 6.3 (SD 5.9), 13.2 (SD 12.4), 17.3 (SD 15.6), 25.2 (SD 19.9); neb 6.3 (SD 8.5), 10.9 (SD 13.9), 10.6 (SD 13.3), 14.3 (SD 15.9) Timing: 30, 60, 150, 240 min Admissions: Side effects: 1 HA & palp, 1 tremor and palp Complications:
Notes	Iv meds given at 30 min after run-in phase (which produced a 6.3% response in PEFR), hence times are 'off' by +30 min

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Sealed envelopes

Femi-Pearse 1 1977

Methods	randomised, parallel protocol Jadad Score: "weak", score < 3
Participants	adults
Interventions	i.v. salbutamol vs. i.v. aminophylline
Outcomes	delta VS, delta PEFR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Femi-Pearse 2 1977

Methods	randomised, parallel Jadad Score: "weak", score < 3
Participants	adults
Interventions	i.v. salbutamol vs. i.v. aminophylline
Outcomes	delta VS, delta PEFR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Hambleton 1979

Methods	randomized, parallel protocol Jadad Score: "weak", score < 3
Participants	children
Interventions	intravenous salbutamol vs. intravenous aminophylline
Outcomes	delta clinical scores, VS, ASE
Notes	

Risk of bias

Hambleton 1979 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Hussein 1986

Methods	Randomized, parallel trial Jadad Score: "weak", score < 3
Participants	Children. N = 18
Interventions	IV repreoterol vs. inhaled reproterol
Outcomes	VS, ABGs, %pred PEFR, clinical score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Johnson 1978

Methods	Randomization: yes (mentioned in passing only) Blinding: no Number excluded: 23 Withdrawals: 8 (6 from iv salb because unsatisfactory response starting at 8 to 32 hrs and 2 from comparison at 24 h due to no response) Baseline characteristics: HR 109 (sd 4) salb, 107 (sd 5) amino, 110 (sd 3) cont; BP 134 (sd 5) / 81 (sd 2) salb, 141 (sd 6) / 83 (sd 3) amino, 137 (sd 3) / 83 (sd 2) cont; PaO2 8.3 (sd 0.3) salb, 7.5 (sd 0.7) amino, 8.0 (sd 0.4) cont; PaCO2 5.1 (sd 0.2) salb, 5.0 (sd 0.1) amino, 5.2 (sd 0.3) cont; pH 7.4 (sd 0.01) salb, 7.38 (sd 0.01), 7.4 (sd 0.01) cont; PEFR/FEV 98 (sd 8) / 0.6 (sd 0.1) salb, 92 (sd 9) / 1.1 (sd 0.2) amino, 108 (sd 10) / 1.0 (sd 0.1) cont Jadad score: "weak", score < 3
Participants	Location: London, England Participants: initially 62, 39 final (23 improved with run in Rx); 16- 65 yrs (mean 36.2 salb, 41.9 amino, 36.7 control); males 9 salb, 4 amino, 11 cont; females 11 salb, 15 amino, 12 cont; height 168.2 cm (SD 1.9) salb, 162.6 cm (SD 1.7) amino, 167.9 cm (SD 1.8) cont; weight 63.9 kg (SD 1.5) salb, 60.8 kg (SD 2.6) amino, 63.5 kg (SD 1.5) cont Asthma definition and severity: PEFR<150 (not mentioned, abstracted from article instead), run in phase for about 45 min of aminophylline/ neb salbutamol/ hydrocortisone, RCT Exclusion criteria: presence of CV or renal disease, improvement with run in phase Inhaled corticosteroid use: 30 equally distributed
Interventions	Run in phase with inclusion and rand at 75 min, consecutive pts, parallel cohort of drug A vs. drug B, crossover possible at MD discretion, compared to 'control' group Standard care: For first 75 min O2 NPV 35%, aminophylline 5 mg/kg iv load, hydrocortisone 200 mg iv, prednisone 40 mg po qd, salbutamol 5 mg IPPB q6h, physioTx

Johnson 1978 *(Continued)*

	Treatment group: aminophylline infusion 1 mg/min at 75 min and 'control group' of inhaled salbutamol vs. salbutamol iv infusion at 10 ug/min at 75 min Placebo: none
Outcomes	PFTs: PEFR/% PEFR Response/FEV salb 146 (sd10)/ FVC 2 (sd 0.2)/ 0.8 (sd 0.1), 133.3 / ? / 0.79, 148 / ? / 1.0; cont 145 (sd 15)/ FVC 1.9 (sd 0.2)/ 0.9 (sd 0.1), 150 / ? / 0.93, 170.8 / ? / 1.07 Timing: 15, 60, 360 min Admissions: Side effects: no details Complications:
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Lawford 1978

Methods	Randomization: yes (mentioned in passing, mentioned as numbered ampules & bottles) Blinding: double-blind Number excluded: no details Withdrawals: 2 Baseline characteristics: HR 119 (sd 21) iv, 115 (sd 30) neb; PaO2 12.3 (sd 2.7) iv, 11.4 (sd 2.4) neb; PaCO2 4.7 (sd 0.5) iv, 5.6 (sd 1.6) neb; PEFR/FEV 86 (sd 26) / 0.68 (sd 0.24) iv, 82 (sd 23) / 0.52 (sd 0.15) neb Jadad score: "strong", score >/= 3
Participants	Location: Harrow, Middlesex, England Participants: 16 eligible, 14 final (2 removed because of side effects to iv meds), 15-65 yrs (mean ?) Asthma definition and severity: unresponsive to hospital meds, no steroids in previous 6 hrs, no recent changes in oral steroid dose, PEF < 120L Exclusion criteria: no details Inhaled corticosteroid use: no details
Interventions	Standard care: O2 40% NPV, hydrocortisone 250 mg iv Treatment group: salb 10 mg NEB at 0 min lasting for 45 min vs. salb iv infusion 20 ug/min at 0 min lasting for 45 min Placebo: saline
Outcomes	PFTs: PEFR/FEV iv pos 38 (sd 68)/ 0.44 (sd 0.35); neb pos 51 (sd 56)/ 0.21 (sd 0.13) Timing: 45 min Admissions: Side effects: 5 of 9 had undesirable SE (2 withdrew, 2 tremor, 1 palp) Complications:
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Investigators unaware as to order of randomisation sequence

Salmeron 1994

Methods	Randomization: yes (method not mentioned) Blinding: double-blind Number excluded: no details Withdrawals: 6 (5 iv and 1 neb due to no improvement) Baseline characteristics: HR 115 (sd 19) iv, 118 (sd 19) neb; BP 153 (sd 28) / 88 (sd 17) iv, 152 (sd 28) / 89 (sd 14) neb; clinical index 10.2 (sd 2.3) iv, 10.0 (sd 2.1) neb; PaCO2 50 (sd 11) iv, 51 (sd 8) neb; PEFR 78 (sd 76) iv, 59 (sd 61) neb Jadad score: "strong", score >/=3
Participants	Location: multicenters in France Participants: 48 eligible, 47 final (one patient was included twice in same group); 16-75 yrs (mean39 (sd 13) iv, 41 (sd 17) neb); males 17 iv, 10 neb; females 8 iv, 12 neb Asthma definition and severity: definition of the American Thoracic Society, severe acute asthma with hypercapnea and severe clinical symptoms, including breathlessness or wheeze refractory to normal meds, PEFR < 150 l/min, PaCO2 >= 40 Exclusion criteria: COPD, LV Failure, use of nonbeta-agonist MDI within the past 60 min Inhaled corticosteroid use: 20 (oral: 5 of 22 neb, 6 of 23 iv), (inhaled 9 overall)
Interventions	Parallel protocol of iv vs. neb albuterol, review for continued Rx at 60 min Standard care: O2 30% NPV, hydrocortisone 200 mg iv, crystalloid bolus Treatment group: albuterol 10 mg RA neb (two 5 mg nebs over 15 min for one hour), then if successful continue Rx 5 mg NEB q2h for 7 h vs. albuterol iv infusion of 8.3 ug/min for 60 min (total 500 ug) at 0 min lasting for 1 hr, then if successful continue Rx 500 ug/hr for 7h Placebo: saline
Outcomes	PFTs: PEFR iv pos 42 (sd 66), 240 (sd 115); neb pos 107 (sd 94)pos 254 (sd 90) Timing: 60, 480 min Admissions: Side effects: no details Complications: 2 intubated
Notes	Author correspondence: "Successful Rx" presence of at least 2 items at 60 min, [1] delta CI >= 3, [2] delta PaCO2 >= neg3, [3] delta PEF >= pos50

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Investigators unaware as to order of randomisation sequence

Sharma 1 1984

Methods	randmoized, parallel protocol Jadad Score: "weak", score < 3
Participants	Adults. N = 20
Interventions	intravenous salbutamol vs. i.v. aminophylline
Outcomes	delta FEV1, delta MMFR, ASE
Notes	

Sharma 1 1984 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Sharma 2 1984

Methods	randomized, parallel protocol Jadad Score: "weak", score < 3
Participants	adults
Interventions	i.v terbutaline vs. i.v. aminophylline
Outcomes	delta FEV1, delta MMFR, ASE
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Swedish Society 1990

Methods	Randomization: yes (blocked randomization in sets of four) Blinding: no Number excluded: 2 Withdrawals: no details Baseline characteristics: HR 111 (sd 10) iv, 112 (sd 9) neb; BP 140 (sd 21) / 88 (sd 12) iv, 145 (sd 20) / 87 (sd 11) neb; PEFR 166 (sd 70) iv, 170 (sd 47) neb (predicted 31 (sd 8) iv, 33 (sd 9) neb) Jadad score: "weak", score < 3
Participants	Location: multicenters in Sweden Participants: initially 178 eligible, 176 final (2 excluded because of incomplete records, 89 iv, 87 neb); mean 55 yrs (sd 13) iv, 58 yrs (sd 12) neb; males 50 iv, 43 neb; females 39 iv, 44 neb Asthma definition and severity: rapid onset, HR >= 100, predPEF <= 50%, Hx of variable SOB & wheezing above and one of the following: [1] diurnal variation of PEF of >= 25%, [2] 15% reversible airway obstruction by beta-agonist, [3] bronchial hyperreactivity by methacholine/histamine Exclusion criteria: extremely severe b/c pred PEF< 15%, known COPD, severe HTN or heart dz, > 75 yrs, those on beta blockers Inhaled corticosteroid use: iv (62% inhaled, 30% po), neb (67% inhaled, 30% po)
Interventions	Convenience sample during office hours, 'open' parallel protocol of iv vs. neb, crossover study for repeaters Standard care: O2 at MD discretion, steroids at 120 min with MD discretion, both groups given iv theophylline 6 mg/kg iv at 60 min over 30 min (excluded those pts who already took theophylline) Treatment group: salbutamol 0.15 mg/kg NEB at 0 min lasting 7 min, repeat x1 at 30 min (total neb = 0.30 mg/kg in 1 hour) vs. salbutamol 5 ug/kg iv over 10 min at 0 min

Swedish Society 1990 *(Continued)*

	Placebo: none
Outcomes	PFTs: PEFR iv 214.7, 210.3, 200, 225, 227.9; neb 235.3, 238.8, 256.2, 276.2, 279.4 Timing: 5, 30, 60, 90, 120 min Admissions: Side effects: iv tremor at 1 hr (35.8 % mild, 9.3% mod, 0% severe), palp at 120 min (9%); neb tremor at 1 hr (59.8 % mild, 20% mod, 4.2% severe), palp at 120 min (23%) Complications:
Notes	Co-administration of theophylline at 60 min, no other standard Rx started until 120 min

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Tribe 1976

Methods	Randomization: yes (method not mentioned) Blinding: double-blind Number excluded: no details Withdrawals: 2 Baseline characteristics: HR 103.7 iv, 114.6 amino; PaO2 8 kpa iv, 7.6 kpa amino; PaCO2 4.2 kpa iv, 4.5 kpa amino; FEV iv 0.7 (0.3 to 1.7) female, 1.7 (0.3 to 3.1) male, amino 0.7 (0.3 to 1.3) female, 0.7 male Jadad score: "strong", score >/= 3
Participants	Location: Perth, Australia Participants: 25 eligible, 23 final (2 lost to follow-up no details given, 11 iv, 12 amino); mean 42 yrs female/ 49 yrs male iv, 48 yrs female/ 17 yrs male amino; males 2 iv, 1 amino; females 9 iv, 11 amino Asthma definition and severity: no specified definition, included if demonstrable wheeze or SOB Exclusion criteria: arrhythmia, PaO2 < 50, PaCO2 > 50, Pts 'poor general condition', 'too ill to await Rx', allergy, excessive drug Rx in previous 3 hrs Inhaled corticosteroid use: 3 iv, 1 theophylline
Interventions	Standard care: hydrocortisone 100 mg iv, iv (4 had beta-agonists within 3 hrs prior), neb (5 had beta-agonists within 3 hrs prior) Treatment group: theophylline 250 mg iv at 0 min over ?5 min vs. salbutamol 100 ug iv at 0 min Placebo: unknown
Outcomes	PFTs: FEV iv pos 26%; amino pos 23% Timing: 60 min Admissions: Side effects: iv "impression" - 2 (1 HA, 1 tremor & palp), amino "impression" - 3 (2 iv pain, 1 HA & vomit) Complications:
Notes	Author correspondence: Severe co-interventions with beta agonists prior to start of trial, questionable if iv agonists started at truly 0 min

Risk of bias

Bias	Authors' judgement	Support for judgement

Tribe 1976 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information not available

Van Renterghem 1987

Methods	Randomization: yes (method not mentioned) Blinding: double-blind Number excluded: no details Withdrawals: none Baseline characteristics: HR 114 (sd 21) iv, 113 (sd 17) neb; MAPs 104 (sd 19) iv, 105 (sd 12) neb; PaO2 56.6 (sd 20.7) iv, 63.9 (sd 12.2) neb; PEFR 89.5 (sd 32.4) iv, 97.3 (sd 34.4) neb (predicted PEFR 19.3 % (sd 7) iv, 16.9% (sd 4.5) neb) Jadad score: "weak", score < 3
Participants	Location: Ghent, Belgium Participants: 23 (11 iv, 12 neb); mean 49.8 yrs (sd 13.5) iv, 52 yrs (sd 7.6) neb; males 10, females 13 Asthma definition and severity: all pts "previously demonstrated" an increase of 20% in FEV1 after MDI use, two of three criteria: [1] HR > 100, [2] predPEFR < 30%, [3] PaO2 < 9.3 kpa on 2 lpm O2 Exclusion criteria: CV Dz, hypoK, hyperGLC, < 2hr iv agonist Rx Inhaled corticosteroid use: no details
Interventions	Standard care: O2 NPV 30%, hydrocortisone 125 mg iv, theophylline (unknown dose) iv prior to randomization Treatment group: terbutaline 0.1 mg/kg NEB over 5 min at 0 min and 60 min vs. terbutaline 6 ug/kg iv over 5 min (q60min x1) at 0 min and 60 min Placebo: saline
Outcomes	PFTs: PEFR/% PEFR Response iv 108 / ?, 104 / ?, 111 / ?, 127.7 (sd 65.4) / 28.2 (sd 12.1); neb 111 / ?, 104 (sd 41.8) / 20.1 (sd 6.7), 111 / ?, 122 (sd 50.1) / ? Timing: 15, 30, 60, 120 min Admissions: Side effects: no details Complications:
Notes	Run in period with theophylline for unknown time, looks like a few minutes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Information not available

Williams 1975

Methods	Randomization: yes (method not mentioned) Blinding: double-blind Number excluded: no details Withdrawals: none Baseline characteristics: HR 128 (sd 11) iv, 125 (sd 7) theoph; BP 139 (sd 17) / 87 (sd 9) iv, 157 (sd 20) / 91 (sd 9) theoph; PaO2 7.5 kpa (sd 1.1) iv, 7.7 (sd 1.6) theoph; PaCO2 5.6 kpa (sd 1.2) iv, 5.3 (sd 1.6) theoph; PEFR 75 (sd 15) iv, 90 (sd 20) theoph Jadad score: "strong", score >/= 3

Williams 1975 *(Continued)*

Participants	Location: Penarth, South Glamorgan Participants: 20 final (11 salbutamol, 9 theoph)Asthma definition and severity: definition not specified, included if HR > 120, pred PEFR < 25%, PaO2 < 69.8 Exclusion criteria: none mentioned Inhaled corticosteroid use: no details
Interventions	Parallel study, iv salbutamol vs. theophylline Standard care: O2 NPV 28%, hydrocortisone 1000 mg iv Treatment group: aminophylline 500 ug iv at 0 min infused over 60 min vs. salbutamol 500 ug iv at 0 min infused over 60 min (8.33 ug/min) Placebo: none
Outcomes	PFTs: PEFR iv 114 (sd 27), 128 (sd 53), 161 (sd 85); theoph 109 (sd 34), 118 (sd 43), 134 (sd 64) Timing: 15, 30, 60 min Admissions: Side effects: iv 5 (3 HA, 2 tremor); theoph 7 (2 HA, 3 tremor, 4 nausea, 1 vomit, 4 extrasystoles) Complications:
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Investigators unaware as to order of randomisation sequence

Williams 1981

Methods	Randomization: not applicable Blinding: double-blind Number excluded: no details Withdrawals: none Baseline characteristics: HR 124 iv, 117 neb; FEV 0.92 iv first, 1.10 neb first Jadad score: "weak", score < 3
Participants	Location: London, England Participants: 15 final (8 iv/neb, 7 neb/iv) Asthma definition and severity: severe acute asthma (otherwise unspecified), PaO2 < 70, HR > 100, pred FEV1 < 25%, run in period of pts able to get consistent FEV1s (within 10% on 3 trials) Exclusion criteria: previous 2hr use of any bronchodilators Inhaled corticosteroid use: no details
Interventions	Crossover of terbutaline iv vs. neb, each repeated twice once FEV was maxed Standard care: O2 NPV, hydrocortisone 200 mg iv q6h Treatment group: terbutaline 2.5 mg NEB over 10 min (repeat X 2 for each time FEV1 maxed) vs. terbutaline 250 ug iv over 10 min at 0 min (repeat X 2 for each time FEV1 maxed) Placebo: saline
Outcomes	PFTs: FEV pos 0.59 when iv first, pos 0.36 when iv second (these are delta FEV); pos 0.58 when neb first, pos 0.32 when neb second Timing: not specified Admissions: Side effects: 3 tremor unspecified Rx sequence Complications:

Williams 1981 *(Continued)*

Notes	Author correspondence: FEV1 were done on 5 min intervals until no more improvement, but times not listed on graph

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Investigators unaware as to order of randomisation sequence

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

Study	Reason for exclusion
Anonymous 1978	Non-experimental study (not randomized controlled clinical trial).
Arnaud 1977	Not randomized controlled clinical trial.
Beswick 1975	Not randomized controlled clinical trial..
Blumenthal 1979	Letter, not a clinical trial.
Boe 1985	Not randomized controlled clinical trial. Intravenous beta-agonists use was not the primary research question (no control; compared 2 doses of terbutaline - dose response curve).
Bohn 1984	Not randomized controlled clinical trial.
Bruguerolle 1991	Not randomized controlled clinical trial.
Crompton 1990	Review.
Downes 1973	Not randomized controlled clinical trial.
Edmunds 1981	Not randomized controlled clinical trial.
Evans 1980	Not randomized controlled clinical trial - cohort study.
Fitchett 1975	Not randomized controlled clinical trial - cohort study.
Grant 1976	Letter to editor.
Greif 1985	Not randomized controlled clinical trial - cohort study.
Herman 1983	Not randomized controlled clinical trial - cohort study.
Hetzel 1976	Not randomized controlled clinical trial - cohort study.
Hirsch 1979	Case report.
Iodice 1980	Not randomized controlled clinical trial - cohort study.
Janson 1992	Not randomized controlled clinical trial.

Study	Reason for exclusion
Marlin 1975	Chronic asthma.
May 1975	Not randomized controlled clinical trial - cohort study.
Nogrady 1977	Case series.
Noseda 1989	Review.
O'Connell 1990	Not randomized controlled clinical trial - cohort study.
Parry 1976	Not randomized controlled clinical trial - cohort study.
Pierce 1981	Patients were not seen in an emergency setting (study done in a lab setting).
Salmeron 1995	Letter to editor.
Schiavi 1987	Not randomized controlled clinical trial.
Smith 1986	Non-experimental study (not randomized controlled clinical trial).
Spiro 1975	Non-experimental study (not randomized controlled clinical trial). Patients were not seen in an emergency setting (study done in a lab setting).
Subias 1989	Not randomized controlled clinical trial.
Teoh 1979	Non emergency patients. Not randomized controlled clinical trial - cohort study.
Thiringer 1976	Non-experimental study (not randomized controlled clinical trial). Patients were not seen in an emergency setting (study done in a lab setting).
Ting 1991	Not randomized controlled clinical trial.
Tirot 1992	Not randomized controlled clinical trial.
Tripathi 1989	Not randomized controlled clinical trial.
Williams 1977	Non-experimental study (not randomized controlled clinical trial).
Wood 1972	Not randomized controlled clinical trial.
Wood 1973	Not randomized controlled clinical trial.

DATA AND ANALYSES

Comparison 1. IV vs. All Treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PEFR (l/min) @ 15 minutes	4	255	Mean Difference (IV, Random, 95% CI)	10.09 [-4.43, 24.61]

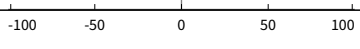
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Intravenous beta-agonist vs. Inhaled beta-agonist	2	196	Mean Difference (IV, Random, 95% CI)	6.24 [-27.17, 39.66]
1.2 Intravenous beta-agonist vs. intravenous methylxanthine	2	59	Mean Difference (IV, Random, 95% CI)	9.53 [-9.75, 28.81]
2 PEFR (l/min) @ 30 minutes	3	63	Mean Difference (IV, Random, 95% CI)	-1.89 [-21.52, 17.74]
2.1 Intravenous beta-agonist vs. inhaled beta-agonist	2	43	Mean Difference (IV, Random, 95% CI)	0.37 [-21.83, 22.57]
2.2 Intravenous beta-agonist vs. intravenous methylxanthine	1	20	Mean Difference (IV, Random, 95% CI)	-10.0 [-52.07, 32.07]
3 PEFR (l/min) @ 45 minutes	3	53	Mean Difference (IV, Random, 95% CI)	-0.42 [-29.94, 29.09]
3.1 Intravenous beta-agonist vs. inhaled beta-agonist	2	33	Mean Difference (IV, Random, 95% CI)	5.80 [-28.09, 39.68]
3.2 Intravenous beta-agonist vs. intravenous methylxanthine	1	20	Mean Difference (IV, Random, 95% CI)	-20.0 [-80.11, 40.11]
4 PEFR (l/min) @ 60 minutes	7	396	Mean Difference (IV, Random, 95% CI)	19.42 [-3.69, 42.53]
4.1 Intravenous beta-agonist vs. inhaled beta-agonist	5	337	Mean Difference (IV, Random, 95% CI)	24.71 [-2.92, 52.34]
4.2 Intravenous beta-agonist vs. intravenous methylxanthine	2	59	Mean Difference (IV, Random, 95% CI)	3.75 [-35.36, 42.86]
5 PEFR (l/min) @ 120 min	2	196	Mean Difference (IV, Random, 95% CI)	47.18 [25.93, 68.42]
5.1 Intravenous beta-agonist vs. inhaled beta-agonist	2	196	Mean Difference (IV, Random, 95% CI)	47.18 [25.93, 68.42]
5.2 Intravenous beta-agonist vs. intravenous methylxanthine	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 PEFR (l/min) Final	3	93	Mean Difference (IV, Random, 95% CI)	19.14 [-9.36, 47.63]
6.1 Intravenous beta-agonist vs. inhaled beta-agonist	2	54	Mean Difference (IV, Random, 95% CI)	17.85 [-27.18, 62.87]
6.2 Intravenous beta-agonist vs.intravenous methylxanthine	1	39	Mean Difference (IV, Random, 95% CI)	20.0 [-16.80, 56.80]
7 Arterial Oxygen Tension (mm Hg)	6	132	Mean Difference (IV, Random, 95% CI)	-3.18 [-8.68, 2.33]

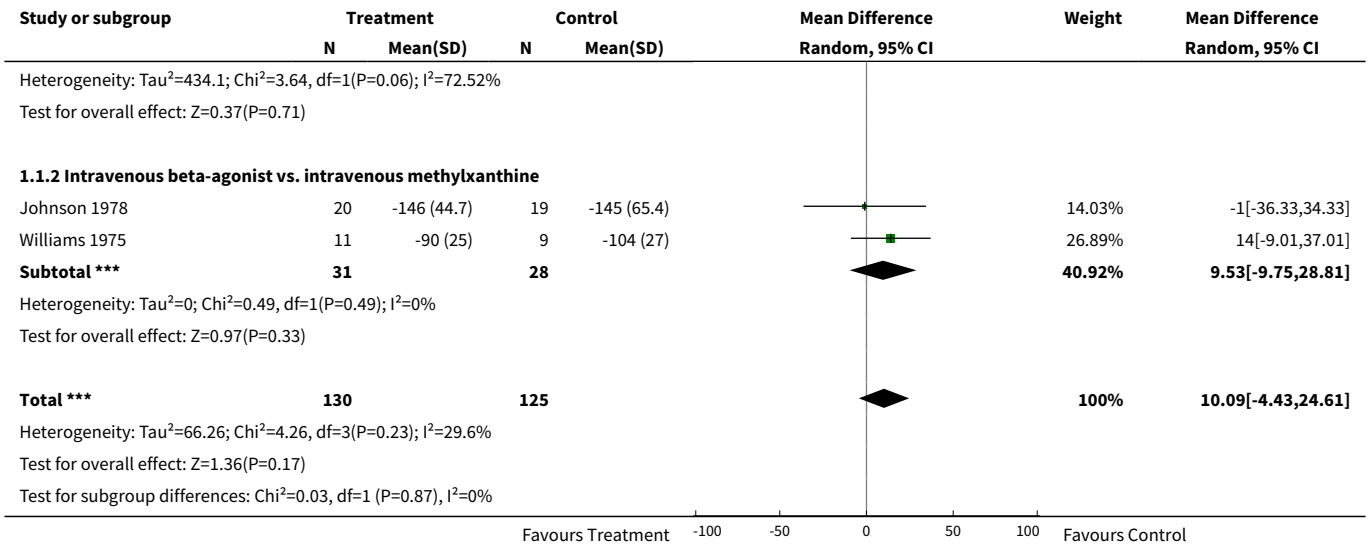
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Intravenous beta-agonist vs. inhaled beta-agonist	4	73	Mean Difference (IV, Random, 95% CI)	-0.77 [-8.27, 6.72]
7.2 Intravenous beta-agonist vs. intravenous methylxanthine	2	59	Mean Difference (IV, Random, 95% CI)	-4.00 [-14.13, 2.13]
8 Arterial Carbon Dioxide Tension (mm Hg)	5	136	Mean Difference (IV, Random, 95% CI)	1.66 [-0.94, 4.25]
8.1 Intravenous beta-agonist vs. inhaled beta-agonist	3	77	Mean Difference (IV, Random, 95% CI)	3.18 [-2.69, 9.05]
8.2 Intravenous beta-agonist vs. intravenous methylxanthine	2	59	Mean Difference (IV, Random, 95% CI)	0.98 [-2.16, 4.12]
9 Heart Rate @ 15 min	5	278	Mean Difference (IV, Random, 95% CI)	7.69 [0.87, 14.51]
9.1 Intravenous beta-agonist vs. inhaled beta-agonist	3	219	Mean Difference (IV, Random, 95% CI)	8.35 [-3.39, 20.10]
9.2 Intravenous beta-agonist vs. intravenous methylxanthine	2	59	Mean Difference (IV, Random, 95% CI)	8.13 [-0.12, 16.37]
10 Heart Rate @ 30 minutes	5	310	Mean Difference (IV, Random, 95% CI)	4.03 [-2.98, 11.03]
10.1 Intravenous beta-agonist vs. inhaled beta-agonist	4	290	Mean Difference (IV, Random, 95% CI)	2.55 [-4.69, 9.79]
10.2 Intravenous beta-agonist vs. intravenous methylxanthine	1	20	Mean Difference (IV, Random, 95% CI)	11.00 [-1.83, 23.83]
11 Heart Rate @ 45 minutes	3	56	Mean Difference (IV, Random, 95% CI)	13.02 [1.58, 24.46]
11.1 Intravenous beta-agonist vs. inhaled beta-agonist	2	36	Mean Difference (IV, Random, 95% CI)	18.31 [-2.57, 39.19]
11.2 Intravenous beta-agonist vs. intravenous methylxanthine	1	20	Mean Difference (IV, Random, 95% CI)	8.0 [-2.52, 18.52]
12 Heart Rate @ 60 minutes	9	437	Mean Difference (IV, Random, 95% CI)	3.65 [-2.90, 10.19]
12.1 Intravenous beta-agonist vs. inhaled beta-agonist	6	355	Mean Difference (IV, Random, 95% CI)	4.54 [-4.89, 13.98]
12.2 Intravenous beta-agonist vs. intravenous methylxanthine	3	82	Mean Difference (IV, Random, 95% CI)	2.54 [-6.28, 11.36]
13 Heart Rate @ 120 minutes	5	321	Mean Difference (IV, Random, 95% CI)	2.84 [-9.27, 14.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Intravenous beta-agonist vs. inhaled beta-agonist	5	321	Mean Difference (IV, Random, 95% CI)	2.84 [-9.27, 14.95]
13.2 Intravenous beta-agonist vs. intravenous methylxanthine	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14 Heart Rate Final	6	192	Mean Difference (IV, Random, 95% CI)	10.82 [5.00, 16.64]
14.1 Intravenous beta-agonist vs. inhaled beta-agonist	5	153	Mean Difference (IV, Random, 95% CI)	10.73 [3.44, 18.01]
14.2 Intravenous beta-agonist vs. intravenous methylxanthine	1	39	Mean Difference (IV, Random, 95% CI)	10.0 [0.99, 19.01]
15 Diastolic Blood Pressure @ 60 minutes	3	235	Mean Difference (IV, Random, 95% CI)	-3.31 [-9.00, 4.37]
15.1 Intravenous beta-agonist vs. inhaled beta-agonist	1	176	Mean Difference (IV, Random, 95% CI)	3.00 [0.67, 5.33]
15.2 Intravenous beta-agonist vs. intravenous methylxanthine	2	59	Mean Difference (IV, Random, 95% CI)	-6.85 [-13.58, -0.11]
16 Autonomic Side Effects	9	380	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.38, 0.95]
16.1 Intravenous beta-agonist vs. inhaled beta-agonist	5	297	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.22, 0.65]
16.2 Intravenous beta-agonist vs. intravenous methylxanthine	4	83	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.10 [0.85, 5.17]
17 Clinical Failure	4	115	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.59, 2.86]
17.1 Intravenous beta-agonist vs. inhaled beta-agonist	3	92	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.57, 3.12]
17.2 Intravenous beta-agonist vs. intravenous methylxanthine	1	23	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.13, 9.13]

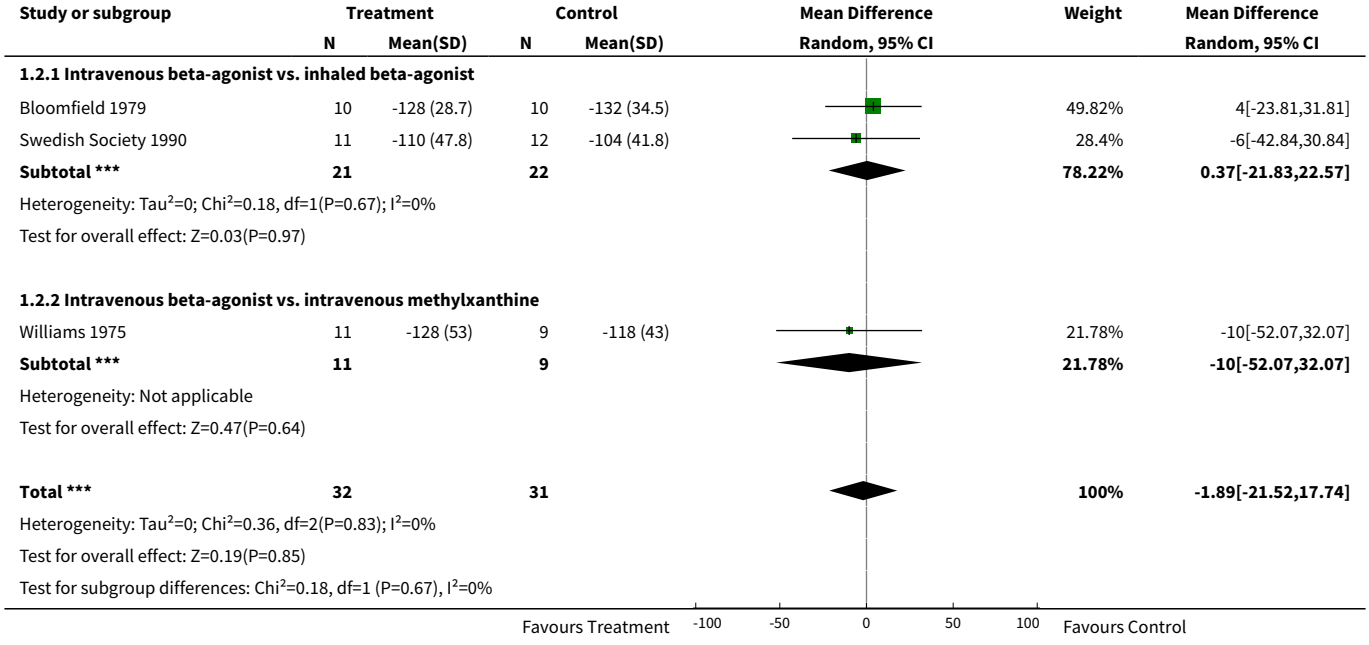
Analysis 1.1. Comparison 1 IV vs. All Treatments, Outcome 1 PEFR (l/min) @ 15 minutes.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 Intravenous beta-agonist vs. Inhaled beta-agonist							
Bloomfield 1979	10	-137 (40.8)	10	-123 (31.6)		16.5%	-14[-45.99,17.99]
Swedish Society 1990	89	-214.7 (52.8)	87	-235.3 (52.2)		42.58%	20.6[5.09,36.11]
Subtotal ***	**99**		**97**			**59.08%**	**6.24[-27.17,39.66]**

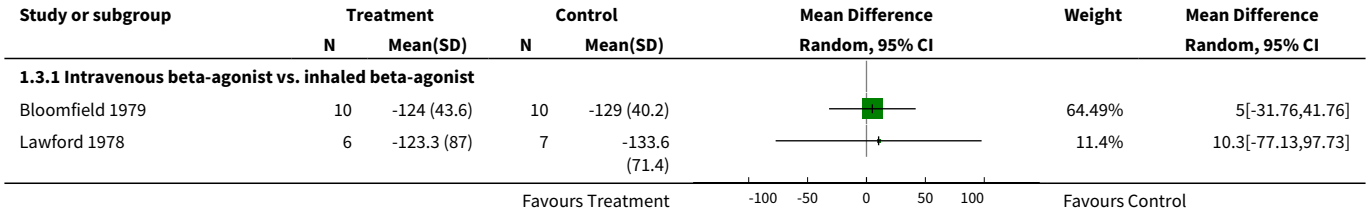


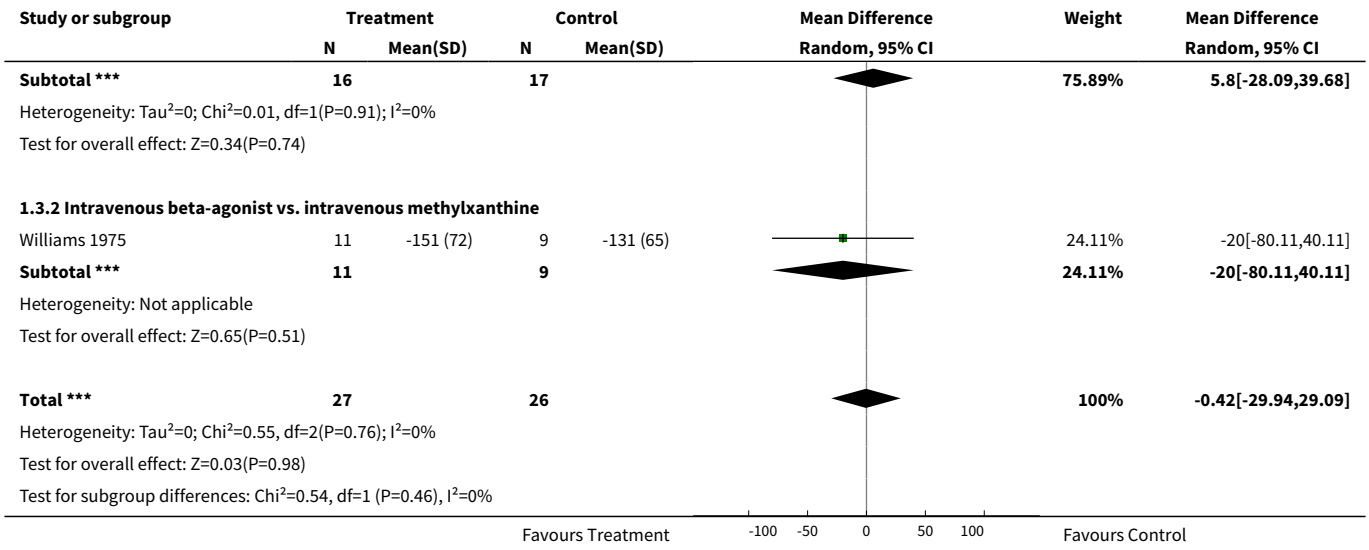


Analysis 1.2. Comparison 1 IV vs. All Treatments, Outcome 2 PEFR (l/min) @ 30 minutes.

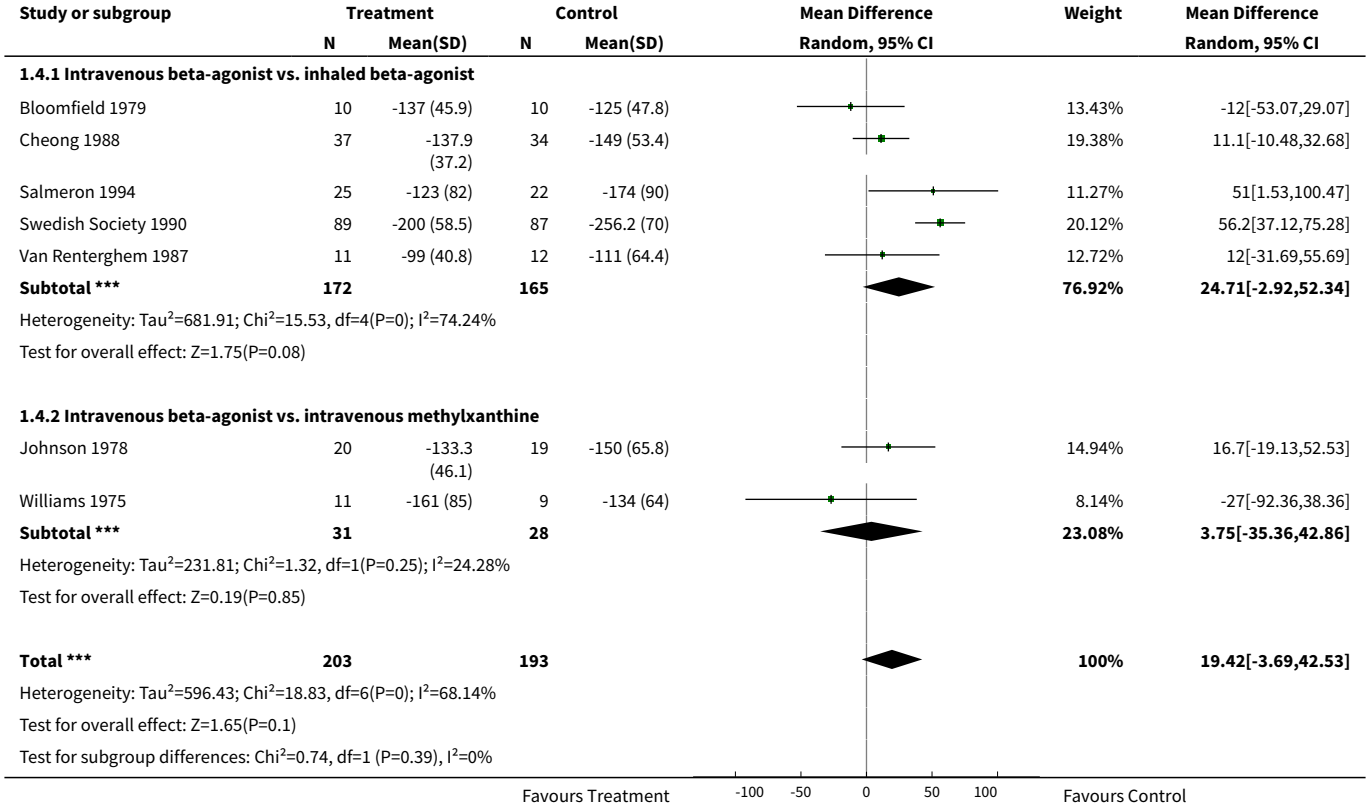


Analysis 1.3. Comparison 1 IV vs. All Treatments, Outcome 3 PEFR (l/min) @ 45 minutes.



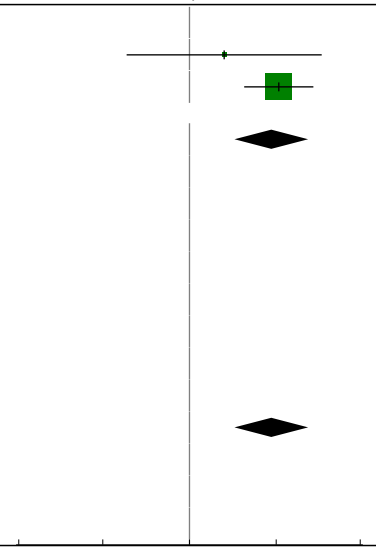


Analysis 1.4. Comparison 1 IV vs. All Treatments, Outcome 4 PEFR (l/min) @ 60 minutes.



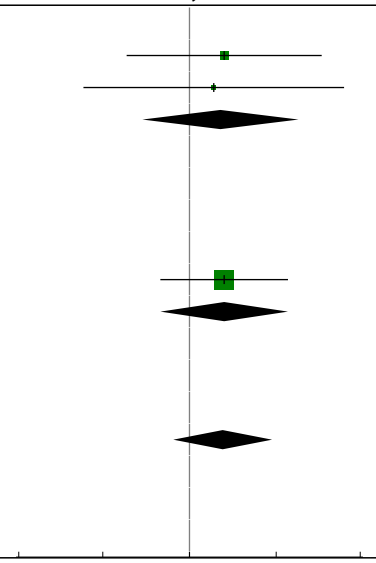
Analysis 1.5. Comparison 1 IV vs. All Treatments, Outcome 5 PEFR (l/min) @ 120 min.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.5.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield 1979	10	-157 (57.5)	10	-177 (70.2)		13.73%	20[-36.24,76.24]
Swedish Society 1990	89	-227.9 (67.9)	87	-279.4 (67.1)		86.27%	51.5[31.56,71.44]
Subtotal ***	**99**		**97**			**100%**	**47.18[25.93,68.42]**
Heterogeneity: Tau^2=32.63; Chi^2=1.07, df=1(P=0.3); I^2=6.58%							
Test for overall effect: Z=4.35(P<0.0001)							
1.5.2 Intravenous beta-agonist vs. intravenous methylxanthine							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**99**		**97**			**100%**	**47.18[25.93,68.42]**
Heterogeneity: Tau^2=32.63; Chi^2=1.07, df=1(P=0.3); I^2=6.58%							
Test for overall effect: Z=4.35(P<0.0001)							
Test for subgroup differences: Not applicable							



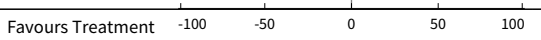
Analysis 1.6. Comparison 1 IV vs. All Treatments, Outcome 6 PEFR (l/min) Final.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield 1979	10	-157 (57.5)	10	-177 (70.2)		25.67%	20[-36.24,76.24]
Salmeron 1994	12	-240 (115)	22	-254 (90)		14.38%	14[-61.15,89.15]
Subtotal ***	**22**		**32**			**40.04%**	**17.85[-27.18,62.87]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%							
Test for overall effect: Z=0.78(P=0.44)							
1.6.2 Intravenous beta-agonist vs.intravenous methylxanthine							
Johnson 1978	20	-148 (46.1)	19	-168 (68.4)		59.96%	20[-16.8,56.8]
Subtotal ***	**20**		**19**			**59.96%**	**20[-16.8,56.8]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.07(P=0.29)							
Total ***	**42**		**51**			**100%**	**19.14[-9.36,47.63]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=2(P=0.99); I^2=0%							
Test for overall effect: Z=1.32(P=0.19)							
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.94), I^2=0%							



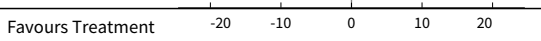
Analysis 1.7. Comparison 1 IV vs. All Treatments, Outcome 7 Arterial Oxygen Tension (mm Hg).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.7.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield 1979	10	-92 (24)	10	-93 (12.2)		10.9%	1[-15.69,17.69]
Hussein 1986	9	-72.5 (11.3)	9	-72.5 (11.3)		28.09%	0[-10.39,10.39]
Lawford 1978	6	-90.4 (16)	6	-83.9 (37.4)		2.86%	-6.5[-39.05,26.05]
Van Renterghem 1987	11	-66.7 (24)	12	-63.9 (12.2)		12.2%	-2.8[-18.57,12.97]
Subtotal ***	**36**		**37**			**54.05%**	**-0.77[-8.27,6.72]**
Heterogeneity: Tau²=0; Chi²=0.25, df=3(P=0.97); I²=0%							
Test for overall effect: Z=0.2(P=0.84)							
1.7.2 Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson 1978	20	-62.2 (10.1)	19	-56.2 (22.9)		24.16%	-6[-17.21,5.21]
Williams 1975	11	-66.7 (14.2)	9	-60.7 (12.7)		21.79%	-6[-17.8,5.8]
Subtotal ***	**31**		**28**			**45.95%**	**-6[-14.13,2.13]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%							
Test for overall effect: Z=1.45(P=0.15)							
Total ***	**67**		**65**			**100%**	**-3.18[-8.68,2.33]**
Heterogeneity: Tau²=0; Chi²=1.11, df=5(P=0.95); I²=0%							
Test for overall effect: Z=1.13(P=0.26)							
Test for subgroup differences: Chi²=0.86, df=1 (P=0.35), I²=0%							



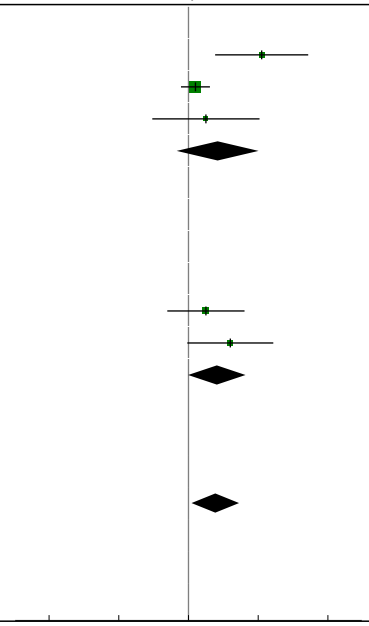
Analysis 1.8. Comparison 1 IV vs. All Treatments, Outcome 8 Arterial Carbon Dioxide Tension (mm Hg).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.8.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Hussein 1986	9	30 (7.5)	9	30 (7.5)		14.05%	0[-6.93,6.93]
Lawford 1978	6	36.9 (9.8)	6	36.4 (7.3)		7.05%	0.5[-9.28,10.28]
Salmeron 1994	25	49 (18)	22	40 (9)		10.55%	9[1,17]
Subtotal ***	**40**		**37**			**31.65%**	**3.18[-2.69,9.05]**
Heterogeneity: Tau²=9.78; Chi²=3.13, df=2(P=0.21); I²=36.15%							
Test for overall effect: Z=1.06(P=0.29)							
1.8.2 Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson 1978	20	38.3 (6.7)	19	37.3 (3.3)		62.31%	1[-2.29,4.29]
Williams 1975	11	39 (6.7)	9	38.2 (15)		6.04%	0.8[-9.77,11.37]
Subtotal ***	**31**		**28**			**68.35%**	**0.98[-2.16,4.12]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.97); I²=0%							
Test for overall effect: Z=0.61(P=0.54)							
Total ***	**71**		**65**			**100%**	**1.66[-0.94,4.25]**
Heterogeneity: Tau²=0; Chi²=3.69, df=4(P=0.45); I²=0%							
Test for overall effect: Z=1.25(P=0.21)							
Test for subgroup differences: Chi²=0.42, df=1 (P=0.52), I²=0%							



Analysis 1.9. Comparison 1 IV vs. All Treatments, Outcome 9 Heart Rate @ 15 min.

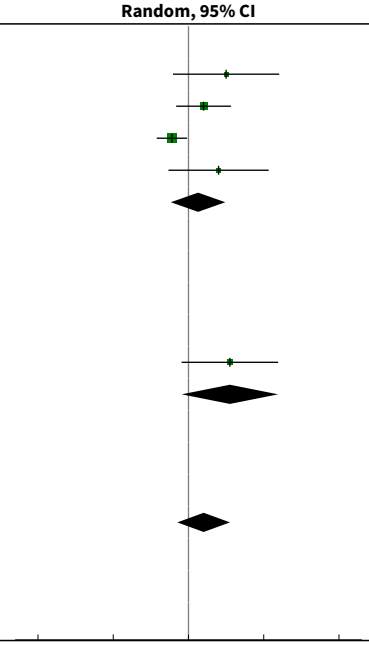
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.9.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield 1979	10	148 (13.1)	10	127 (17.1)		15.73%	21[7.65,34.35]
Swedish Society 1990	89	107 (14.1)	87	105 (14)		34.51%	2[-2.15,6.15]
Van Renterghem 1987	11	118 (22.2)	12	113 (14.2)		13.14%	5[-10.38,20.38]
Subtotal ***	**110**		**109**			**63.38%**	**8.35[-3.39,20.1]**
Heterogeneity: Tau^2=76.09; Chi^2=7.12, df=2(P=0.03); I^2=71.91%							
Test for overall effect: Z=1.39(P=0.16)							
1.9.2 Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson 1978	20	115 (17.9)	19	110 (17.4)		19.36%	5[-6.08,16.08]
Williams 1975	11	128 (14)	9	116 (14)		17.26%	12[-0.33,24.33]
Subtotal ***	**31**		**28**			**36.62%**	**8.13[-0.12,16.37]**
Heterogeneity: Tau^2=0; Chi^2=0.68, df=1(P=0.41); I^2=0%							
Test for overall effect: Z=1.93(P=0.05)							
Total ***	**141**		**137**			**100%**	**7.69[0.87,14.51]**
Heterogeneity: Tau^2=30.62; Chi^2=8.69, df=4(P=0.07); I^2=53.98%							
Test for overall effect: Z=2.21(P=0.03)							
Test for subgroup differences: Chi^2=0, df=1 (P=0.98), I^2=0%							



Favours Treatment Favours Control

Analysis 1.10. Comparison 1 IV vs. All Treatments, Outcome 10 Heart Rate @ 30 minutes.

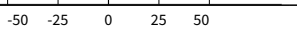
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.10.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield 1979	10	136 (16.1)	10	126 (16.1)		14.21%	10[-4.11,24.11]
Cheong 1988	37	105 (14)	34	101 (17)		24.63%	4[-3.28,11.28]
Swedish Society 1990	89	98 (12.3)	87	102.4 (14.9)		30.2%	-4.4[-8.44,-0.36]
Van Renterghem 1987	11	119 (17.2)	12	111 (15.2)		15.17%	8[-5.31,21.31]
Subtotal ***	**147**		**143**			**84.21%**	**2.55[-4.69,9.79]**
Heterogeneity: Tau^2=32.57; Chi^2=8.62, df=3(P=0.03); I^2=65.19%							
Test for overall effect: Z=0.69(P=0.49)							
1.10.2 Intravenous beta-agonist vs. intravenous methylxanthine							
Williams 1975	11	126 (14)	9	115 (15)		15.79%	11[-1.83,23.83]
Subtotal ***	**11**		**9**			**15.79%**	**11[-1.83,23.83]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=1.68(P=0.09)							
Total ***	**158**		**152**			**100%**	**4.03[-2.98,11.03]**
Heterogeneity: Tau^2=38.04; Chi^2=11.81, df=4(P=0.02); I^2=66.14%							
Test for overall effect: Z=1.13(P=0.26)							
Test for subgroup differences: Chi^2=1.26, df=1 (P=0.26), I^2=20.92%							



Favours Treatment Favours Control

Analysis 1.11. Comparison 1 IV vs. All Treatments, Outcome 11 Heart Rate @ 45 minutes.

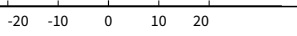
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.11.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield 1979	10	129 (15.4)	10	120 (18)		33.46%	9[-5.68,23.68]
Lawford 1978	7	135.4 (17.1)	9	104.9 (26.2)		20.81%	30.5[9.21,51.79]
Subtotal ***	**17**		**19**			**54.27%**	**18.31[-2.57,39.19]**
Heterogeneity: Tau^2=144.05; Chi^2=2.65, df=1(P=0.1); I^2=62.32%							
Test for overall effect: Z=1.72(P=0.09)							
1.11.2 Intravenous beta-agonist vs. intravenous methylxanthine							
Williams 1975	11	126 (13)	9	118 (11)		45.73%	8[-2.52,18.52]
Subtotal ***	**11**		**9**			**45.73%**	**8[-2.52,18.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.49(P=0.14)							
Total ***	**28**		**28**			**100%**	**13.02[1.58,24.46]**
Heterogeneity: Tau^2=45.72; Chi^2=3.59, df=2(P=0.17); I^2=44.36%							
Test for overall effect: Z=2.23(P=0.03)							
Test for subgroup differences: Chi^2=0.75, df=1 (P=0.39), I^2=0%							



Favours Treatment — Favours Control

Analysis 1.12. Comparison 1 IV vs. All Treatments, Outcome 12 Heart Rate @ 60 minutes.

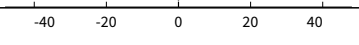
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.12.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield 1979	10	129 (12.2)	10	118 (19)		9.33%	11[-2.99,24.99]
Cheong 1988	37	114 (17)	34	106 (15)		13.44%	8[0.56,15.44]
Hussein 1986	9	155 (17.4)	9	140 (23.7)		6.77%	15[-4.21,34.21]
Salmeron 1994	25	122 (18)	22	115 (19)		11.39%	7[-3.62,17.62]
Swedish Society 1990	89	95 (14.1)	87	105 (19.6)		14.83%	-10[-15.05,-4.95]
Van Renterghem 1987	11	117 (19.9)	12	114 (16.7)		8.72%	3[-12.09,18.09]
Subtotal ***	**181**		**174**			**64.48%**	**4.54[-4.89,13.98]**
Heterogeneity: Tau^2=102.14; Chi^2=25.73, df=5(P=0); I^2=80.57%							
Test for overall effect: Z=0.94(P=0.35)							
1.12.2 Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson 1978	20	115.4 (16.5)	19	108 (15.3)		11.8%	7.4[-2.58,17.38]
Tribe 1976	11	101 (9.3)	12	106.6 (12.2)		12.55%	-5.6[-14.42,3.22]
Williams 1975	11	126 (14)	9	119 (11)		11.17%	7[-3.96,17.96]
Subtotal ***	**42**		**40**			**35.52%**	**2.54[-6.28,11.36]**
Heterogeneity: Tau^2=35.27; Chi^2=4.77, df=2(P=0.09); I^2=58.1%							
Test for overall effect: Z=0.56(P=0.57)							
Total ***	**223**		**214**			**100%**	**3.65[-2.9,10.19]**
Heterogeneity: Tau^2=68.53; Chi^2=31.23, df=8(P=0); I^2=74.38%							
Test for overall effect: Z=1.09(P=0.27)							
Test for subgroup differences: Chi^2=0.09, df=1 (P=0.76), I^2=0%							



Favours Treatment — Favours Control

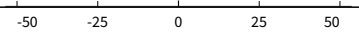
Analysis 1.13. Comparison 1 IV vs. All Treatments, Outcome 13 Heart Rate @ 120 minutes.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.13.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield 1979	10	118 (18.9)	10	123 (9.8)		18.05%	-5[-18.2,8.2]
Cheong 1988	37	113 (17)	34	101 (14)		21.23%	12[4.78,19.22]
Salmeron 1994	12	126 (15)	19	111 (16)		19.24%	15[3.87,26.13]
Swedish Society 1990	89	94 (15.1)	87	105 (14)		22.32%	-11[-15.3,-6.7]
Van Renterghem 1987	11	114 (14.3)	12	110 (13.2)		19.15%	4[-7.28,15.28]
Subtotal ***	**159**		**162**			**100%**	**2.84[-9.27,14.95]**
Heterogeneity: Tau^2=166.27; Chi^2=41.41, df=4(P<0.0001); I^2=90.34%							
Test for overall effect: Z=0.46(P=0.65)							
1.13.2 Intravenous beta-agonist vs. intravenous methylxanthine							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**159**		**162**			**100%**	**2.84[-9.27,14.95]**
Heterogeneity: Tau^2=166.27; Chi^2=41.41, df=4(P<0.0001); I^2=90.34%							
Test for overall effect: Z=0.46(P=0.65)							
Test for subgroup differences: Not applicable							



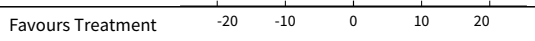
Analysis 1.14. Comparison 1 IV vs. All Treatments, Outcome 14 Heart Rate Final.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.14.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield 1979	10	118 (18.9)	10	123 (9.8)		12.53%	-5[-18.2,8.2]
Browne 1997	14	152 (18.9)	15	142 (9.8)		15.47%	10[-1.07,21.07]
Cheong 1988	37	116 (14)	34	98 (14.4)		24.19%	18[11.38,24.62]
Hussein 1986	9	152 (20.1)	9	138 (14.4)		9.48%	14[-2.15,30.15]
Williams 1981	8	114 (8.2)	7	102 (9.3)		19.24%	12[3.07,20.93]
Subtotal ***	**78**		**75**			**80.91%**	**10.73[3.44,18.01]**
Heterogeneity: Tau^2=38.53; Chi^2=9.65, df=4(P=0.05); I^2=58.55%							
Test for overall effect: Z=2.89(P=0)							
1.14.2 Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson 1978	20	114 (14.3)	19	104 (14.4)		19.09%	10[0.99,19.01]
Subtotal ***	**20**		**19**			**19.09%**	**10[0.99,19.01]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.18(P=0.03)							
Total ***	**98**		**94**			**100%**	**10.82[5,16.64]**
Heterogeneity: Tau^2=25.05; Chi^2=9.91, df=5(P=0.08); I^2=49.53%							
Test for overall effect: Z=3.64(P=0)							
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.9), I^2=0%							



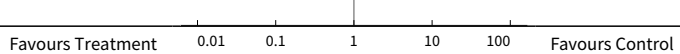
Analysis 1.15. Comparison 1 IV vs. All Treatments, Outcome 15 Diastolic Blood Pressure @ 60 minutes.

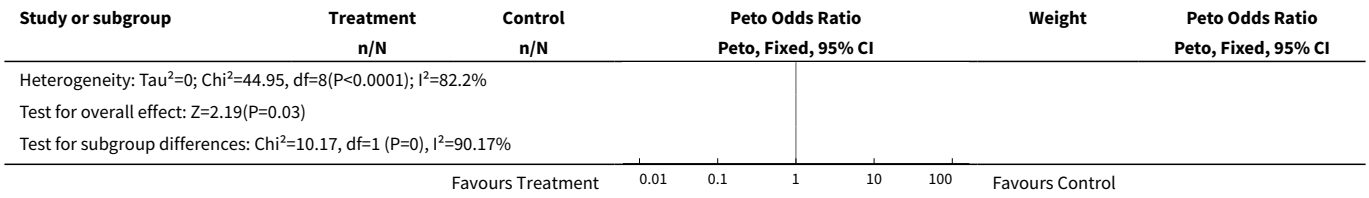
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.15.1 Intravenous beta-agonist vs. inhaled beta-agonist							
Swedish Society 1990	89	84 (8)	87	81 (7.8)		38.01%	3[0.67,5.33]
Subtotal ***	**89**		**87**			**38.01%**	**3[0.67,5.33]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=2.52(P=0.01)							
1.15.2 Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson 1978	20	75 (8)	19	79 (7.8)		33.84%	-4[-8.96,0.96]
Williams 1975	11	73 (7)	9	84 (10)		28.16%	-11[-18.73,-3.27]
Subtotal ***	**31**		**28**			**61.99%**	**-6.85[-13.58,-0.11]**
Heterogeneity: Tau^2=13.52; Chi^2=2.23, df=1(P=0.14); I^2=55.17%							
Test for overall effect: Z=1.99(P=0.05)							
Total ***	**120**		**115**			**100%**	**-3.31[-11,4.37]**
Heterogeneity: Tau^2=39.03; Chi^2=15.95, df=2(P=0); I^2=87.46%							
Test for overall effect: Z=0.84(P=0.4)							
Test for subgroup differences: Chi^2=7.32, df=1 (P=0.01), I^2=86.34%							



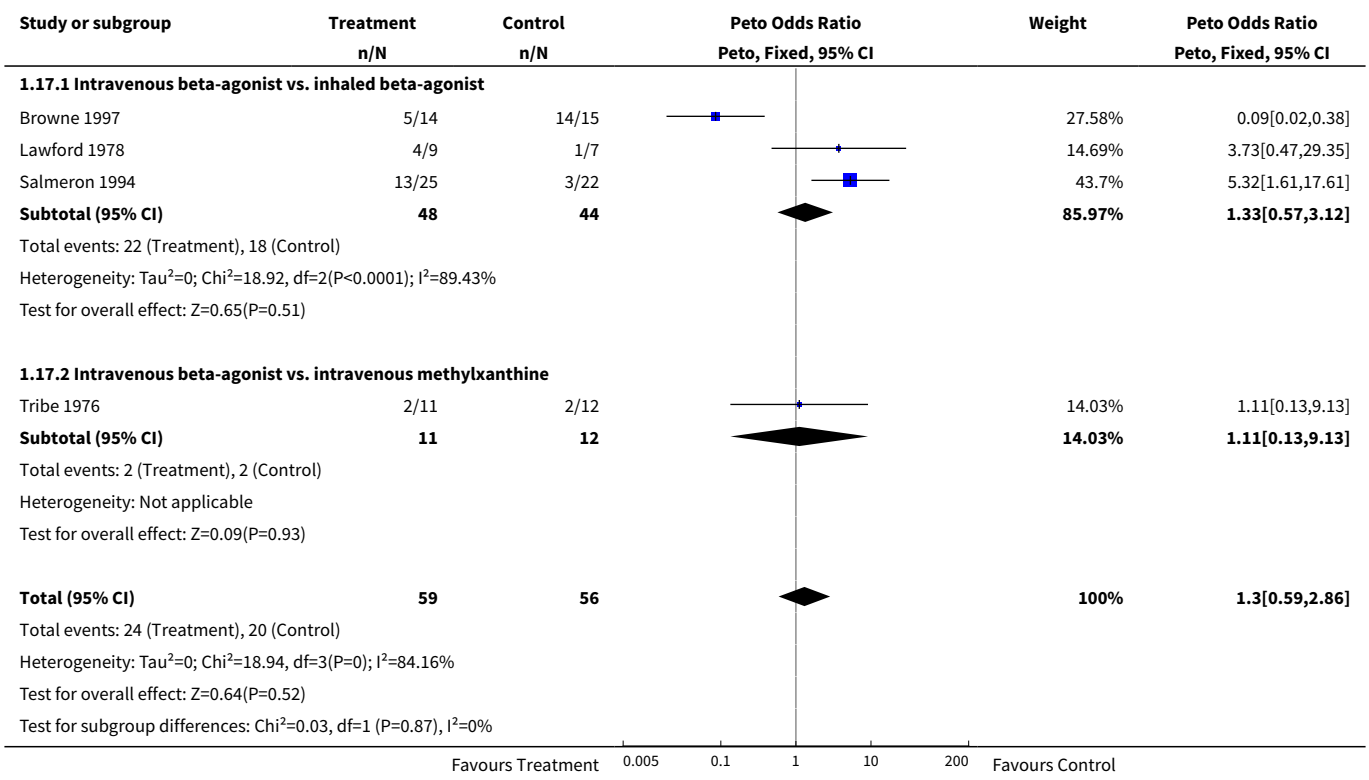
Analysis 1.16. Comparison 1 IV vs. All Treatments, Outcome 16 Autonomic Side Effects.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.16.1 Intravenous beta-agonist vs. inhaled beta-agonist					
Bloomfield 1979	4/10	0/10		4.69%	10.75[1.27,91]
Cheong 1988	2/37	0/34		2.74%	7.01[0.43,114.55]
Lawford 1978	4/9	0/6		4.2%	8.34[0.87,79.67]
Swedish Society 1990	40/89	73/87		56.65%	0.19[0.1,0.34]
Williams 1981	3/8	3/7		5.35%	0.81[0.11,6]
Subtotal (95% CI)	**153**	**144**		**73.64%**	**0.38[0.22,0.65]**
Total events: 53 (Treatment), 76 (Control)					
Heterogeneity: Tau^2=0; Chi^2=26.58, df=4(P<0.0001); I^2=84.95%					
Test for overall effect: Z=3.52(P=0)					
1.16.2 Intravenous beta-agonist vs. intravenous methylxanthine					
Sharma 1 1984	9/10	4/10		6.67%	8.07[1.35,48.38]
Sharma 2 1984	8/10	4/10		7.04%	4.87[0.85,27.86]
Tribe 1976	3/11	2/12		5.69%	1.82[0.26,12.63]
Williams 1975	5/11	7/9		6.97%	0.28[0.05,1.61]
Subtotal (95% CI)	**42**	**41**		**26.36%**	**2.1[0.85,5.17]**
Total events: 25 (Treatment), 17 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.19, df=3(P=0.04); I^2=63.39%					
Test for overall effect: Z=1.61(P=0.11)					
Total (95% CI)	**195**	**185**		**100%**	**0.6[0.38,0.95]**
Total events: 78 (Treatment), 93 (Control)					





Analysis 1.17. Comparison 1 IV vs. All Treatments, Outcome 17 Clinical Failure.



Comparison 2. % Predicted PEFR Trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 % pred PEFR at 1 hour	3	109	Mean Difference (IV, Random, 95% CI)	-1.42 [-7.00, 4.16]
2 % pred PEFR at 2 hours	2	95	Mean Difference (IV, Random, 95% CI)	-2.64 [-6.14, 0.86]
3 % pred PEFR at 3 hours	2	86	Mean Difference (IV, Random, 95% CI)	-6.85 [-17.03, 3.33]
4 % pred PEFR at 6 hours	2	86	Mean Difference (IV, Random, 95% CI)	-8.75 [-17.90, 0.39]

Analysis 2.1. Comparison 2 % Predicted PEFR Trials, Outcome 1 % pred PEFR at 1 hour.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cheong 1988	37	-31 (6.9)	35	-32 (9.1)		62.57%	1[-2.75,4.75]
Hussein 1986	7	-42 (15.1)	7	-31 (10.4)		14.14%	-11[-24.58,2.58]
Van Renterghem 1987	11	-21.3 (12.1)	12	-19.2 (12.1)		23.29%	-2.1[-12,7.8]
Total ***	**55**		**54**			**100%**	**-1.42[-7,4.16]**

Heterogeneity: Tau^2=9.31; Chi^2=2.96, df=2(P=0.23); I^2=32.48%

Test for overall effect: Z=0.5(P=0.62)

Analysis 2.2. Comparison 2 % Predicted PEFR Trials, Outcome 2 % pred PEFR at 2 hours.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cheong 1988	37	-34 (6.9)	35	-32 (9.1)		87.47%	-2[-5.75,1.75]
Van Renterghem 1987	11	-28.2 (12.1)	12	-21.1 (12.1)		12.53%	-7.1[-17,2.8]
Total ***	**48**		**47**			**100%**	**-2.64[-6.14,0.86]**

Heterogeneity: Tau^2=0; Chi^2=0.89, df=1(P=0.34); I^2=0%

Test for overall effect: Z=1.48(P=0.14)

Analysis 2.3. Comparison 2 % Predicted PEFR Trials, Outcome 3 % pred PEFR at 3 hours.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cheong 1988	37	-36.9 (6.9)	35	-33.1 (9.1)		74.37%	-3.8[-7.55,-0.05]
Hussein 1986	7	-46.7 (21.6)	7	-31 (6.5)		25.63%	-15.7[-32.41,1.01]
Total ***	**44**		**42**			**100%**	**-6.85[-17.03,3.33]**

Heterogeneity: Tau^2=32.64; Chi^2=1.85, df=1(P=0.17); I^2=46.09%

Test for overall effect: Z=1.32(P=0.19)

Analysis 2.4. Comparison 2 % Predicted PEFR Trials, Outcome 4 % pred PEFR at 6 hours.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cheong 1988	37	-40.4 (6.9)	35	-34 (9.1)		79.72%	-6.4[-10.15,-2.65]
Hussein 1986	7	-54 (21.6)	7	-36 (10.9)		20.28%	-18[-35.92,-0.08]
Total ***	**44**		**42**			**100%**	**-8.75[-17.9,0.39]**

Heterogeneity: Tau^2=23.64; Chi^2=1.54, df=1(P=0.21); I^2=35.14%

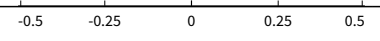
Test for overall effect: Z=1.88(P=0.06)

Comparison 3. FEV1 Trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L) at 15 minutes	2	59	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.11, 0.09]
2 FEV1 (L) at 1 hour	4	87	Mean Difference (IV, Random, 95% CI)	0.01 [-0.16, 0.17]
3 FEV1 (L) at 3 hours	2	59	Mean Difference (IV, Random, 95% CI)	0.04 [-0.15, 0.24]

Analysis 3.1. Comparison 3 FEV1 Trials, Outcome 1 FEV1 (L) at 15 minutes.

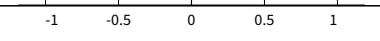
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Johnson 1978	20	-0.8 (0.2)	19	-0.8 (0.2)		64.87%	-0.03[-0.15,0.09]
Sharma 1 1984	10	-0.8 (0.2)	10	-0.9 (0.2)		35.13%	0.02[-0.15,0.19]
Total ***	**30**		**29**			**100%**	**-0.01[-0.11,0.09]**
Heterogeneity: Tau^2=0; Chi^2=0.22, df=1(P=0.64); I^2=0%							
Test for overall effect: Z=0.25(P=0.8)							



Favours Treatment — Favours Control

Analysis 3.2. Comparison 3 FEV1 Trials, Outcome 2 FEV1 (L) at 1 hour.

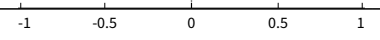
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Johnson 1978	20	-0.8 (0.3)	19	-0.9 (0.4)		33.9%	0.14[-0.08,0.36]
Lawford 1978	7	-1.1 (0.5)	6	-0.7 (0.2)		12.79%	-0.35[-0.77,0.07]
Sharma 1 1984	10	-0.9 (0.3)	10	-0.9 (0.3)		25%	0.01[-0.26,0.28]
Williams 1981	8	-0.9 (0.3)	7	-0.9 (0.2)		28.3%	0[-0.25,0.25]
Total ***	**45**		**42**			**100%**	**0.01[-0.16,0.17]**
Heterogeneity: Tau^2=0.01; Chi^2=4.25, df=3(P=0.24); I^2=29.42%							
Test for overall effect: Z=0.06(P=0.95)							



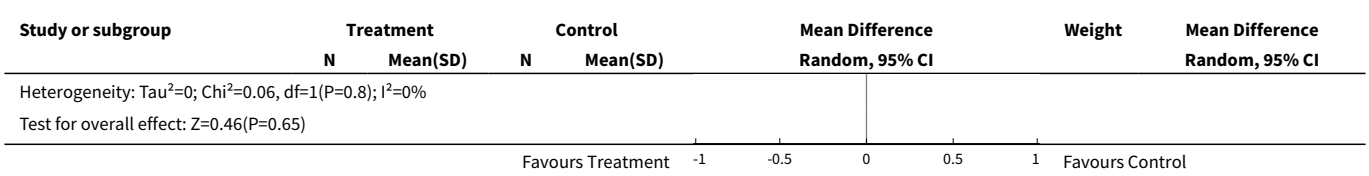
Favours Treatment — Favours Control

Analysis 3.3. Comparison 3 FEV1 Trials, Outcome 3 FEV1 (L) at 3 hours.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Johnson 1978	20	-1 (0.4)	19	-1 (0.5)		49.58%	0.07[-0.2,0.34]
Sharma 1 1984	10	-0.9 (0.3)	10	-0.9 (0.3)		50.42%	0.02[-0.25,0.29]
Total ***	**30**		**29**			**100%**	**0.04[-0.15,0.24]**



Favours Treatment — Favours Control



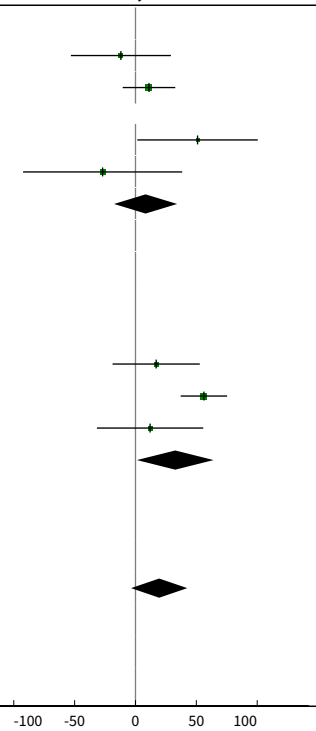
Comparison 4. Comparison by Quality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PEFR (l/min) at 60 minutes	7	396	Mean Difference (IV, Random, 95% CI)	19.47 [-3.63, 42.57]
1.1 Strong Methodological Quality	4	158	Mean Difference (IV, Random, 95% CI)	8.30 [-17.63, 34.22]
1.2 Weak Methodological Quality	3	238	Mean Difference (IV, Random, 95% CI)	32.67 [1.18, 64.16]
2 PEFR (l/min) at 120 minutes	4	290	Mean Difference (IV, Random, 95% CI)	16.91 [-18.60, 52.42]
2.1 Strong Methodological Quality	2	91	Mean Difference (IV, Random, 95% CI)	-1.27 [-21.42, 18.88]
2.2 Weak Methodological Quality	2	199	Mean Difference (IV, Random, 95% CI)	27.22 [-28.19, 82.63]
3 PEFR (l/min) Final	6	363	Mean Difference (IV, Random, 95% CI)	13.89 [-17.37, 45.16]
3.1 Strong Methodological Quality	3	125	Mean Difference (IV, Random, 95% CI)	-10.76 [-32.84, 11.33]
3.2 Weak Methodological Quality	3	238	Mean Difference (IV, Random, 95% CI)	27.24 [-6.20, 60.69]
4 Heart Rate at 60 minutes	8	419	Mean Difference (IV, Random, 95% CI)	2.81 [-3.90, 9.52]
4.1 Strong Methodological Quality	5	181	Mean Difference (IV, Random, 95% CI)	4.89 [-1.08, 10.86]
4.2 Weak Methodological Quality	3	238	Mean Difference (IV, Random, 95% CI)	-0.69 [-13.41, 12.03]
5 Heart Rate at 120 minutes	6	350	Mean Difference (IV, Random, 95% CI)	3.95 [-6.85, 14.76]
5.1 Strong Methodological Quality	4	151	Mean Difference (IV, Random, 95% CI)	8.92 [1.38, 16.45]
5.2 Weak Methodological Quality	2	199	Mean Difference (IV, Random, 95% CI)	-4.44 [-19.03, 10.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Autonomic Side Effects	7	360	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.25, 0.68]
6.1 Strong Methodological Quality	5	169	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.23 [0.88, 5.66]
6.2 Weak Methodological Quality	2	191	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.12, 0.38]
7 Clinical Failure	5	291	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.93 [2.39, 6.46]
7.1 Strong Methodological Quality	4	115	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.59, 2.86]
7.2 Weak Methodological Quality	1	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.11 [4.28, 15.36]

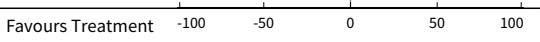
Analysis 4.1. Comparison 4 Comparison by Quality, Outcome 1 PEFR (l/min) at 60 minutes.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.1.1 Strong Methodological Quality							
Bloomfield 1979	10	-137 (45.9)	10	-125 (47.8)		13.43%	-12[-53.07,29.07]
Cheong 1988	37	-137.9 (37.2)	34	-149 (53.4)		19.38%	11.1[-10.48,32.68]
Salmeron 1994	25	-123 (82)	22	-174 (90)		11.27%	51[1.53,100.47]
Williams 1975	11	-161 (85)	9	-134 (64)		8.14%	-27[-92.36,38.36]
Subtotal ***	**83**		**75**			**52.21%**	**8.3[-17.63,34.22]**
Heterogeneity: Tau^2=277.75; Chi^2=4.97, df=3(P=0.17); I^2=39.69%							
Test for overall effect: Z=0.63(P=0.53)							
4.1.2 Weak Methodological Quality							
Johnson 1978	20	-133 (46.1)	19	-150 (65.8)		14.94%	17[-18.83,52.83]
Swedish Society 1990	89	-200 (58.5)	87	-256.2 (70)		20.13%	56.2[37.12,75.28]
Van Renterghem 1987	11	-99 (40.8)	12	-111 (64.4)		12.72%	12[-31.69,55.69]
Subtotal ***	**120**		**118**			**47.79%**	**32.67[1.18,64.16]**
Heterogeneity: Tau^2=501.78; Chi^2=5.8, df=2(P=0.06); I^2=65.49%							
Test for overall effect: Z=2.03(P=0.04)							
Total ***	**203**		**193**			**100%**	**19.47[-3.63,42.57]**
Heterogeneity: Tau^2=595.53; Chi^2=18.81, df=6(P=0); I^2=68.11%							
Test for overall effect: Z=1.65(P=0.1)							
Test for subgroup differences: Chi^2=1.37, df=1 (P=0.24), I^2=27.1%							



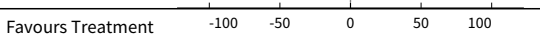
Analysis 4.2. Comparison 4 Comparison by Quality, Outcome 2 PEFR (l/min) at 120 minutes.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.2.1 Strong Methodological Quality							
Bloomfield 1979	10	-157 (57.5)	10	-177 (70.2)		18.32%	20[-36.24,76.24]
Cheong 1988	37	-152.4 (37.2)	34	-148 (53.4)		30.12%	-4.4[-25.98,17.18]
Subtotal ***	**47**		**44**			**48.43%**	**-1.27[-21.42,18.88]**
Heterogeneity: Tau^2=0; Chi^2=0.63, df=1(P=0.43); I^2=0%							
Test for overall effect: Z=0.12(P=0.9)							
4.2.2 Weak Methodological Quality							
Swedish Society 1990	89	-227.9 (67.9)	87	-279.4 (67.1)		30.62%	51.5[31.56,71.44]
Van Renterghem 1987	11	-127.7 (65.4)	12	-122 (50.1)		20.95%	-5.7[-53.63,42.23]
Subtotal ***	**100**		**99**			**51.57%**	**27.22[-28.19,82.63]**
Heterogeneity: Tau^2=1285.14; Chi^2=4.66, df=1(P=0.03); I^2=78.56%							
Test for overall effect: Z=0.96(P=0.34)							
Total ***	**147**		**143**			**100%**	**16.91[-18.6,52.42]**
Heterogeneity: Tau^2=968.42; Chi^2=15.42, df=3(P=0); I^2=80.55%							
Test for overall effect: Z=0.93(P=0.35)							
Test for subgroup differences: Chi^2=0.9, df=1 (P=0.34), I^2=0%							



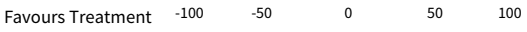
Analysis 4.3. Comparison 4 Comparison by Quality, Outcome 3 PEFR (l/min) Final.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.3.1 Strong Methodological Quality							
Bloomfield 1979	10	-157 (57.5)	10	-177 (70.2)		13.48%	20[-36.24,76.24]
Cheong 1988	37	-180.5 (37.2)	34	-161.2 (53.4)		21.45%	-19.3[-40.88,2.28]
Salmeron 1994	12	-240 (115)	22	-254 (90)		10.04%	14[-61.15,89.15]
Subtotal ***	**59**		**66**			**44.97%**	**-10.76[-32.84,11.33]**
Heterogeneity: Tau^2=43.61; Chi^2=2.14, df=2(P=0.34); I^2=6.61%							
Test for overall effect: Z=0.95(P=0.34)							
4.3.2 Weak Methodological Quality							
Johnson 1978	20	-148 (46.1)	19	-168 (68.4)		17.95%	20[-16.8,56.8]
Swedish Society 1990	89	-227.9 (67.9)	87	-279.4 (67.1)		21.78%	51.5[31.56,71.44]
Van Renterghem 1987	11	-127.7 (65.4)	12	-122 (50.1)		15.3%	-5.7[-53.63,42.23]
Subtotal ***	**120**		**118**			**55.03%**	**27.24[-6.2,60.69]**
Heterogeneity: Tau^2=567.64; Chi^2=5.87, df=2(P=0.05); I^2=65.93%							
Test for overall effect: Z=1.6(P=0.11)							
Total ***	**179**		**184**			**100%**	**13.89[-17.37,45.16]**
Heterogeneity: Tau^2=1065.08; Chi^2=23.26, df=5(P=0); I^2=78.51%							
Test for overall effect: Z=0.87(P=0.38)							
Test for subgroup differences: Chi^2=3.45, df=1 (P=0.06), I^2=71.05%							



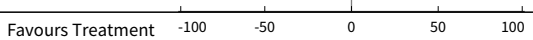
Analysis 4.4. Comparison 4 Comparison by Quality, Outcome 4 Heart Rate at 60 minutes.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.4.1 Strong Methodological Quality							
Bloomfield 1979	10	129 (12.2)	10	118 (19)		9.96%	11[-2.99,24.99]
Cheong 1988	37	114 (17)	34	106 (15)		14.45%	8[0.56,15.44]
Salmeron 1994	25	122 (18)	22	115 (19)		12.2%	7[-3.62,17.62]
Tribe 1976	11	101 (9.3)	12	106.6 (12.2)		13.48%	-5.6[-14.42,3.22]
Williams 1975	11	126 (14)	9	119 (11)		11.97%	7[-3.96,17.96]
Subtotal ***	**94**		**87**			**62.06%**	**4.89[-1.08,10.86]**
Heterogeneity: Tau²=19.94; Chi²=7.12, df=4(P=0.13); I²=43.8%							
Test for overall effect: Z=1.61(P=0.11)							
4.4.2 Weak Methodological Quality							
Johnson 1978	20	115.4 (16.5)	19	108 (15.3)		12.65%	7.4[-2.58,17.38]
Swedish Society 1990	89	95 (14.1)	87	105 (19.6)		15.98%	-10[-15.05,-4.95]
Van Renterghem 1987	11	117 (19.9)	12	114 (16.7)		9.31%	3[-12.09,18.09]
Subtotal ***	**120**		**118**			**37.94%**	**-0.69[-13.41,12.03]**
Heterogeneity: Tau²=99.33; Chi²=10.68, df=2(P=0); I²=81.27%							
Test for overall effect: Z=0.11(P=0.92)							
Total ***	**214**		**205**			**100%**	**2.81[-3.9,9.52]**
Heterogeneity: Tau²=66.67; Chi²=28.79, df=7(P=0); I²=75.68%							
Test for overall effect: Z=0.82(P=0.41)							
Test for subgroup differences: Chi²=0.6, df=1 (P=0.44), I²=0%							

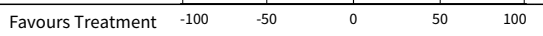


Analysis 4.5. Comparison 4 Comparison by Quality, Outcome 5 Heart Rate at 120 minutes.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.5.1 Strong Methodological Quality							
Bloomfield 1979	10	118 (18.9)	10	123 (9.8)		15.13%	-5[-18.2,8.2]
Browne 1997	14	152 (18.9)	15	142 (14)		15.66%	10[-2.17,22.17]
Cheong 1988	37	113 (17)	34	101 (14)		17.97%	12[4.78,19.22]
Salmeron 1994	12	126 (15)	19	111 (16)		16.19%	15[3.87,26.13]
Subtotal ***	**73**		**78**			**64.94%**	**8.92[1.38,16.45]**
Heterogeneity: Tau²=29.34; Chi²=6.03, df=3(P=0.11); I²=50.24%							
Test for overall effect: Z=2.32(P=0.02)							
4.5.2 Weak Methodological Quality							
Swedish Society 1990	89	94 (15.1)	87	105 (14)		18.95%	-11[-15.3,-6.7]
Van Renterghem 1987	11	114 (14.3)	12	110 (13.2)		16.11%	4[-7.28,15.28]
Subtotal ***	**100**		**99**			**35.06%**	**-4.44[-19.03,10.14]**
Heterogeneity: Tau²=93.54; Chi²=5.93, df=1(P=0.01); I²=83.14%							
Test for overall effect: Z=0.6(P=0.55)							
Total ***	**173**		**177**			**100%**	**3.95[-6.85,14.76]**
Heterogeneity: Tau²=155.58; Chi²=45.21, df=5(P<0.0001); I²=88.94%							

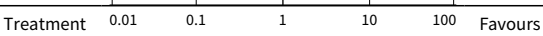


Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=0.72(P=0.47)							
Test for subgroup differences: Chi²=2.55, df=1 (P=0.11), I²=60.72%							



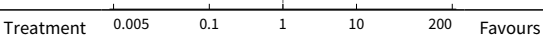
Analysis 4.6. Comparison 4 Comparison by Quality, Outcome 6 Autonomic Side Effects.

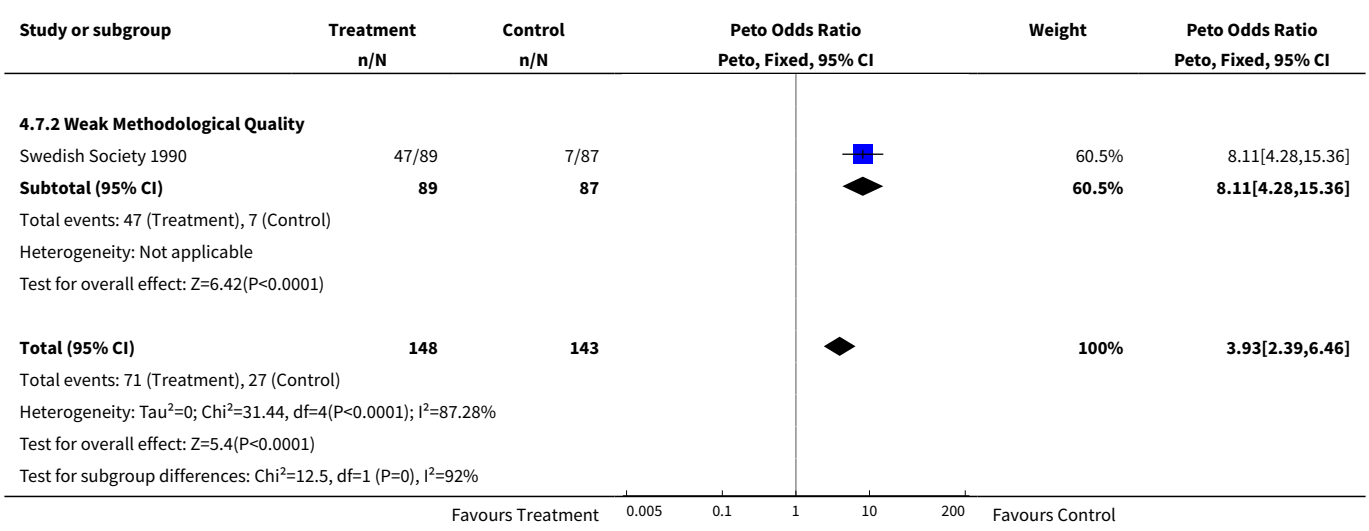
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
4.6.1 Strong Methodological Quality					
Bloomfield 1979	4/20	0/20		5.93%	8.73[1.14,67.13]
Cheong 1988	2/37	0/34		3.16%	7.01[0.43,114.55]
Lawford 1978	4/9	0/6		4.84%	8.34[0.87,79.67]
Tribe 1976	3/11	2/12		6.56%	1.82[0.26,12.63]
Williams 1975	5/11	7/9		8.03%	0.28[0.05,1.61]
Subtotal (95% CI)	**88**	**81**		**28.52%**	**2.23[0.88,5.66]**
Total events: 18 (Treatment), 9 (Control)					
Heterogeneity: Tau²=0; Chi²=9.14, df=4(P=0.06); I²=56.22%					
Test for overall effect: Z=1.69(P=0.09)					
4.6.2 Weak Methodological Quality					
Swedish Society 1990	40/89	73/87		65.31%	0.19[0.1,0.34]
Williams 1981	3/8	3/7		6.17%	0.81[0.11,6]
Subtotal (95% CI)	**97**	**94**		**71.48%**	**0.21[0.12,0.38]**
Total events: 43 (Treatment), 76 (Control)					
Heterogeneity: Tau²=0; Chi²=1.91, df=1(P=0.17); I²=47.77%					
Test for overall effect: Z=5.2(P<0.0001)					
Total (95% CI)	**185**	**175**		**100%**	**0.41[0.25,0.68]**
Total events: 61 (Treatment), 85 (Control)					
Heterogeneity: Tau²=0; Chi²=28.75, df=6(P<0.0001); I²=79.13%					
Test for overall effect: Z=3.49(P=0)					
Test for subgroup differences: Chi²=17.7, df=1 (P<0.0001), I²=94.35%					



Analysis 4.7. Comparison 4 Comparison by Quality, Outcome 7 Clinical Failure.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
4.7.1 Strong Methodological Quality					
Browne 1997	5/14	14/15		10.89%	0.09[0.02,0.38]
Lawford 1978	4/9	1/7		5.8%	3.73[0.47,29.35]
Salmeron 1994	13/25	3/22		17.26%	5.32[1.61,17.61]
Tribe 1976	2/11	2/12		5.54%	1.11[0.13,9.13]
Subtotal (95% CI)	**59**	**56**		**39.5%**	**1.3[0.59,2.86]**
Total events: 24 (Treatment), 20 (Control)					
Heterogeneity: Tau²=0; Chi²=18.94, df=3(P=0); I²=84.16%					
Test for overall effect: Z=0.64(P=0.52)					





WHAT'S NEW

Date	Event	Description
7 February 2012	Review declared as stable	This review is no longer being updated as it is out of date. The review is being replaced by two new reviews with the titles "Intravenous beta2-agonists versus intravenous aminophylline for acute asthma" and "Addition of intravenous beta2-agonists to inhaled beta2-agonists for acute asthma".

HISTORY

Protocol first published: Issue 2, 1997
Review first published: Issue 4, 2000

Date	Event	Description
1 August 2008	Amended	Converted to new review format.
14 October 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Travers A: Initiated the review, wrote the protocol, performed searches, performed quality assessments, entered data and performed analysis, and primary author of review.
Jones AP: study selection, quality assessment, review of protocol.
Kelly KD: data extraction, entry and review.
Barker SJ: data extraction, entry and review.
Camargo CA Jr: Protocol development, methodological input, statistical support, manuscript review.
Rowe BH: Co-authored protocol, performed selection for inclusion and quality assessment, data extraction and data entry, manuscript review, conversion to RevMan 4, and assigned editor for ARG.

DECLARATIONS OF INTEREST

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

SOURCES OF SUPPORT

Internal sources

- University of Alberta, Faculty of Medicine & Dentistry, Canada.
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- NHS Research and Development, UK.

External sources

- Canadian Association of Emergency Physicians (CAEP), Canada.
- National Heart, Lung and Blood Institute (HL-03533 NIH; CA Camargo, Jr), USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Adrenergic beta-Agonists [*therapeutic use]; Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy]; Emergencies; Emergency Service, Hospital; Injections, Intravenous; Randomized Controlled Trials as Topic

MeSH check words

Humans