Drug Class Review on Quick-relief Medications for Asthma

Preliminary Scan Report #3

November 2013

The Agency for Healthcare Research and Quality has not yet seen or approved this report

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.
OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations’ consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA since the last report. Other important studies could exist.

Date of Last Update Report:

Update #1 was completed in October 2008, with searches through May 2008.

Date of Previous Scans:

Scan #1: October 2009
Scan #2: September 2010

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy and effectiveness of quick-relief medications used to treat outpatients with bronchospasm due to asthma, or to prevent or treat exercise-induced bronchospasm?
2. What is the comparative incidence and severity of adverse events reported from using quick-relief medications to treat outpatients with bronchospasm due to asthma, or to prevent or treat exercise-induced bronchospasm?
3. Are there subgroups of patients for which quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm, differ in efficacy, effectiveness, or frequency and severity of adverse events?
Inclusion criteria

**Populations**
1. Adults or children with asthma including those with exercise-induced bronchospasm

Excluded populations:
1. COPD
2. Acute bronchitis
3. Bronchiectasis
4. Children < 2 years with recurrent or persistent wheezing
5. Cystic fibrosis
6. High-altitude pulmonary edema

**Interventions**
1. Inhaled short-acting beta₂-agonists (SABA)
   a. Albuterol (salbutamol in Canada) MDI and nebulizer solution
   b. Levalbuterol (R-albuterol) MDI and nebulizer solution (levalbuterol is not available in Canada)
   c. Pirbuterol (not available in Canada)
   d. Terbutaline: available only in Canada
   e. Fenoterol: available only in Canada
2. Short-acting anticholinergics
   a. Ipratropium bromide MDI and nebulizer solution
3. Combination products
   a. Ipratropium bromide with albuterol MDI or ipratropium bromide with albuterol nebulizer solution

Excluded interventions
1. Systemic corticosteroids
   a. Prednisone
   b. Methylprednisolone
   c. Prednisolone
2. Inhaled Corticosteroids
3. Inhaled Cromolyn
4. Salmeterol
5. Long-acting anticholinergics: tiotropium
6. Studies where bronchospasm was induced by methacholine, histamine, cold
7. Combination products which include a quick-relief agent and another agent not included in this review
8. Formoterol

**Comparators**
1. Head-to-head studies examining the above bronchodilators
Excluded comparators
1. Comparisons to other drugs or to placebo (to achieve indirect comparisons)

**Effectiveness Outcomes**
1. Symptoms: e.g., cough, wheezing, shortness of breath
2. Change in treatment regimen for the exacerbation
3. Healthcare utilization: length of stay in the ER or other clinical facility, need for re-treatment within 24 hours, hospital admissions, length of hospital stay
4. For exercise induced bronchospasm: exercise tolerance, symptoms
5. Mortality

**Harms Outcomes**
1. Overall adverse events reported
2. Withdrawals due to adverse events
3. Serious adverse events

**Setting**
1. Outpatient settings including urgent care facilities and the emergency room

**Study Designs**
1. For effectiveness: Head-to-head RCTs or controlled clinical trials with total sample size ≥ 20. No minimum duration of follow-up.
2. For adverse events: Head-to-head RCTs, controlled clinical trials, or observational studies with sample size ≥ 10. No minimum duration of follow-up.

**METHODS**

**Literature Search**
To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from 2010 through October Week 3 2013, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA web site for identification of new drugs, indications, and safety alerts and Canadian Agency for Drugs and Technologies in Health and Agency for Healthcare Research and Quality for Comparative Effectiveness Reviews.

**Study Selection**
One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.
RESULTS

New Drugs/Indications

No new drugs or indications were identified.

New Boxed Warnings

No new boxed warnings were identified.

Comparative Effectiveness Reviews

No new comparative effectiveness reviews were identified.

Randomized Controlled Trials

Searches resulted in 128 potentially relevant citations. Of those, 8 new trials meeting inclusion criteria were identified. (See Table 1) One new head-to-head trial compared racemic albuterol nebulizer treatment with levalbuterol nebulizer treatment. Five head-to-head studies compared different delivery methods of the same drug (e.g., with or without a spacer, nebs vs MDI, delivery by mask vs by hood). One relevant placebo-controlled and one active-controlled trial were also identified. (See Appendix A for abstracts of included studies)

Table 1. Potentially relevant trials of drugs for quick relief of asthma symptoms

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Comparison</th>
<th>N</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews 2009</td>
<td>Levalbuterol nebs</td>
<td>81</td>
<td>Children aged 6-18</td>
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<td></td>
<td>Racemic albuterol nebs</td>
<td></td>
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<tr>
<td>Punj 2009</td>
<td>Levosalbutamol</td>
<td>60</td>
<td>Children aged 5-18</td>
</tr>
<tr>
<td></td>
<td>Racemic Salbutamol</td>
<td></td>
<td></td>
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<tr>
<td>Wilkinson 2011</td>
<td>Racemic albuterol nebs</td>
<td>99</td>
<td>Children aged 6-17</td>
</tr>
<tr>
<td></td>
<td>Levalbuterol nebs</td>
<td></td>
<td></td>
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<tr>
<td>Head-to-head delivery method</td>
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<tr>
<td>Bar-Yishay 2011</td>
<td>Salbutamol 0.30 mg/kg by mask</td>
<td>26</td>
<td>Wheezy infants</td>
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<tr>
<td></td>
<td>Salbutamol 0.30 mg/kg by hood</td>
<td></td>
<td></td>
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<tr>
<td>Direkwatanachai 2011</td>
<td>Salbutamol pMDI 6 puffs with Volumatic spacer</td>
<td>216</td>
<td>Children aged 5-18 in Thailand</td>
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<td>Study Year</td>
<td>Comparison</td>
<td>N</td>
<td>Focus</td>
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<tr>
<td>Salbutamol 6 puffs with Easyhaler (DPI)</td>
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<tr>
<td>Salbutamol 0.15 mg/kg nebs</td>
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<tr>
<td>Dhuper 2011</td>
<td>Albuterol with MDI/spacer</td>
<td>60</td>
<td>Inner city adults; crossover study</td>
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<td></td>
<td>Albuterol nebs</td>
<td></td>
<td></td>
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<tr>
<td>Rotta 2010</td>
<td>Salbutamol pMDI with spacer</td>
<td>46</td>
<td>Children aged 1-5</td>
</tr>
<tr>
<td></td>
<td>Salbutamol nebs</td>
<td></td>
<td></td>
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<tr>
<td>Sabato 2011</td>
<td>1 hour of continuous nebulized albuterol</td>
<td>149</td>
<td>Children aged 0-18</td>
</tr>
<tr>
<td></td>
<td>1-time albuterol treatment with AeroEclipse breath-actuated nebulizer</td>
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<tr>
<td>Placebo-controlled</td>
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<tr>
<td>Wechsler 2011</td>
<td>Albuterol inhaler</td>
<td>46</td>
<td>Crossover study</td>
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<td></td>
<td>Placebo inhaler</td>
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<td>Active-controlled</td>
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<tr>
<td>Mangunnegoro 2011</td>
<td>Salbutamol nebs (1 ampule)</td>
<td>140</td>
<td>Indonesians with moderate acute asthma age 15-60</td>
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<tr>
<td></td>
<td>Procaterol nebs (1 ampule)</td>
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Previous scans identified two head-to-head trials comparing levalbuterol with albuterol in a pediatric population, for a total of 10 new studies published since the last update. Of these, three studies compared one included drug with another included drug; all three compared racemic albuterol with levalbuterol in children (combined N=240).
APPENDIX A. Abstracts of potentially relevant new trials for quick relief of asthma symptoms (N=8)

Head-to-head trials (drug vs drug, N=3)


OBJECTIVE: To assess the use of high-dose continuous levalbuterol (LEV), the single active (R)-enantiomer of racemic albuterol (RAC), in the treatment of status asthmaticus. STUDY DESIGN: Children age 6 to 18 years with severe asthma exacerbation were enrolled in this randomized, double-blind trial if they failed initial emergency department (ED) therapy with RAC and systemic steroids. Subjects received equipotent doses of RAC (20 mg/hour) or LEV (10 mg/hour) within a standardized inpatient protocol. Blood samples for measurements of albuterol enantiomer, potassium, and glucose levels were obtained from the first 40 subjects. The median time until discontinuation of continuous therapy was compared using the rank-sum test, and other outcomes were compared using general linear mixed models. RESULTS: A total of 81 subjects (40 in the RAC group and 41 in the LEV group) were enrolled; the 2 groups were similar at baseline. Both groups tolerated continuous therapy with similar changes in heart rate and serum potassium and glucose levels but higher serum (S)-albuterol concentrations in the subjects treated with RAC. The median time for continuous therapy was similar in the RAC and LEV groups (18.3 hours vs 16.0 hours), as were the other clinical measures. CONCLUSIONS: Substituting high-dose continuous LEV for RAC did not reduce the time on continuous therapy and had similar adverse effects in children who had failed initial treatment with RAC.


OBJECTIVE: To compare efficacy and tolerability of levosalbutamol (Group 1) and racemic salbutamol (Group 2) for the treatment of acute exacerbation of asthma in children age 5 to 18 yr. METHODS: A randomized double blind clinical study involving 60 children was undertaken between October’ 06 to December’ 07. RESULTS: The following baseline clinical characteristic were recorded initially and after giving 3 nebulizations at 20 min intervals in the 1st hour of presentation viz respiratory rate (RR), heart rate (HR), oxygen saturation in room air SPO2, PEFR (peak expiratory flow rate), serum K+ level and asthma score. In Group 1 patients (levosalbutamol), there was significant increment in SPO2 and PEFR (P < 0.05). CONCLUSION: Levosalbutamol appears to be more efficacious than racemic salbutamol in terms of improvement in PEFR, SPO2 and asthma score while deleterious effects of tachycardia and fall in serum K+ were seen with racemic salbutamol.

OBJECTIVE: To compare racemic albuterol (RAC) with levalbuterol (LEV) in continuous form for the treatment of acute pediatric asthma exacerbations in the emergency department.

STUDY DESIGN: Children between the ages of 6 and 17 inclusive were enrolled if they had a history of asthma, presented to the emergency department with an acute asthma exacerbation, and had an initial forced expiratory volume in 1 second (FEV1) <70% predicted. Patients were then randomized to receive either 7.5 mg of RAC or 3.75 mg of LEV over 1 hour, in addition to standard asthma therapies. Spirometry and asthma scoring were performed at the end of the first hour, and a second hour-long nebulization with the same drug was administered if deemed necessary. Spirometry and asthma scoring were again performed and the final disposition was recorded. As a second, optional part of the study, baseline serum albuterol levels were collected on some patients before treatment.

RESULTS: A total of 99 patients completed the study (44 RAC and 55 LEV). Baseline characteristics were similar except that the RAC group had a higher baseline asthma score. Children in the RAC group had a greater improvement in their FEV1 (p = .043) as well as in their asthma scores (p = .01) after 1 hour of continuous treatment compared to the LEV group. The greater improvement in asthma scores was maintained after the second hour of continuous therapy in the RAC group (p = .008) but not for FEV1 measurements (p = .57). There were no differences between groups for changes in heart rate, respiratory rate, oxygen saturation, or rates of admission.

CONCLUSIONS: At the doses used, RAC appears to be superior to LEV with respect to changes in FEV1 and asthma score. There was no significant difference between the drugs with respect to admission rates or side-effect profile.

Head-to-head trials (delivery method vs delivery method, N=5)


BACKGROUND: In infants, small volume nebulizers with a face mask are commonly used to facilitate aerosol therapy. However, infants may be disturbed by mask application, causing poor mask-to-face seal and thus reducing the dose delivered.

OBJECTIVES: To compare lung function response to bronchodilator nebulization via two delivery devices: hood versus mask.

METHODS: We studied 26 recurrently wheezy infants aged 45.8 weeks (95% confidence interval 39.6-52.0). Inhalations of 0.30 mg/kg salbutamol were administered in two alliqots 30 minutes apart using mask and hood in alternating order (M+H or H+M). Response to inhalations was measured by maximal
expiratory flows at functional residual capacity (V'maxFRC) at 5 minute intervals after each dose, and area under the V'maxFRC curve (AUC) was documented.

RESULTS: A small but significant response to salbutamol was observed following the second inhalation with V'maxFRC, improving by 31.7% (7.2-56.2, P (0.02) and AUC by 425% x min (-154, 1004; P < 0.02). The improvement following salbutamol was similar by both delivery modalities but with a small but significantly better response when H was used after M (P < 0.01).

CONCLUSIONS: Nebulized salbutamol induced a variable but positive response in wheezy infants. Salbutamol via hood was as effective as conventional face mask delivery. Since it is simple and patient-friendly, it could replace the face mask method particularly with uncooperative infants.


BACKGROUND: Beta(2) agonist administered via a nebulizer is the standard treatment for acute asthma exacerbation. There are some limitations for the use of nebulization. We conducted a study to determine the efficacy of salbutamol administered via the pMDI with Volumatic spacer and the Easyhaler (DPI) compared to nebulization in mild to moderate asthma exacerbations in children.

METHODS: A multicenter, randomized, controlled study was conducted in children between 5 and 18 years of age who presented at an emergency or outpatient department. They were randomized to receive either 6 puffs of salbutamol via the pMDI with Volumatic spacer, or via the Easyhaler, or 0.15 mg/kg of salbutamol nebulized via oxygen (or compressed air). The primary outcome was the clinical response which was assessed using the modified Wood's asthma score. The secondary outcomes were: hospitalization, asthma revisit within 3 days, systemic corticosteroid use and adverse events. The clinical score, oxygen saturation, PR, RR, BP and adverse events were recorded at time 0 (before treatment) and 20, 40 and 60 minutes after drug administration.

RESULTS: There were no statistically significant differences in the clinical response between the three groups at the 1st, 2nd or 3rd dose or for the SpO(2) or the respiratory rate while the children in the Easyhaler group had significantly less tachycardia after the 2nd dose. No significant adverse events were noted among the three groups.

CONCLUSIONS: Salbutamol administered via pMDI with Volumatic spacer or DPI (Easyhaler) are as effective as salbutamol given via a nebulizer in providing effective relief of mild to moderate severity acute asthma exacerbation in children between 5 and 18 years of age.

Dhuper S. Chandra A. Ahmed A. Bista S. Moghekar A. Verma R. Chong C. Shim C. Cohen H. Choksi S. Efficacy and cost comparisons of bronchodilatator administration

BACKGROUND: Despite demonstration of equivalent efficacy of beta agonist delivery using a metered dose inhaler (MDI) with spacer vs. nebulizer in asthma patients, use of a nebulizer remains standard practice.

OBJECTIVES: We hypothesize that beta agonist delivery with a MDI/disposable spacer combination is an effective and low-cost alternative to nebulizer delivery for acute asthma in an inner-city population.

METHODS: This study was a prospective, randomized, double-blinded, placebo-controlled trial with 60 acute asthma adult patients in two inner-city emergency departments. Subjects (n = 60) received albuterol with either a MDI/spacer combination or nebulizer. The spacer group (n = 29) received albuterol by MDI/spacer followed by placebo nebulization. The nebulizer group (n = 29) received placebo by MDI/spacer followed by albuterol nebulization. Peak flows, symptom scores, and need for rescue bronchodilator were monitored. Median values were compared with the Kolmogorov-Smirnov test.

RESULTS: Patients in the two randomized groups had similar baseline characteristics. The severity of asthma exacerbation, median peak flows, and symptom scores were not significantly different between the two groups. The median (interquartile range) improvement in peak flow was 120 (75-180) L/min vs. 120 (80-155) L/min in the spacer and nebulizer groups, respectively (p = 0.56). The median improvement in the symptom score was 7 (5-9) vs. 7 (4-9) in the spacer and nebulizer groups, respectively (p = 0.78). The median cost of treatment per patient was $10.11 ($10.03-$10.28) vs. $18.26 ($9.88-$22.45) in the spacer and nebulizer groups, respectively (p < 0.001).

CONCLUSION: There is no evidence of superiority of nebulizer to MDI/spacer beta agonist delivery for emergency management of acute asthma in the inner-city adult population. MDI/spacer may be a more economical alternative to nebulizer delivery.


OBJECTIVE: The objective was to determine if the plasma concentrations of salbutamol, obtained during inhalation treatment of infantile acute asthma, are influenced by age range and by the aerosol system used.

METHOD: A randomized clinical trial was conducted in 46 children (1-5 years of age) with a diagnosis of acute asthma crisis, established in an emergency room pediatric service. Twenty-five children received salbutamol using a pressurized metered-dose inhaler with spacer (50 microg/kg), and 21 children received salbutamol by nebulization (150 microg/kg), three times during a 1-h period. At the end of the treatment, one blood sample was drawn and the plasma was stored for later determination of salbutamol concentration (liquid chromatography). Salbutamol plasma concentrations were compared in two age groups (< or =2 years and >2 years of age). The type of device used (pressurized metered-dose inhaler or
nebulizer) and the need of hospitalization were also tested. The Mann-Whitney U test was used with the level of significance set at 5% (P < 0.05).

RESULTS: No differences were detected regarding either the aerosol delivery system used or the need for hospitalization in relation to the plasma concentrations of salbutamol. However, higher plasma levels were found in patients >2 years vs patients ≤2 years [median (IQR): 9.40 (6.32-18.22) vs. 4.65 (2.77-10.10) ng/mL], demonstrating a significance difference (P = 0.05).

CONCLUSION: Salbutamol plasma concentrations were influenced by age group of the patients submitted to inhalation therapy, even with doses adjusted for body weight. After correcting for the differences in the bioavailabilities of the delivery systems, the concentrations were independent of the aerosol delivery device used.


BACKGROUND: Bronchodilator treatment for asthma can be provided with various aerosol-generating devices and methods. There have been no randomized trials of a breath-actuated nebulizer versus continuous 1-hour nebulization and/or small-volume constant-output nebulizer in pediatric asthma patients.

METHODS: We conducted a randomized study of one-time albuterol treatment with the AeroEclipse breath-actuated nebulizer versus standard therapy (single treatment via small-volume nebulizer or 1-hour of continuous nebulized albuterol) in pediatric asthma patients in the emergency department. Eligible patients were those admitted to the emergency department, ≤ to 18 years of age, who presented with asthma or wheezing. We assessed all the patients with our clinical asthma scoring system and peak-flow measurement if possible. We stratified the patients by clinical asthma score and weight, and then randomized them to receive their initial albuterol treatment in the emergency department via either AeroEclipse or standard therapy. We recorded time in the emergency department, change in clinical asthma score, need for additional bronchodilator treatments, need for admission, patient response, ability to actuate the AeroEclipse, and adverse effects.

RESULTS: We enrolled 149 patients between October 14, 2004 and November 11, 2005, and we randomized 84 patients to AeroEclipse and 65 to standard therapy. The cohort's average age was 5.5 years. There were no significant differences in demographics. The initial mean clinical asthma scores were 5.1 +/- 2.4 in the AeroEclipse group, and 5.1 +/- 2.1 in the standard-therapy group. Time in the emergency department was not different (AeroEclipse 102 min, standard therapy 125 min, P = .10), but the AeroEclipse group had a significantly greater improvement in clinical asthma score (1.9 +/- 1.2 vs 1.2 +/- 1.4, P = .001) and respiratory rate (P = .002), and significantly lower admission rate (38% vs 57%, P = .03). There was no difference in adverse effects.

CONCLUSIONS: Although AeroEclipse did not reduce the time in the ED, it significantly improved clinical asthma score, decreased admissions, and decreased respiratory rate.
Placebo-controlled trial (N=1)


BACKGROUND: In prospective experimental studies in patients with asthma, it is difficult to determine whether responses to placebo differ from the natural course of physiological changes that occur without any intervention. We compared the effects of a bronchodilator, two placebo interventions, and no intervention on outcomes in patients with asthma.

METHODS: In a double-blind, crossover pilot study, we randomly assigned 46 patients with asthma to active treatment with an albuterol inhaler, a placebo inhaler, sham acupuncture, or no intervention. Using a block design, we administered one of these four interventions in random order during four sequential visits (3 to 7 days apart); this procedure was repeated in two more blocks of visits (for a total of 12 visits by each patient). At each visit, spirometry was performed repeatedly over a period of 2 hours. Maximum forced expiratory volume in 1 second (FEV(1)) was measured, and patients' self-reported improvement ratings were recorded.

RESULTS: Among the 39 patients who completed the study, albuterol resulted in a 20% increase in FEV(1), as compared with approximately 7% with each of the other three interventions (P<0.001). However, patients' reports of improvement after the intervention did not differ significantly for the albuterol inhaler (50% improvement), placebo inhaler (45%), or sham acupuncture (46%), but the subjective improvement with all three of these interventions was significantly greater than that with the no-intervention control (21%) (P<0.001).

CONCLUSIONS: Although albuterol, but not the two placebo interventions, improved FEV(1) in these patients with asthma, albuterol provided no incremental benefit with respect to the self-reported outcomes. Placebo effects can be clinically meaningful and can rival the effects of active medication in patients with asthma. However, from a clinical-management and research-design perspective, patient self-reports can be unreliable. An assessment of untreated responses in asthma may be essential in evaluating patient-reported outcomes.

Active-controlled trial (N=1)


OBJECTIVE: 2 agonists have been used widely as relievers in asthma management. Procaterol is a selective 2 agonist, claimed to be more selective than salbutamol. The present study aimed to compare the efficacy of nebulized procaterol with nebulized salbutamol in the treatment of moderate acute asthma.

METHODS: This was a randomized, double-blind, parallel group study in 140 patients with moderate acute asthma according to modified GINA 1998 who visited emergency department of Persahabatan Hospital, Jakarta. Patients were randomly
assigned to receive three doses of either nebulized procaterol or salbutamol. The primary efficacy variable was the improvement in predicted peak expiratory flow rate (PEFR), while the secondary efficacy variable was the improvement in asthma score and the incidence and severity of adverse events. This study is registered at Current Controlled Trials, number ISCTRNN25669625.

RESULTS: Baseline characteristics were similar in both groups. After treatment, there were significant improvement of % PEFR (p < 0.001) and asthma score (p < 0.001) in procaterol (n = 68) and salbutamol (n = 69) groups. It was shown that procaterol and salbutamol produced similar efficacy in improving % predicted PEFR and decreasing asthma score. Both treatments were well tolerated. Palpitation and sinus tachycardia were found as adverse events with low incidence.

CONCLUSION: In moderate acute asthma, nebulized procaterol and nebulized salbutamol were both effective in improving PEFR and decreasing asthma score. Both treatments were well tolerated, adverse reactions were rare.