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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Medication Administration via Multi-Dose Inhalers and Aerochambers Versus Nebulizers: Clinical Effectiveness

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Authors: Kendra Brett, Caitlyn Ford

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Research Question

What is the clinical effectiveness of medication administration via multi-dose inhalers compared to nebulizers?

Key Findings

Three systematic reviews with meta-analyses, four randomized controlled trials, and two non-randomized studies, were identified regarding the clinical effectiveness of medication administered through multi-dose inhalers with spacers compared to medication administered through a nebulizer.

Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were metered dose inhalers and nebulizers. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and April 21, 2020. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (any age) in any healthcare setting requiring medication administered (via multi-dose dose inhaler or nebulization)
Intervention	Multi-dose inhaler (MDI) and aerochambers
Comparator	Nebulizer
Outcomes	Clinical effectiveness (e.g., reduction in disease transmission, peak flow, expiratory volume, length of hospital stay, relapse)
Study Designs	Health technology assessments, systematic review, randomized controlled trials, non-randomized studies

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports and systematic reviews are presented first. These are followed by randomized controlled trials and non-randomized studies.

Three systematic reviews with meta-analyses,[1-3] four randomized controlled trials,[4-7] and two non-randomized studies,[8-9] were identified regarding the clinical effectiveness of

medication administered through multi-dose inhalers (MDIs) with spacers compared to medication administered through a nebulizer. No relevant health technology assessments were identified.

References of potential interest that did not meet the inclusion criteria are provided in the appendix.

Overall Summary of Findings

Three systematic reviews with meta-analyses,[1-3] four randomized controlled trials,[4-7] and two non-randomized studies,[8-9] were identified regarding the clinical effectiveness of medication administered through MDIs with spacers compared to medication administered through a nebulizer. Detailed study characteristics are provided in Table 2.

Two systematic reviews with meta-analyses,[1,3] two RCTs,[4,7] and one non-randomized study,[8] compared MDIs with spacers to nebulizers in pediatric patients with asthma and the findings differed across studies, however, for all outcomes there was either no difference between devices or the findings were in favour of the MDI with spacer.

In adult patients with asthma, one systematic review with meta-analysis[3] and one non-randomized study[9] found no differences in outcomes (e.g., pulmonary function, hospital admission, length of stay) when comparing medication administration through an MDI with spacer compared to a nebulizer. One RCT[6] also found no significant difference in the length of stay or the number of ventilation days when comparing an MDI with an aerochamber vent to the use of a nebulizer (jet or vibrating mesh) in adults with asthma who are mechanically ventilated.

For patients with chronic obstructive pulmonary disease (COPD), a systematic review and meta-analysis[2] of patients with COPD exacerbations treated with bronchodilator therapy found a lack of evidence in favour of one device over another (i.e., a pressurized MDI with spacer compared to a nebulizer) with regards to lung function and adverse events. Moreover, in patients with COPD who are mechanically ventilated, one RCT[5] found that an MDI with aerochamber vent resulted in better delivery of salbutamol, as measured through urine excretions, compared to vibrating mesh nebulizers.

Table 2: Summary of Included Studies on Medication Delivered through a Multi-Dose Inhaler with a Spacer compared to Medication Delivered through a Nebulizer

First Author, Year	Study Characteristics	Intervention	Comparators	Relevant Outcomes Assessed	Conclusions
Systematic Reviews and Meta-Analyses					
Roncada, 2018[1]	• Meta-analysis performed • 9 RCTs included • Pediatric asthma patients treated at emergency units	• MDI with spacer • Bronchodilator (beta-2 agonist)	• Nebulizer • Bronchodilator (beta-2 agonist)	• Heart rate • Respiratory rate • Oxygen saturation • Asthma score	No difference between inhalation technique (MDI with spacer vs. nebulizer) for any of the outcomes analyzed

First Author, Year	Study Characteristics	Intervention	Comparators	Relevant Outcomes Assessed	Conclusions
Van Geffen, 2016[2]	• Meta-analysis performed (where possible) • 8 RCTs and 250 patients included • COPD exacerbations in hospital or outpatient setting (excluded mechanically ventilated patients)	• Pressurized MDI with spacer • Bronchodilator	• Nebulizer • Bronchodilator	• Change in forced expiratory volume • Adverse events	No difference between devices in forced expiratory volume at one hour and adverse events. Change in forced expiratory volume closest to one hour was significantly in favour for the nebulizer.
Cates. 2013[3]	• Meta-analysis performed • 39 RCTs with 1897 children and 729 adults • Acute asthma (emergency room, inpatient settings)	• MDI with holding chamber (spacer) • Bronchodilator (beta-2 agonist)	• Nebulizer • Bronchodilator (beta-2 agonist)	• Hospital admission rates • Length of stay in emergency department • Peak flow volume • Forced expiratory volume • Pulse rate • Risk of developing tremor	No difference in hospital admission rates (adults and children), length of stay (adults), peak flow and expiratory volume (adults and children). In children the MDI with spacer was associated with significantly shorter length of stay, lower pulse rate, and lower risk of developing tremor.
Randomized Controlled Trials					
Iramain, 2019[4]	• N = 103 children (2 to 14 years) • Severe asthma exacerbations at emergency room • Follow up 4 hours after treatment	• MDI with valved holding chamber and mask • Salbutamol and ipratropium	• Nebulizer • Salbutamol and ipratropium	• Rate of hospitalization • Oxygen saturation	Children with the MDI with holding chamber and mask had significantly lower rate of hospitalization 4 hours after treatment, significantly better oxygen saturation after 90 minutes.
El Hansy, 2017[5]	• N = 60 • Mechanically ventilated COPD patients • Follow up 30 minutes post inhalation	• MDI with aerochamber vent • Salbutamol • Placed in the inspiratory limb of ventilator downstream from humidifier	• Vibrating mesh nebulizers • Jet nebulizer • Salbutamol • Placed in the inspiratory limb of ventilator downstream from humidifier	• Salbutamol excreted in urine	The MDI with aerochamber vent resulted in better delivery compared to the vibrating mesh nebulizers.

First Author, Year	Study Characteristics	Intervention	Comparators	Relevant Outcomes Assessed	Conclusions
Moustafa, 2017[6]	• N = 72 • Mechanically ventilated patients with asthma	• MDI with aerochamber vent with and without humidification • Placed in the inspiratory limb of ventilator downstream from humidifier	• Vibrating mesh nebulizer with and without humidification • Jet nebulizer with and without humidification • Placed in the inspiratory limb of ventilator downstream from humidifier	• Patient response • Length of stay in the ICU • Mechanical ventilation days	No significant difference was found in any of the outcomes between method of delivery.
Mitselou, 2016[7]	• N = not reported • Acute asthma in preschool children in the pediatric emergency department	• MDI with spacer • Bronchodilator	• Nebulizer • Bronchodilator	• Length of stay in emergency department • Rate of hospitalization • Heart rate • Respiratory rate • Oxygen saturation	No significant differences observed in any of the outcomes between method of delivery.
Non-Randomized Studies					
Spin, 2017[8]	• Retrospective cohort • N = 822 • Asthma patients in the pediatric emergency departments	• MDI with spacer • salbutamol	• Nebulizer • salbutamol	• Hospitalization • Length of stay	MDI with spacer was associated with a significant decrease in hospitalization and length of stay
Kolasani, 2013[9]	• Controlled, cross-over clinical trial • N = 39 • Adults with chronic stable bronchial asthma • Follow up 1 hour after drug administration	• MDI with and without spacer • fluticasone propionate	• Nebulizer • fluticasone	• Pulmonary function	No difference between device in any measures of pulmonary function

COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; MDI = metered dose inhaler; RCT = randomized controlled trial;

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Roncada C, Andrade J, Bischoff LC, Pitrez PM. Comparison of two inhalational techniques for bronchodilator administration in children and adolescents with acute asthma crisis: A meta-analysis. *Rev Paul Pediatr*. 2018 Jul-Sep;36(3):364-371. PubMed: PM29995144

2. van Geffen WH, Douma WR, Slebos DJ, Kerstjens HA. Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for exacerbations of COPD. *Cochrane Database Syst Rev*. 2016 Aug 29(8):Cd011826. PubMed: PM27569680

3. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev*. 2013 Sep 13(9):Cd000052. PubMed: PM24037768

Randomized Controlled Trials

4. Iramain R, Castro-Rodriguez JA, Jara A, et al. Salbutamol and ipratropium by inhaler is superior to nebulizer in children with severe acute asthma exacerbation: Randomized clinical trial. *Pediatr Pulmonol*. 2019 Apr;54(4):372-377. PubMed: PM30672140

5. ElHansy MHE, Boules ME, El Essawy AFM, et al. Inhaled salbutamol dose delivered by jet nebulizer, vibrating mesh nebulizer and metered dose inhaler with spacer during invasive mechanical ventilation. *Pulm Pharmacol Ther*. 2017 Aug;45:159-163. PubMed: PM28627376

6. Moustafa IOF, ElHansy MHE, Al Hallag M, et al. Clinical outcome associated with the use of different inhalation method with and without humidification in asthmatic mechanically ventilated patients. *Pulm Pharmacol Ther*. 2017 Aug;45:40-46. PubMed: PM28435031

7. Mitselou N, Hedlin G, Hederos CA. Spacers versus nebulizers in treatment of acute asthma - a prospective randomized study in preschool children. *J Asthma*. 2016 Dec;53(10):1059-1062. PubMed: PM27186989

Non-Randomized Studies

8. Spin P, Sketris I, Hill-Taylor B, Ward C, Hurley KF. A Cost Analysis of Salbutamol Administration by Metered-Dose Inhalers with Spacers versus Nebulization for Patients with Wheeze in the Pediatric Emergency Department: Evidence from Observational Data in Nova Scotia. *CJEM*. 2017 Jan;19(1):1-8. PubMed: PM27506243

9. Kolasani BP, Lanke VM, Diyya S. Influence of delivery devices on efficacy of inhaled fluticasone propionate: a comparative study in stable asthma patients. *J Clin Diagn Res*. 2013 Sep;7(9):1908-1912.
PubMed: PM24179895

Appendix — Further Information

Previous CADTH Reports

10. Asthma treatments for acute asthma in pediatric patients: clinical effectiveness, cost effectiveness, and guidelines. (Rapid response report: Summary of abstracts). Ottawa (ON): CADTH; 2020. https://www.cadth.ca/asthma-treatments-acute-asthma-pediatric-patients-clinical-effectiveness-cost-effectiveness-and Accessed 2020 May 4

11. Salbutamol administration via nebulizer versus metered-dose inhalers: Clinical effectiveness and cost-effectiveness. (Rapid response report: Summary of abstracts). Ottawa (ON): CADTH; 2019. https://www.cadth.ca/salbutamol-administration-nebulizer-versus-metered-dose-inhalers-clinical-effectiveness-and-cost Accessed 2020 May 4

12. Vibrating mesh nebulizers for patients with respiratory conditions: Clinical effectiveness, cost-effectiveness, and guidelines. (Rapid response: Summary with critical appraisal). Ottawa (ON): CADTH; 2019. https://cadth.ca/vibrating-mesh-nebulizers-patients-respiratory-conditions-clinical-effectiveness-cost-effectiveness Accessed 2020 May 4

13. Medication administration via metered dose inhalers and aerochambers versus nebulizers for adult patients: Clinical effectiveness. (Rapid response report: Summary of abstracts). Ottawa (ON): CADTH; 2013. https://www.cadth.ca/medication-administration-metered-dose-inhalers-and-aerochambers-versus-nebulizers-adult-patients Accessed 2020 May 4

Overview of Systematic Reviews

Unclear Intervention

14. Castro-Rodriguez JA, Rodrigo GJ, Rodriguez-Martinez CE. Principal findings of systematic reviews of acute asthma treatment in childhood. *J Asthma*. 2015;52(10):1038-1045.
PubMed: PM26303207

Systematic Reviews

Unclear if MDI Intervention includes Spacer/Aerochamber

15. Dugernier J, Ehrmann S, Sottiaux T, et al. Aerosol delivery during invasive mechanical ventilation: a systematic review. *Crit Care*. 2017 Oct 21;21(1):264.
PubMed: PM29058607

16. Holland A, Smith F, Penny K, McCrossan G, Veitch L, Nicholson C. Metered dose inhalers versus nebulizers for aerosol bronchodilator delivery for adult patients receiving mechanical ventilation in critical care units. *Cochrane Database Syst Rev*. 2013 Jun 6(6):Cd008863.
PubMed: PM23740736

Randomized Controlled Trial

Unclear if MDI Intervention includes Spacer/Aerochamber

17. Snider MA, Wan JY, Jacobs J, Kink R, Gilmore B, Arnold SR. A Randomized Trial Comparing Metered Dose Inhalers and Breath Actuated Nebulizers. *J Emerg Med*. 2018 Jul;55(1):7-14.
PubMed: PM29716819

Alternative Intervention

18. Leelathipkul L, Tanticharoenwiwat P, Ithiawatchakul J, et al. MDI with DIY Spacer versus Nebulizer for Bronchodilator Therapy in Children Admitted with Asthmatic Attack. *J Med Assoc Thai*. 2016 Jul;99 Suppl 4:S265-274.
PubMed: PM29927182

Non-Randomized Studies

Unclear if MDI Intervention includes Spacer/Aerochamber

19. Dubosky MN, Chen YF, Henriksen ME, Vines DL. Vibrating Mesh Nebulizer Compared With Metered-Dose Inhaler in Mechanically Ventilated Subjects. *Respir Care*. 2017 Apr;62(4):391-395.
PubMed: PM28073994

Alternative Outcome

20. Ramlal SK, Visser FJ, Hop WC, Dekhuijzen PN, Heijdra YF. The effect of bronchodilators administered via aerochamber or a nebulizer on inspiratory lung function parameters. *Respir Med*. 2013 Sep;107(9):1393-1399.
PubMed: PM23768736