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RESEARCH LETTER

Epinephrine metered-dose inhaler for pediatric croup

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Croup is a common childhood disease of young children caused by viral infections that trigger varying degrees of upper airway obstruction. While croup of all severity is effectively treated with systemic corticosteroids,[1] nebulized epinephrine provides rapid and safe reduction in respiratory distress that lasts for 1–2 h.[2]

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) raised concerns about nebulization as an aerosol-generating medical procedure (AGMP), prompting a search for alternative delivery methods to provide effective epinephrine therapy in children with croup to minimize SARS-CoV-2 transmission. Primatene Mist is an epinephrine metered-dose inhaler (MDI) manufactured and available over the counter in the United States.[3] At the request of Canadian pediatric emergency departments (PEDs), Health Canada provided a letter of no objection to direct import of the Primatene MDI to these PEDs. Given the absence of evidence regarding appropriate dosing, nine PEDs established a national quality assurance (QA) network and seven contributed data to monitor the safety and efficacy of using an epinephrine MDI for the off-label treatment of croup.

The QA network formed a committee of Canadian experts in pediatric emergency medicine, pharmacology, critical care, and aerosol delivery who, through consensus, approved an assessment and dosing algorithm that incorporated relevant evidence identified through literature review. Using a standardized bedside data collection form, the algorithm recommended administering five puffs (125 μg/puff) via MDI with a valved holding chamber (VHC), with assessment recommended 10 min later for clinical improvement using the Westley Croup Score (WCS)[4] and for adverse effects by documenting heart rate (HR), cardiac rhythm, and presence of tremor or agitation. Because the medication delivery by MDI is more efficient than by nebulization, the typical epinephrine dose we administered via MDI/VHC (625 μg) was one-eighth that typically given via nebulization (5 mg L-epinephrine). Additional administration of five puffs was recommended up to a total of 15 puffs if there was no or minimal change (<2 points) in WCS and no adverse effects documented. The decision to treat with the epinephrine MDI/VHC in place of a nebulizer was at the discretion of the treating ED physician; however, this was the preferred method to minimize AGMP. While other treatments such as corticosteroids were not tracked, it is standard of care at all participating sites to treat all symptomatic croup with systemic corticosteroids. The primary outcome measure was improvement in the WCS assessed within 60 min after medication administration (Table 1). Secondary outcome measures were adverse effects

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TABLE 1 Effect of epinephrine MDI treatment on Westley Croup Score and physiologic parameters

Time	WCS	HR	Pulse oximetry
Pretreatment			
Mean	3.90	140.78	97.68
(Median)	(4)	(142)	(98)
[IQR]	[3–5]	[120.75–160]	[97–99]
Within 60 min posttreatment			
Mean	1.74	138.85	97.8
(Median)	(1)	(138)	(98)
[IQR]	[1–3]	[121–155]	[97–99]
Change			
Mean	2.16		
(Median)	(2)		
[IQR]	[1–3]		

Abbreviations: HR, heart rate; IQR, interquartile range; MDI, metered-dose inhaler; WCS, Westley croup score.

including extreme tachycardia (>200 beats/min), arrhythmia, tremor, or agitation. Participating sites submitted protocols for research ethics review; one site approved this study as a quality initiative not requiring research review and all others received standard ethics approval. Parental consent was not required. Seven Canadian PEDs documented outcomes as outlined above of children with croup treated with epinephrine MDI from August 2020 through October 2021 and sent deidentified data to a national REDCap database housed at the University of Calgary. Data were assessed for normal distribution using the Shapiro–Wilk test, and accordingly mean and standard deviation or median and interquartile range were used to describe its central tendency. For nonparametric data, paired data were assessed using the Wilcoxon signed-rank test.

A total of 210 of the 293 children treated with epinephrine MDI had sufficient data (including both pretreatment and posttreatment WCS evaluated within 60 min of epinephrine administration) to be included in our evaluation. The 210 children were treated with epinephrine MDI a total of 274 times. The mean age (±SD) was 36.4 (±29.27) months. Pretreatment WCS was mild (score range 0–2) in 27 children (12.9%), moderate (3–4) in 118 (56.2%), severe (5–7) in 60 (28.6%), and impending respiratory failure (≥8) in five (2.4%) children. The median pre- and posttreatment WCSs for all treatments was 4 and 1 with a median change of 2 (IQR 1–3) within 60 min of treatment ($p < 0.001$). Table 1 summarizes the effect of epinephrine MDI on WCS and physiologic parameters and provides mean (±SD) values to allow for comparisons with historical data. There were two reports of agitation (2/274 = 0.7%), and two children had HR ≥ 200 posttreatment (one with HR of 200 beats/min who had a pretreatment HR of 198 and the other with HR of 202 who had a pretreatment HR of 205. Both were noted to be agitated at the time of assessment). No other adverse effects were recorded. A single treatment of five puffs was administered in 165/210 (78.6%) children, two doses in 33/210 (15.7%), and three doses or more in 12/210 (5.7%). Table S2 shows the response to treatment by presenting severity of disease.

The mean improvement in the WCS (2.16) was very similar to the mean improvement (2.2) reported by Westley in a randomized trial using nebulized racemic epinephrine.[4] Excluding children with initial mild respiratory distress (WCS ≤ 2), the vast majority (150/183 [82.0%]) of children treated with five, 10, or 15 puffs (625, 1250, or 1875 μg) of epinephrine using MDI and VHC with facemask had clinically significant improvement in respiratory distress within 60 min of treatment. The only adverse effects observed were agitation and the continuation of preexisting extreme tachycardia in <1% of epinephrine administrations and there were no challenges identified with administration of epinephrine via MDI and VHC with mask. Results of this collaborative suggest epinephrine administration via MDI may be a safe and effective non–aerosol-generating alternative to the traditional nebulized epinephrine delivery for the treatment of croup.

Limitations of our study were the absence of a control group and lack of viral testing to identify the proportion of cases associated with SARS-CoV-2, which has been identified with clinical croup.[5–7] The optimal dose of epinephrine via the MDI route is currently unknown and while we used cumulative doses of almost 2 mg, it is possible that the lack of treatment response in some children was the result of underdosing.

AUTHOR CONTRIBUTIONS

All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. Waleed Alqurashi, Sarah J. Curtis, Mohamed Eltorki, April J. Kam, Rodrick Lim, Shannon MacPhee, and Suzanne Schuh helped to design the study and the data collection instruments and reviewed and revised the manuscript for intellectual content. Garth D. Meckler and David W. Johnson were involved in all aspects of the study design, collection, and analysis of data and drafting of the initial manuscript as well as subsequent revisions and approval of the final manuscript.

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CONFLICTS OF INTEREST

The authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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