Continuous vs intermittent beta-agonists in the treatment of acute adult asthma: a systematic review with meta-analysis
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Authors' objectives
To compare continuous with intermittent nebuliser delivery of beta-agonists, in the treatment of adults with acute asthma in emergency departments.

Searching
MEDLINE (from 1966 to 2001), EMBASE (from 1980 to 2001), CINAHL (from 1982 to 2001) and the Cochrane Controlled Trials Register were searched. The search terms were stated. The bibliographies of all identified trials and reviews were screened. Articles published in any language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared the early use of continuous with intermittent nebuliser delivery of beta-agonists were eligible for inclusion. Continuous delivery could include frequent refilling of the nebuliser, use of a nebuliser or infusion pump, or use of a large volume nebuliser with high output extended respiratory therapy (HEART). The included studies used nebulised albuterol with a dose in the first hour ranging from 2.5 to 16 mg. Systemic steroids were used in all of the included studies.

Participants included in the review
Studies of adults (aged 18 years or more) who were treated for acute asthma in the emergency room were eligible for inclusion. The patients in the primary studies included adults with severe acute asthma (pulmonary function tests less than 50% of predicted).

Outcomes assessed in the review
Studies that reported changes in pulmonary function tests as the primary outcome were eligible for inclusion. The studies could assess the absolute or per cent predicted of either the peak expiratory flow rate (PEF) or the forced expiratory volume in one second (FEV1). The secondary outcomes assessed in the review were side-effects and admission to hospital. The review assessed outcomes up to 3 hours of treatment.

How were decisions on the relevance of primary studies made?
Two authors independently screened the titles and abstracts, and selected potentially relevant studies. They then reviewed the full publication of each identified study with respect to the eligibility criteria. Any disagreements were resolved by consensus. The two authors were masked to the authors' names, journal and date of publication. Inter-author agreement was assessed using the Kappa (K) statistic.

Assessment of study quality
Study quality was assessed using the 5-point scale described by Jadad et al. (see Other Publications of Related Interest). This scale assesses the adequacy of randomisation, blinding, and the handling of withdrawals and drop-outs. The authors do not state how the papers were assessed for quality, or how many of the reviewers performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The following information was tabulated in the review: the number of participants, baseline severity of asthma, drug dose and the delivery method used for the drug.

Methods of synthesis
How were the studies combined?
The data were combined in meta-analyses using random-effects models, with weighting by the inverse of the variance. The pooled standardised mean differences (SMDs) and 95% confidence intervals (CIs) were calculated where different units were used to assess the change in pulmonary function tests. The pooled weighted mean differences (WMDs) and 95% CIs were used to pool pulmonary function data when the results were reported using the same units. Hospital admissions were assessed using the pooled relative risks.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the DerSimonian and Laird method, with statistically-significant heterogeneity defined as a p-value of less than 0.01. Forest plots were used to explore heterogeneity graphically. Sensitivity analyses were conducted to explore the influence of the following factors on the results: severity of asthma (PEF or FEV1 less than 50% predicted versus 50% or more of predicted), study quality (Jadad score of 3 or more versus less than 3), and beta-agonist dose (high versus low).

Results of the review
Six RCTs (393 adults) were included in the review.

The inter-author agreement on study selection (K) was 1.0 (i.e. complete agreement). Out of a possible maximum of 5 points for quality, two trials scored 3 and four trials scored 2.

Pulmonary function.
There was no significant difference between continuous and intermittent nebulised albuterol after 1 hour or 2 to 3 hours after the start of treatment. The SMD was -0.15 (95% CI: -0.35, +0.05) at 1 hour and -0.19 (95% CI: -0.39, +0.01) at 2 to 3 hours. No significant heterogeneity was found (p=0.61 and p=0.78, respectively). The WMD in percentage change in FEV1 (4 RCTs) was -1.73 (95% CI: -8.51, +5.05) at 1 hour and -2.18 (95% CI: -6.24, +1.88) at 2 to 3 hours.

Side-effects.
Continuous albuterol significantly decreased the final pulse rate compared with intermittent albuterol. The WMD (5 RCTs) was -6.82 beats/minute (95% CI: -8.67, -3.90). No significant heterogeneity was found (p=0.6). Intermittent albuterol significantly decreased the final serum potassium compared with continuous albuterol: 3.87 versus 3.76 mEq/L. The WMD (2 RCTs) was 0.12 mmol/L (95% CI: 0.01, 0.24). No significant heterogeneity was found (p=0.8). There were insufficient data to assess the other side-effects such as palpitations and tremor.

Hospital admissions.
There was no significant difference between continuous and intermittent nebulised albuterol in hospital admissions. The relative risk (2 RCTs) was 0.68 (95% CI: 0.33, 1.38). No significant heterogeneity was found (p=0.2).

Sensitivity analysis.
There was no significant difference between continuous and intermittent nebulised albuterol when the studies were grouped by severity of asthma, study quality or dose of albuterol. The results these analyses were presented in the review.

Authors’ conclusions
The data indicate that continuous and intermittent nebulised albuterol are equivalent in the treatment of adults with
acute asthma. The authors caution that these results may not apply to patients with life-threatening asthma.

**CRD commentary**
The review question was clear in terms of the study design, intervention, participants and outcomes of interest. A number of relevant electronic databases were searched and the terms used in the search strategy were given. No attempts were made to locate unpublished data and this raises the possibility of publication bias. The study selection process was carried out in duplicate, which helps to reduce bias, but no details were presented of the procedures used to assess quality or extract the data.

Relevant information on the individual studies was tabulated. The data were appropriately combined in a meta-analysis and statistical heterogeneity was assessed. The review found no statistically significant difference in pulmonary function between continuous and intermittent albuterol. This could either mean that the interventions were equivalent, or that the number of patients in the review was too small to detect a difference. Either of these explanations is possible. A more accurate conclusion would be that the available data show no difference between continuous and intermittent nebulised albuterol.

**Implications of the review for practice and research**
Practice: The authors state that the method of delivery should depend upon local circumstances and economic considerations.

Research: The authors did not state any implications for further research.

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