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Review Article

Comparison of Salbutamol and Intravenous Aminophylline in Acute Severe Asthma in the Paediatric Population

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Abstract

Introduction: Acute severe asthma presenting in the paediatric population is a medical emergency. The British Thoracic Society (BTS) recommends salbutamol as first line therapy. Intravenous (IV) aminophylline has been shown to be of clinical importance.

Methods: A systematic review of literature was conducted using Cochrane Library, MEDLINE and EMBASE. Using a PICO question, the authors compared clinical outcomes of salbutamol and intravenous aminophylline.

Results/Evidence synthesis: 3 studies were included in the review. They were a Cochrane review of randomised controlled trials (RCTs) and two RCTs. The studies demonstrated that IV aminophylline is as effective as salbutamol in the treatment of children with acute severe asthma in hospital.

Lay Summary/Conclusion: Either IV aminophylline or salbutamol can be used as first line therapy in acute severe asthma in the paediatric population.

Level of Evidence: 1.

Keywords: Salbutamol; Aminophylline; Asthma

Clinical question

Compared to IV aminophylline, does IV salbutamol result in a better outcome in the treatment of acute severe asthma in children?

- P = Children with acute severe asthma attack in hospital
- I = Salbutamol
- C = Intravenous aminophylline
- O = Better outcome (e.g. length of stay in hospital).

Search strategy

Embase 1974 to 2014 week 41, Medline 1950 to present and Cochrane databases were searched for relevant articles using both text words and MeSH terms. The databases: Cochrane, Embase and Medline produced 33, 56 and 42 results respectively. The table below shows a modified version of the search strategy used for the Medline database, no language restriction was set for these search strategies.

#	Searches	Hits
1	beta-2-agonist/ad, tu	614
2	salbutamol*.tw	6231
3	aminophylline*.tw	3311
4	exp asthma/de, dt, tu, th	45064
5	asthma*.tw	119012
6	severe.tw	622383
7	acute.tw	837092
8	1 or 2	6782
9	4 or 5	126059
10	3 and 6 and 7 and 8 and 9	42

Table 1: Search criteria.

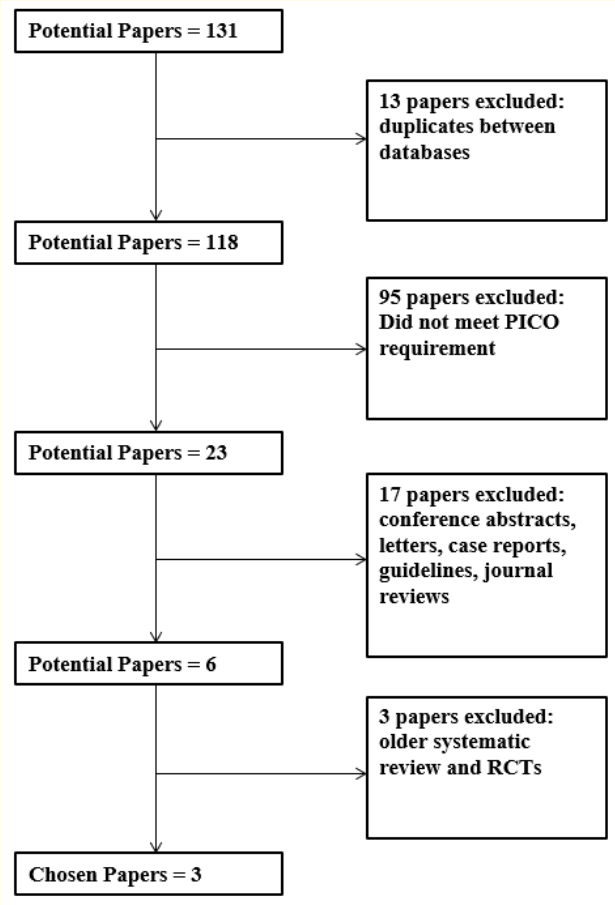

Figure 1: Flow diagram of search criteria.

Justification of the papers selected

The first paper (a Cochrane review) was selected as it was the most recent and relevant systematic review retrieved from the search. Systematic reviews are the highest in the hierarchy of evidence and therefore, are likely to provide the best data from years of high quality research. Although this review was comparing IV beta-2-agonists to IV aminophylline, it fulfilled most of the criteria for my PICO, as salbutamol is a member of the beta-2-agonist family. Also, the review has a subgroup analysis based on the type of beta-2-agonist used and also of paediatric versus adult population.

The second and third papers selected are both randomised controlled trials (RCTs). The evidence they provide will be second only to evidence from systematic reviews with regards to addressing the question from the clinical scenario. Paper 2 fulfilled all the criteria for my PICO; while paper 3 fulfilled all of the criteria for my PICO it compared IV salbutamol bolus to IV aminophylline infusion in children with acute severe asthma.

Paper 1

Travers AH., *et al*. 2012 [1]

Summary

This paper is a systematic review set out to compare the benefits of IV beta-2-agonists to IV aminophylline in patients with acute severe asthma presenting to hospital. The primary outcome measures are length of hospital stay and number of hospital admissions, and secondary outcome measures include pulmonary function (measured by FEV_1 and PEF), adverse effects and vital signs.

Only RCTs were included in the review and subjects included adults and children. Studies were identified from the Cochrane Airways Group Specialised Register (CAGR) of trials, which includes references from systematic searches of the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, AMED, CINAHL and PsycINFO databases. ClinicalTrails.gov was also searched as well as hand searching of major respiratory journals and meeting abstracts. There were no restrictions on the language of publication.

References retrieved from the search strategies were assessed separately by two authors and relevant articles identified. 97 potential studies were retrieved with only 11 meeting the inclusion criteria. 4 of these were carried out with paediatric subjects contributing 157 out of the cumulative total of 350 subjects.

Based on length of hospital stay; PEF, FEV_1 and heart rate at 60 minutes, there were no statistically significant differences in the mean difference (MD) between the IV beta-2-agonist group and the IV aminophylline group. MD 23.19 hours (95% CI: -2.4 to 48.77); MD -3.57 L/min (95% CI: -42.86 to 35.36); MD -0.09 L (95% CI: -0.26 to 0.08); MD 2.54 bpm (95% CI: -6.28 to 11.36) for length of hospital stay, PEF, FEV_1 and heart rate respectively. The incidence of adverse effects such as giddiness, nausea/vomiting and nausea were significantly higher in the aminophylline group with the end heart rate significantly raised in the salbutamol group.

The authors concluded that there is no consistent evidence supporting the preferential use of either IV beta-2-agonists or IV aminophylline in acute severe asthma attacks.

Critical appraisal

The authors clearly stated the objectives of the review, employed an extensive and thorough search strategy over a broad range of databases, using a good variety of search terms. To further strengthen the evidence from this review and reduce the potentials of publication bias, they also made inquiries regarding other published and unpublished works known or supported by authors of the primary studies; contacted scientific advisors of the pharmaceutical companies for current published or unpublished results from beta-2-agonists research and made personal contact with colleagues and collaborators in the field of asthma. This ensures that very few articles are left out with most of the available evidence on the subject matter included in the review, making the conclusion from the review more dependable.

To decrease selection bias and further improve the authority of the conclusion that may be drawn from this review, two authors independently assessed all the potential papers retrieved for inclusion or exclusion based on clearly stated inclusion criteria. This helps to ensure that only high quality papers are included in the study without the prejudice that may be associated with a single author doing this.

The studies were combined using RevMan 2011 software. However, few studies reported similar outcome measures and the heterogeneity of variables limited data collection and comparisons between studies. This can potentially weaken the strength of the evidence from the study, as it may be difficult to combine and detect the cumulative effect of treatment on specific outcome measures since the studies are reporting different outcome measures.

The review authors were not blinded to journal of publication, authors and results from the studies, as investigator bias was considered unlikely. However, I think this can potentially introduce selection bias and thus, weaken the strength of the evidence from the review because the review authors for example, can be inclined to recruiting only studies done by colleagues and friends.

Two review authors carefully assessed the methodological quality of each of the included studies independently. The risk of bias was assessed using the Cochrane Collaboration's risk of bias methodology, and specifically, they assessed the risk of bias with regards to random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting in all the included studies. This strengthens the evidence from the review as a thorough approach to bias minimisation has been used.

As only four of the included RCTs were done with children, one can argue that the results of this review may not be generalizable to paediatric patients. However, about 45% of total number of patients included in the review were children so I am happy to extend the conclusion from the review to my PICO question, although cautiously.

Also, the review authors mentioned that they were going to carry out a subgroup analysis based on the type of beta-2-agonist used. However, none of the paediatric studies was used for this analysis, which weakens the evidence from the review with respect to answering my PICO question, as I am particularly interested in the comparison between IV salbutamol and IV aminophylline in children with acute severe asthma. Furthermore, one of the primary outcome measures (number of hospital admissions) was not reported by any of the included RCTs, further weakening the evidence from this review.

During the analysis of the outcome measures, length of stay in hospital is the only outcome measure which the review authors used data exclusively from the paediatric studies. This weakens the strength of the evidence from the review in terms of its applicability to paediatric patients as the vast majority of the stated outcome measures were analysed using data from adult patients only.

Paper 2

Hambleton G, 1979 [2]

Summary

This is a double blind prospective RCT involving subjects aged between 18 months to 7 years admitted to hospital with acute uncontrolled asthma. To be included, a child must be significantly ill clinically, to the point of requiring intensive hospital treatment. 18 children were recruited to the study and were randomly allocated to double blind treatment, of either 4 ug/kg immediately, then 0.6 ug/kg per hour continuously for 24 hours of IV salbutamol or 4 mg/kg immediately, then 0.6 mg/kg per hour continuously for 24 hours of IV aminophylline using the random number tables. Two hours following the start of the initial intervention, all children were offered oxygen via facemasks and also received 4 mg/kg immediately and 2 mg/kg per hour continuously of hydrocortisone

for 24 hours. The outcome measures are clinical signs, pulse rate and respiratory rate all assessed at 1, 2, 4, 6, 12, 18 and 24 hours.

Employing the student's t-test, no statistically significant difference was found between the IV salbutamol and IV aminophylline groups. There was relative tachycardia at 18 and 24 hours in the IV salbutamol arm.

Critical appraisal

This RCT met all the criteria for answering my PICO question as the authors set out to compare IV salbutamol to IV aminophylline in the treatment of children with acute severe asthma. Although this was a relatively old study and may not meet the strict criteria for the publication of RCTs today, it was included in the Cochrane review by Travers AH., *et al* [1]. Of note worthy in this study is the fact that there were no p-values and confidence intervals in the results stated, hence, reliance on these results for answering by PICO question might be an issue. However, a student's t-test was carried out to show the statistical significance of the results obtained which increases the confidence I have on the evidence from the study.

The authors stated that allocation and randomisation were done using random number tables, which decreases selection bias therefore, strengthening the reliability of the evidence. However, it is not clear if allocation concealment was adequately carried out, this may mean that investigators may be aware of the randomisation sequence and treatment allocation. Therefore, they may want to manipulate subjects' treatment based on prognosis, which may weaken the strength of the evidence.

The trial was described as 'double blind' even if it was not exactly clear who was blinded. If successfully done, it means that patients and researchers were blinded to the intervention, which reduces the possibility of performance and detection biases, strengthening the evidence from the trial with regards to answering my pico.

The study was conducted in one hospital with a small sample size of 18 subjects. Also, no sample size calculation was done, so the power and smallest expected change in outcome was not determined or documented. This limits the generalizability and authority from the conclusion of the study. A larger sample size with priori sample size analysis will provide better evidence.

All the subjects recruited for the trial completed the treatment and so there was no loss to follow up bias in this study, which further strengthens the evidence from the study. There was no mention of any intention to treat (ITT) analysis in the study. This is can result in attrition bias further weakening the evidence form this study. However, this may not be a problem as all participants were accounted for at the end of the study.

Paper 3

Roberts G., *et al*. 2003 [3]

Summary

This study is an RCT, which recruited subjects aged 1 to 16 years with acute severe asthma from 5 district general hospitals in the North West Thames region. The aims and objectives of the study was clearly stated and subjects were included if they presented with acute severe asthma and have responded poorly to a well defined standard therapy over a 1 hour period. A very clear definition of 'poor response' was given. Potential participants were excluded if they had: a life threatening exacerbation, any respiratory disease other than asthma, cardiac disease, or are treated with drugs that affect the metabolism of aminophylline.

44 subjects were recruited they were randomly allocated to receive either a single bolus of intravenous salbutamol (15 μg/kg over 20 minutes) followed by an infusion of saline or a continuous aminophylline infusion (bolus of 5 mg/kg over 20 minutes followed by an infusion of 0.9 mg/kg/h). 18 subjects received the salbutamol treatment while 26 got aminophylline.

The primary outcome measure is asthma severity scale (ASS) score; other outcome measures are length of hospital stay and supplemental oxygen requirement. Families gave a written consent and the Thames Multicentre Research ethics committee and the local ethics committee approved the study.

There was no statistically significant difference in the ASS between both arms of the trial before and 24 hours after the commencement of IV treatment. The mean difference in the change in the ASS at 2 hours between the two groups was –0.08 (95% CI: –0.97 to 0.80). Participants in the salbutamol group were more likely ($p = 0.07$) to have a longer duration of supplementary oxygen therapy (17.8 hours (95% CI 8.5 to 37.5) v 7.0 hours (95% CI 3.4 to 14.2)) a significantly ($p = 0.02$) longer length of hospital stay (85.4 (95% CI 66.1 to 110.2) hours v 57.3 hours (95% CI 45.6 to 72.0)). The authors suggested in their conclusion that in children with acute severe asthma, there is no statistically significant difference in the effectiveness of IV salbutamol bolus compared to IV infusion of aminophylline at 2 hours following onset of treatment. Although aminophylline was found to significantly reduce the length of stay in hospital.

Critical appraisal

A suitable method of randomisation, allocation concealment and double blinding was employed by the authors to reduce the likelihood of selection, performance and measurement bias that may adversely affect the strength of the evidence from the study. To achieve this, participants were randomly assigned to either the salbutamol or aminophylline group using a random number table; the treatment packs were identical and visibly numbered and prepared by the pharmacy department of one of the hospitals; and only one investigator with no involvement in the enrolment or care of participants was aware of treatment allocation. This strengthens the evidence from the study and improves its applicability to answering my pico question.

Sample size calculation was done and showed that data from 42 subjects was adequate to detect a 30% difference in ASS, 90% power and a 5% significance level. The sample size for the trial is 44, which increases the confidence I have in the conclusions from the trial.

Eligibility and exclusion criteria were well defined and there was no significant difference in the baseline demographics of participants, meaning that any changes in outcome measures observed would have been almost exclusively due to the treatment administered and not as a result of any confounders, therefore strengthening the validity of the evidence from the study.

There were three dropouts from study with well-documented reasons. This could potentially introduce attrition bias. An intention-to-treat analysis was performed and this means that participants are assessed according to the group they were randomly assigned irrespective of whether or not they completed treatment. This minimises attrition bias and increases the confidence I have on this study in addressing my pico.

One investigator who was not privy to the participants' treatment allocation carefully, accurately and precisely measured all outcome measures thereby reducing the possibility of inter observer variation in measurements as well reduce likelihood of detection bias, further strengthening the evidence.

Evidence synthesis

All three studies arrived at a similar conclusion and because they were conducted at different time intervals spanning over three decades (1979, 2003, 2012), my confidence in the strength and reliability of the conclusion is reinforced. However, because they were all carried out in a hospital setting, it may be difficult to extend conclusions to other settings, for example general practice.

The Cochrane review was of high quality with only RCTs analysed. In terms of generalizability, especially to children, I will be very cautious as only 4 of the 11 included studies exclusively involved children. The second RCT was old and the authors failed to adequately describe their research and statistical methodology, which reduces my confidence in the results. The last RCT was almost pristinely done so I will be less worried in applying its results even if the comparison was done between IV bolus of salbutamol and IV infusion of aminophylline.

In summary, I am convinced that there is sufficient evidence to arrive at the conclusion that there is no significant benefit of using IV salbutamol in preference to IV aminophylline in the treatment of children with acute severe asthma presenting to hospital.

Lay Summary/Conclusion

There is hardly any evidence that intravenous salbutamol is more effective than intravenous aminophylline in the treatment of children with acute severe asthma in hospital. However, some research has shown that IV aminophylline is associated with increased incidence of nausea, vomiting and giddiness while IV salbutamol may cause a higher heart rate after treatment.

Conflict of Interest

The authors have no conflicts of interest.

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