Pilot study of salbutamol in the treatment of acute asthma – Little apparent benefit to dose and frequency adjustments

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STUDY OBJECTIVE: To compare two dosing regimens of salbutamol in acute asthma.

DESIGN: Prospective randomized double-blind trial.

SETTING: Urban emergency department.

TYPE OF PARTICIPANTS: Patients who presented to the emergency department with moderate to severe asthma.

INTERVENTIONS: All patients had pulmonary function testing and were randomized to group A (control; n=25) or group B (experimental; n=23). Group A (control) patients received salbutamol 2.5 mg delivered by wet aerosol at 0, 1 and 2 h (total dose 7.5 mg). At 20, 40, 80 and 100 mins a placebo aerosol was given. Group B patients received salbutamol 5 mg at 0 min and one-third the initial dose every 20 mins for a total of six doses by wet aerosol (total dose 15 mg).

RESULTS: There were no differences in age, sex, preadmission medications or initial forced expiratory volume in 1 s (FEV₁) between the groups. Forty-eight patients completed the study. Both groups of patients improved with mean absolute change in FEV₁ of 700 mL in group A and 590 mL in group B. There were no statistical differences between the two groups in terms of treatment response, admission rates or side effects.

CONCLUSIONS: This study of patients presenting with acute asthma demonstrated no differences in improvement during the initial 3 h of treatment with a standard dose of aerosolized salbutamol given at hourly intervals (total dose 7.5 mg) compared with a higher total dose given at 20 min intervals (total dose 15 mg).

Key Words: Aerosol, Asthma, Dose adjustments, Salbutamol

Étude pilote sur le salbutamol pour le traitement de l’asthme aigu – Peu d’avantages apparents liés à l’ajustement des doses et de la fréquence d’administration

OBJECTIF DE L’ÉTUDE: comparer deux schémas posologiques de salbutamol pour le traitement de l’asthme aigu.

MODÈLE: Essai prospectif à double insu randomisé.

CONTEXTE: Service des Urgences en milieu urbain.

TYPE DES PARTICIPANTS: Patients qui se sont présentés aux Urgences, et qui souffraient d’un asthme modéré à grave.

INTERVENTIONS: Tous les patients ont subi des épreuves de fonction respiratoire et ont été randomisés dans le groupe A (témoin; n=25) ou dans le groupe B (expérimental; n=23). Les patients du groupe témoin ont reçu du salbutamol à raison de 2,5 mg en aérosol à 0, 1 et 2 h (dose totale de 7,5 mg). À 20, 40, 80 et 100 minutes, ces patients ont reçu un placebo en aérosol. Les patients du groupe expérimental ont reçu du salbutamol à raison de 5 mg à 0 min et un tiers de la dose initiale toutes les 20 minutes jusqu’à un total de six doses en aérosol (dose totale de 15 mg).

RÉSULTATS: On a noté aucune différence entre les deux groupes.
The treatment of the asthmatic patient in the emergency department is often a challenging problem because a number of therapies are available. In the asthmatic patient presenting acutely, the initial drug of choice is a beta-agonist. While there is widespread agreement on the indications for use of a beta-agonist in the acute therapy of asthma, there is much controversy on the dose, frequency and route of administration. Recently predose nebulisers of salbutamol have become available containing 2.5 mg of salbutamol in 2.5 mL of total solution. It was our hypothesis that larger doses of aerosolised salbutamol should result in greater bronchodilatation as it has been shown in more stable asthma patients. The following study was designed to evaluate two dosing regimens of salbutamol delivered via a wet aerosol in the treatment of acutely ill asthma patients in the emergency department.

**PATIENTS AND METHODS**

A prospective double-blind study was conducted over a six-month period in 1990 in the emergency department of Victoria General Hospital, Halifax, Nova Scotia, a 600-bed adult tertiary care facility with an emergency census of 46,000 patient-visits per year. Any adult patient over 18 years of age who presented to the emergency department with an acute episode of asthma as defined by the American Thoracic Society was eligible for study. Patients were excluded if they had ischemic heart disease; allergy to salbutamol; evidence of arrhythmia; history of chronic obstructive lung disease; or were unable to cooperate for pulmonary function testing. Informed consent was obtained before study enrolment.

Patients were under the care of emergency physicians who were able to select any other adjunctive therapy during the study period except other aerosolized medication. All drugs were prepared in the hospital pharmacy to achieve randomized double-blinding.

At presentation, all patients had pulmonary function testing (forced expiratory volume in 1 s [FEV1], peak expiratory flow rate, forced vital capacity) completed by a respiratory therapist, based on the best of three attempts. Initial assessment was completed, and patients were assigned to group A or B. Group A patients received salbutamol 2.5 mg premixed with 3.5 mL of saline and delivered by an aerosol from a ‘power mist’ nebulizer (Hospitalak USA, location?), at a flow rate of 6 L of oxygen per minute at time 0, 1 and 2 h. At 20, 40, 80 and 100 mins, a placebo saline aerosol was given. The total dose of salbutamol given was 7.5 mg. Group B patients received salbutamol 5 mg at 0 min and one-third of the dose mixed with normal saline every 20 mins for a total of six doses. The total dose of salbutamol given was 15 mg. All aerosols were premixed to a total volume of 4 mL. Measurement of vital signs was carried out after each dose of medication, and assessment of accessory muscle use and classification of wheezing as mild/moderate/severe was performed. At the conclusion of the study period, pulmonary function studies were repeated. Further therapy was initiated as required, and the patient was either admitted to hospital or discharged from the emergency department with follow-up instructions. Patients were contacted within 10 days of hospital discharge to determine medication side effects and evidence of relapse or admission to hospital. Specific side effects monitored included tremor, palpitations, irritability, nausea and vomiting. Results were analyzed using Student’s t test or χ2 as appropriate.

**RESULTS**

Fifty-nine patients were initially eligible for study. Two patients were excluded because they had evidence of chronic obstructive lung disease; four patients improved during the study period except other aerosolized medication. All drugs were prepared in the hospital pharmacy to achieve randomized double-blinding.

At presentation, all patients had pulmonary function testing (forced expiratory volume in 1 s [FEV1]), peak expiratory flow rate, forced vital capacity) completed by a respiratory therapist, based on the best of three attempts. Initial assessment was completed, and patients were assigned to group A or B. Group A patients received salbutamol 2.5 mg premixed with 3.5 mL of saline and delivered by an aerosol from a ‘power mist’ nebulizer (Hospitalak USA, location?), at a flow rate of 6 L of oxygen per minute at time 0, 1 and 2 h. At 20, 40, 80 and 100 mins, a placebo saline aerosol was given. The total dose of salbutamol given was 7.5 mg. Group B patients received salbutamol 5 mg at 0 min and one-third of the dose mixed with normal saline every 20 mins for a total of six doses. The total dose of salbutamol given was 15 mg. All aerosols were premixed to a total volume of 4 mL. Measurement of vital signs was carried out after each dose of medication, and assessment of accessory muscle use and classification of wheezing as mild/moderate/severe was performed. At the conclusion of the study period, pulmonary function studies were repeated. Further therapy was initiated as required, and the patient was either admitted to hospital or discharged from the emergency department with follow-up instructions. Patients were contacted within 10 days of hospital discharge to determine medication side effects and evidence of relapse or admission to hospital. Specific side effects monitored included tremor, palpitations, irritability, nausea and vomiting. Results were analyzed using Student’s t test or χ2 as appropriate.

**TABLE 1**

<table>
<thead>
<tr>
<th>Clinical characteristics of patients</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>33.2</td>
<td>38.5</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>7/18</td>
<td>7/16</td>
<td>NS</td>
</tr>
<tr>
<td>Medication preadmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>12</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Beta-agonist</td>
<td>25</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>3</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Initial FEV1*</td>
<td>1.16±0.54</td>
<td>1.16±0.65</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± SEM. FEV1 Forced expiratory volume in 1 s; NS Not significant

**TABLE 2**

<table>
<thead>
<tr>
<th>Study results</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-treatment FEV1*</td>
<td>1.86±0.6</td>
<td>1.75±0.51</td>
<td>NS</td>
</tr>
<tr>
<td>Change in mL*</td>
<td>700±630</td>
<td>590±520</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage change*</td>
<td>67.8±33.6</td>
<td>74.5±81.7</td>
<td>NS</td>
</tr>
<tr>
<td>Admission</td>
<td>6</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Relapse</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Discharged on steroids</td>
<td>12</td>
<td>10</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Mean ± SEM. FEV1 Forced expiratory volume in 1 s; NS Not significant
study period and did not complete the protocol; data was incomplete on four patients; and one patient did not complete the study due to asthma. Forty-eight patients were thus available for study. Both group A and B patients were similar with respect to age, sex distribution, duration of asthma, regular medications and initial FEV1 (Table 1).

At the completion of the study, both groups of patients had improved with a mean absolute change in FEV1 of 700 mL (67.8%) in group A and 590 mL (74.5%) in group B. Because of the wide variation of response to medication, there was no statistical difference between high and low dose therapy. There were no differences between the groups with respect to other drugs given during the emergency department visit. The incidence of side effects and number of patients admitted to hospital or returning to the emergency department was not significantly different between the two groups. Twelve patients in group A and 10 patients in group B were discharged from the emergency department on a short course of oral steroids (Tables 2,3).

### DISCUSSION

This study has shown no difference in the improvement of acute asthma in patients treated for 3 h either with a standard dose (2.5 mg) of aerosolized salbutamol given at hourly intervals (total dose 7.5 mg) or a higher total dose administered more frequently, every 20 mins (total dose 15 mg). Both dose regimens improved FEV1 by 60% to 70% with a low incidence of side effects and an acceptable rate of relapse of therapy and hospital admission. There were no deaths in the study.

Other studies have been conducted to determine the dose of a beta-agonist for acute asthma. Robertson et al (7) used a 20-minute dosing interval versus the standard 1 h interval with the same total dose of salbutamol in pediatric patients and found a 48% improvement in FEV1 in the frequent dose group. Nelson et al (8) studied adult asthma patients in the emergency department, comparing aerosolized metaproterenol (0.3 mL) delivered every 20 mins for a total of three doses, with a single dose of metaproterenol followed by two saline aerosols. There was an improved response in the split dose group as measured by the FEV1 at 60 and 120 min without any change in side effects.

Horn et al (9) were able to show the value of high dose inhaled therapy in stable asthmatics. Therapy was increased from salbutamol 400 µg qid via rotahaler to 2000 µg qid. All chronic symptoms were abolished, and the number of acute attacks was reduced. Bellamy and Penketh (10) compared salbutamol with fenoterol in stable asthmatics. They showed a greater degree of bronchodilation with increasing doses over the range of two, four and six puffs delivered by metered dose inhaler (MDI). They suggested that six puffs of salbutamol was an effective dose and free from major side effects.

Other investigators have shown different results. Bardin and Joubert (11) compared high dose (1000 µg) with conventional dose (200 µg) salbutamol delivered by MDI in stable asthmatics. They did not show any difference in bronchodilator effect or side effects. Lipworth et al (12) studied 14 stable asthmatics with cumulative doubling doses of salbutamol by MDI of 100, 200, 500, 1000, 2000 and 4000 µg. They showed an increased bronchodilator effect at high doses, but there was great individual variation and some patients with severe asthma did not respond. Lin et al (13) and Rudnitsky et al (14) compared the effect of albuterol given by continuous or intermittent nebulization and found no difference in clinical effect or side effects in adult patients with exacerbations of asthma.

Regular use of beta-agonist drugs in stable asthma patients has been suggested as a cause of the increase in mortality recently observed (15). Some authors think the etiology for this may be the hypokalemic effect of beta-agonists and the production of a lethal arrhythmia (16,17). With the use of high dose beta-agonist therapy in acute asthma becoming widespread, concern is being raised that this may be an unsafe practice. Gilmartin et al (18) monitored asthmatic patients receiving salbutamol by nebulizers (total dose 10 to 17.5 mg per 24 h) with Holter monitors. No arrhythmias were noted. Newhouse et al (19) compared acute asthma patients using fenoterol and salbutamol delivered by MDI. No clinically significant arrhythmias, hypokalemia or prolongation of QT was noted.

Our study shows no significant difference in the amount of bronchodilation between high dose salbutamol (15 mg) and the lower dose of 7.5 mg given less often, which is in contrast to Robertson and colleagues (7). The reasons for this may be that the numbers were too small or that the 7.5 mg dose was sufficient to achieve maximum bronchodilation. We calculated that to detect a 20% difference between the two groups, we would need 377 patients in each treatment arm. Secondly, we cannot rule out an effect of nebulizer output as suggested by Alvine et al (20). However, we used the same nebulizer with the same amount of fluid (4 mL) throughout the study. Given that there was a significant bronchodilation in each group and that each group received no other treatment, we do not think nebulizer output influenced the results.

### CONCLUSIONS

This study has shown no differences or improvement of acute asthma treated with a standard dose of aerosolized salbutamol given at hourly intervals compared with a higher total dose and more frequent administration (every 20 mins).

Further studies are required to determine the safety of high dose beta-agonist therapy in the severe acute asthma patient and the optimal total dose and interval to achieve maximum therapeutic benefit.
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REFERENCES