



Efficacy of low-dose nebulized epinephrine as treatment for croup: A randomized, placebo-controlled, double-blind trial

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ABSTRACT

Objective: Croup treatment usually involves a single dose of systemic dexamethasone combined with nebulized epinephrine. However, the optimal dose of l-epinephrine remains unclear. We examined whether a low dose (0.1 mg/kg) was inferior to the conventional dose (0.5 mg/kg) of 1:1000 nebulized l-epinephrine in patients with moderate to severe croup.

Methods: This randomized double-blind clinical non-inferiority trial was conducted in three pediatric emergency departments from May 2015 to October 2017. Children 6 months to 5 years old with moderate to severe croup (Westley scale scores 3–11) were eligible. Subjects were randomly assigned to the conventional dose (0.5 mg/kg; maximum 5 mg) or low dose (0.1 mg/kg; maximum 1 mg) group. All subjects received 0.6 mg/kg dexamethasone. Croup scores and other vital signs were measured before and at 30, 60, 90, and 120 min after nebulized l-epinephrine administration. The primary outcome was the change in croup score after 30 min.

Results: The final analysis included 84 patients. The groups did not differ significantly in terms of demographic parameters. At 30 min after treatment with nebulized l-epinephrine, the croup scores in both groups were significantly reduced from the baseline values ($p < 0.05$) and did not differ between the two groups ($p = 0.42$). Neither blood pressure nor heart rate differed between the two groups.

Conclusions: Low-dose 1:1000 l-epinephrine was not inferior in croup score reduction to the conventional dose in patients with moderate to severe croup.

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1. Introduction

1.1. Background

Croup is an illness of infants and children <6 years of age that causes upper airway obstruction [1]. Standard croup treatment involves single-dose oral or intramuscular dexamethasone (0.15–0.6 mg/kg) combined with nebulized epinephrine [1]. Racemic epi-

nephrine is generally used to treat moderate to severe croup, but it is expensive and unavailable in some countries so l-epinephrine is widely used. The recommended dose of 2.25% racemic epinephrine is 0.05 mL/kg (maximum 0.5 mL) in children. The dose of 1:1000 l-epinephrine was determined by reference to the dose of racemic epinephrine. A dose of 0.05 mL 2.25% racemic epinephrine contains approximately 0.56 mg l-form and can be converted into about 0.5 mL (0.5 mg) 1:1000 l-epinephrine. A dose of 0.05 mL/kg racemic epinephrine is equivalent to 0.5 mL/kg 1:1000 l-epinephrine [2].

1.2. Importance

A previous study indicated no differences in treatment effects of 0.5, 2.5, and 5 mL of nebulized 1:1000 l-epinephrine in manage-

Abbreviations: CD, conventional dose; CI, confidence interval; ED, emergency department; LD, low dose.

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ment of post-extubation stridor. However, clinically significant increases in undesirable side effects, such as increased heart rate and blood pressure, were noted with increasing l-epinephrine dose [3]. Some reviews and guidelines recommend the use of 0.5 mg/kg (5 mg maximum) of 1:1000 l-epinephrine to treat croup, depending on its severity [1,4–6].

Although we have used less than the recommended dose for many years, our treatment is effective and lacks major side effects. Therefore, we hypothesized that nebulized 1:1000 l-epinephrine at doses <0.5 mL/kg (low dose, LD) would be as effective (without side effects) as a dose of 0.5 mL/kg (conventional dose, CD) in patients with moderate to severe croup.

1.3. Goals of this investigation

We examined whether there were any differences in treatment effects between CD and LD of l-epinephrine in patients with moderate to severe croup.

2. Methods

2.1. Study design and setting

This was a prospective randomized double-blind non-inferiority clinical trial. From May 2015 to October 2017, we enrolled children treated for croup in the pediatric emergency departments (EDs) of three teaching hospitals, all of which were tertiary care medical centers. The study was conducted only during research nurses' working hours.

2.2. Selection of participants

Children aged 6 months to 5 years old with moderate to severe croup were eligible for inclusion (Westley scale scores 3–11) (Table 1) [7]. Croup was defined as acute inspiratory stridor and barking cough preceding upper respiratory symptoms. We included only patients with clinically defined viral croup following 12–72 h of coughing and coryza.

Exclusion criteria were a history of contact with chickenpox within the preceding 3 weeks, prior enrollment in the study, respiratory failure, a history of intubation or apnea, congenital or

Table 1
Westley croup scores.

| Clinical findings | Points |
|---|--------|
| Level of consciousness | |
| Normal (including sleep) | 0 |
| Disoriented | 5 |
| Cyanosis | |
| None | 0 |
| Cyanosis with agitation | 4 |
| Cyanosis at rest | 5 |
| Stridor | |
| None | 0 |
| When agitated | 1 |
| At rest | 2 |
| Air entry | |
| Normal | 0 |
| Decreased | 1 |
| Markedly decreased | 2 |
| Retraction | |
| None | 0 |
| Mild (alar flaring) | 1 |
| Moderate (suprasternal and intercostal) | 2 |
| Severe (all accessory muscles used) | 3 |
| Maximum total points | 17 |

Modified from Westley et al. [7].

Levels of severity based on Westley scores: mild (0–2), moderate (3–5), severe (6–11), and impending respiratory failure (12–17).

acquired stridor, chronic lung disease, congenital heart disease, a history of premature birth (gestational age <36 weeks), a known immune dysfunction, corticosteroid treatment within the preceding 2 weeks, and epinephrine treatment prior to enrollment.

2.3. Treatment allocation and intervention

A random allocation sequence was created using a computer-generated random number table featuring a 1:1 ratio without blocking. All numbers were placed in sealed envelopes that were locked in drawers. Sequentially numbered, sealed, opaque envelopes containing treatment assignments were opened when the eligibility criteria were met. A research nurse and a researcher screened patients in pediatric EDs, and when children with croup were encountered, the researcher checked patient eligibility. All subjects were assigned to one of two groups, i.e., the CD group (inhalation of 0.5 mg/kg l-epinephrine ; maximum 5 mg) or LD group (0.1 mg/kg; maximum 1 mg). The research nurses prepared 5-mL solutions of epinephrine mixed with normal saline and gave them to the treating nurses. These medications were prepared by the research nurse in an area that was inaccessible to the treating physicians or nurses to prevent observation of the medication preparation process. Moreover, because the color and volume of the drugs were the same, the treating physician was blinded to the dose administered to particular patients. None of the physicians, legal guardians, or patients knew which preparation any child received. All patients received 0.6 mg/kg dexamethasone orally or via intramuscular injection.

Fig. 1 shows the details of the study protocol. Briefly, 30 min after epinephrine treatment, the treating physician checked the croup score and patient condition and decided whether to prescribe an additional dose of epinephrine. If the clinical condition did not improve with a second dose, the physician was allowed to engage in other management without following the study protocol. The subjects were discharged after 4 h of observation if they met the discharge criteria. Croup scores and vital signs for each time period were monitored by treating physicians and nurses.

2.4. Measurements

Before randomization, the age, gender, weight, and medical and family histories of the enrolled participants were assessed.

We used the Westley croup score to assess clinical outcomes. The croup score, blood pressure, heart and respiratory rates, and extent of oxygen saturation were measured before any medication and at 30, 60, 90, and 120 min after initial delivery of nebulized l-epinephrine .

2.5. Outcome

The primary outcome was the difference of change in Westley croup score at 30 min after nebulized l-epinephrine treatment from the initial score between the two groups. Secondary outcomes were the change in Westley croup score over time, side effects of epinephrine (tachycardia, hypertension [>95 th age percentile], pallor, arrhythmia, and/or tremor), the need for additional epinephrine, treatment failure (unblinding was required), and health care utilization (length of stay, admission rate, revisit status within 7 days after discharge, the rate of intubation, and/or intensive care unit admission).

2.6. Sample size calculation and data analysis

We hypothesized that the mean change in croup score at 30 min after the first epinephrine dose would not be inferior in

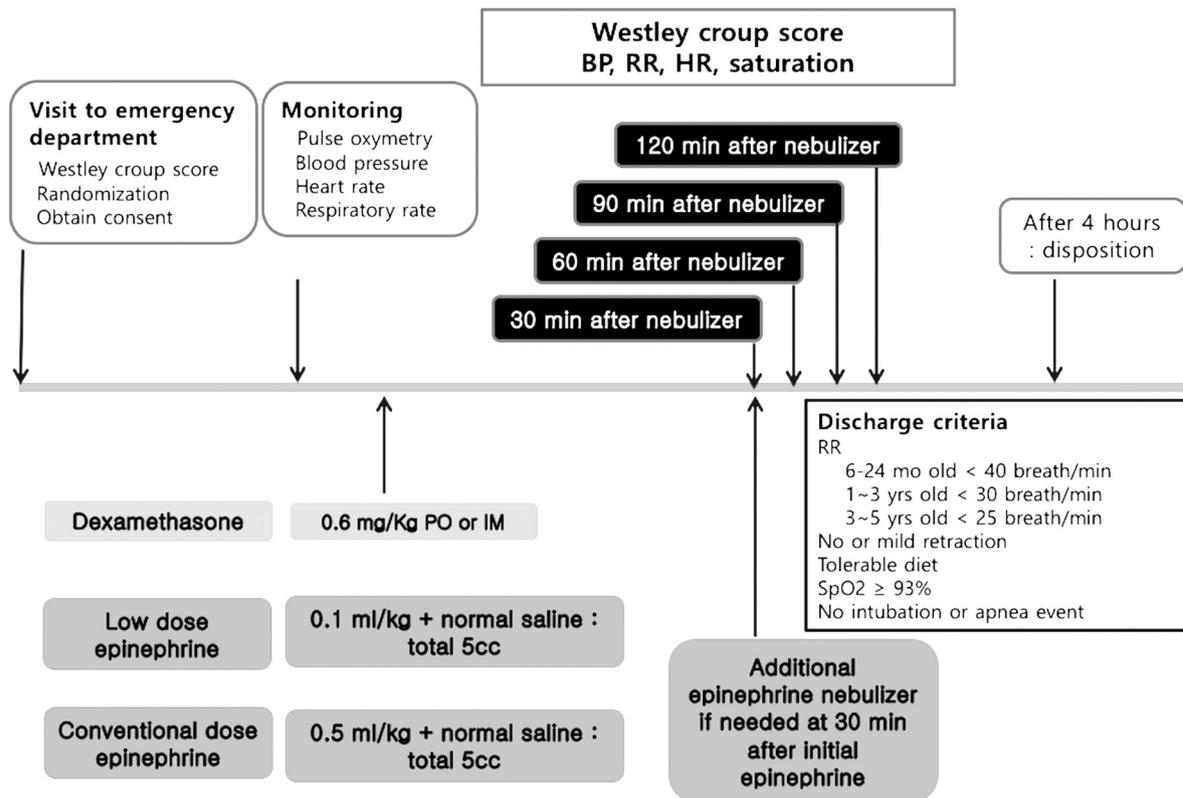


Fig. 1. Study flow. BP: Blood pressure RR: Respiratory rate HR: Heart rate.

the LD group, as compared to the CD group. There have been no previous studies in this setting, so the sample size was calculated using the value of the post-extubation stridor study [3]. The difference in croup score 20 min after nebulized ι -epinephrine treatment was $-0.68 (\pm 0.82)$ in the 0.5 mL group and $-0.28 (\pm 1.48)$ in the 5 mL group. Based on these data, it was calculated that 214 patients were needed, considering a 10% dropout rate. Unlike the post-extubation stridor study, however, intended interim analysis indicated that the croup score was significantly reduced $-1.81 (\pm 1.22)$ in the LD group and $-2.04 (\pm 1.55)$ in the CD group. Therefore, a final sample size of 84 was required to afford 80% power and a one-sided significance level of 2.5% to identify a difference between the LD and CD groups in the mean Westley croup score change with the lower limit of confidence interval greater than the non-inferiority limit of -1 , assuming a rate of withdrawal or loss to follow-up of approximately 10%. The inferiority margin is based on a croup score of ≥ 2 in the post-extubation stridor study [3], but this was a non-inferiority test and was based on 1 point for conservative application.

All data were analyzed using STATA software (ver. 14.1) and SPSS (ver. 22). Categorical variables were compared using Fisher's exact or the chi-squared test, and continuous variables were compared using Student's *t*-test, paired *t*-test, or repeated-measures analysis of variance (ANOVA). In all analyses, $p < 0.05$ was taken to indicate statistical significance. We performed intention-to-treat analysis, and all children were included in the final analysis.

2.7. Ethics

The study was approved by the institutional review boards of all participating hospitals. Legal guardians provided written informed consent after we explained the research objectives and study methods, and imparted other relevant information.

3. Results

3.1. Characteristics of the study subjects

A total of 517 patients were screened for eligibility, and 86 were enrolled (48 in the LD group and 38 in the CD group). Of these, one patient with a croup score of 2 and one patient who was discharged early were excluded. Therefore, 84 patients were finally included in the analysis (47 in the LD group and 37 in the CD group) (Fig. 2). There were no significant between-group differences in age, sex, weight, croup score, passive smoking status, history of bronchodilator use, or family history of asthma (Table 2).

The mean baseline croup scores were $3.68 (\pm 0.84)$ in the LD group and $4.30 (\pm 1.24)$ in the CD group ($p = 0.012$); however, the median croup score did not differ between the groups ($p = 0.053$). Baseline oxygen saturation, blood pressure, and heart and respiratory rates did not differ significantly between the two groups (Table 2).

3.2. Primary outcome

Thirty minutes after treatment, the mean croup scores in both groups fell significantly from the baseline values ($p < 0.01$); the decreases did not differ between the two groups ($-1.85 (\pm 1.08)$ in the LD group, $-2.08 (\pm 1.53)$ in the CD group, CI -0.36 – 0.82 , $p = 0.42$). The mean croup scores of the two groups did not differ at any time (Fig. 3).

3.3. Secondary outcomes

Systolic and diastolic blood pressure and heart rate did not differ between the two groups. We encountered no clinically significant hypertension or tachycardia (Fig. 4). Three patients (6.4%) in

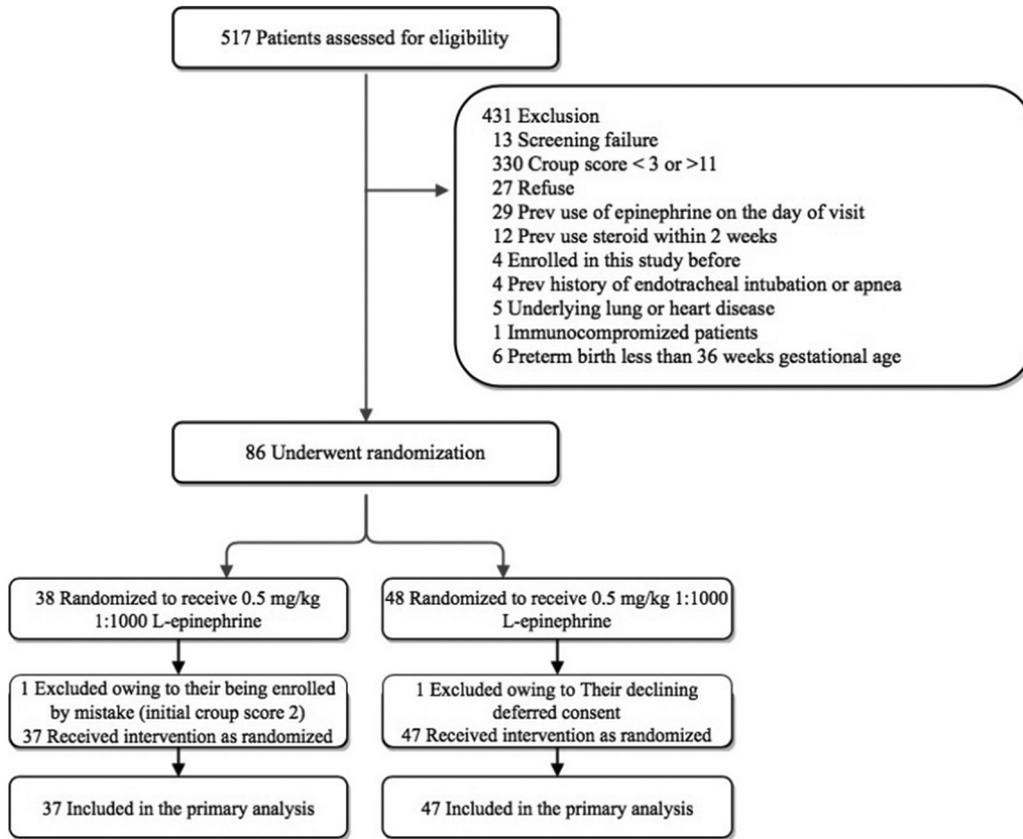


Fig. 2. Study participant flow.

Table 2
Patient characteristics.

| | Low dose group ^a (n = 47) | Conventional dose group ^b (n = 37) | p- Value |
|---|---|--|-------------|
| Age (months), mean (±SD) | 21.9 (±10.0) | 21.4 (±12.0) | 0.86 |
| Male, n (%) | 29 (61.7) | 23 (62.2) | 0.97 |
| Weight (kg), mean (±SD) | 12.4 (±2.5) | 11.8 (±2.0) | 0.25 |
| Past history, n (%) | | | |
| Croup | 9 (19.1) | 6 (16.2) | 0.73 |
| Bronchodilator use | 1 (2.1) | 2 (5.4) | 0.42 |
| Family history, n (%) | | | |
| Asthma | 3 (6.4) | 3 (8.1) | 0.76 |
| Smoking | 12 (25.5) | 13 (35.1) | 0.34 |
| I-croup score, mean (±SD) | 3.68 (±0.84) | 4.30 (±1.24) | 0.01 |
| Median (IQR) | 4.00 (3.00–4.00) | 4.00 (3.50–5.00) | 0.05 |
| Additional epinephrine, n (%) | | | 0.82 |
| 1 | 18 (38.3) | 12 (32.4) | |
| 2 | 3 (6.4) | 2 (5.4) | |
| Adm ^c from ED ^d , n (%) | 3 (6.4) | 6 (16.2) | 0.15 |
| Adm ^c within 7 days, n (%) | 0 (0) | 0 (0) | |
| Revisit within 7 days, n (%) | 6 (12.8) | 1 (2.8) | 0.13 |
| Length of stay, mean (±SD) (min) | 297.1 (±232.2) | 312.1 (±220.5) | 0.76 |

^a Low dose group: 0.1 mg/kg of 1:1000 (v/v) L-epinephrine.
^b Conventional dose group: 0.5 mg/kg of 1:1000 (v/v) L-epinephrine.
^c Adm: admission.
^d ED: emergency department.

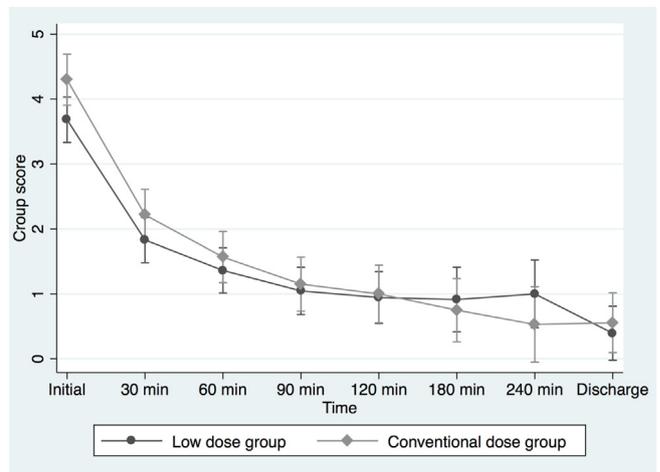


Fig. 3. Changes in croup scores. Croup scores decreased with time in both groups after administration of 1:1000 nebulized L-epinephrine ($p < 0.05$) but did not differ between the groups ($p = 0.42$).

in the LD group and one (2.8%) in the CD group revisited the ED within 7 days ($p = 0.13$), but no patients were admitted at the time of revisit (Table 2). Nebulized epinephrine did not cause any side effects.

4. Limitations

This study had some limitations. First, the random-number table was generated without using a block, and the number of patients assigned to each group differed. However, as the required

the LD group and six (16.2%) in the CD group were admitted; these rates were not significantly different ($p = 0.15$). Six patients (12.8%)

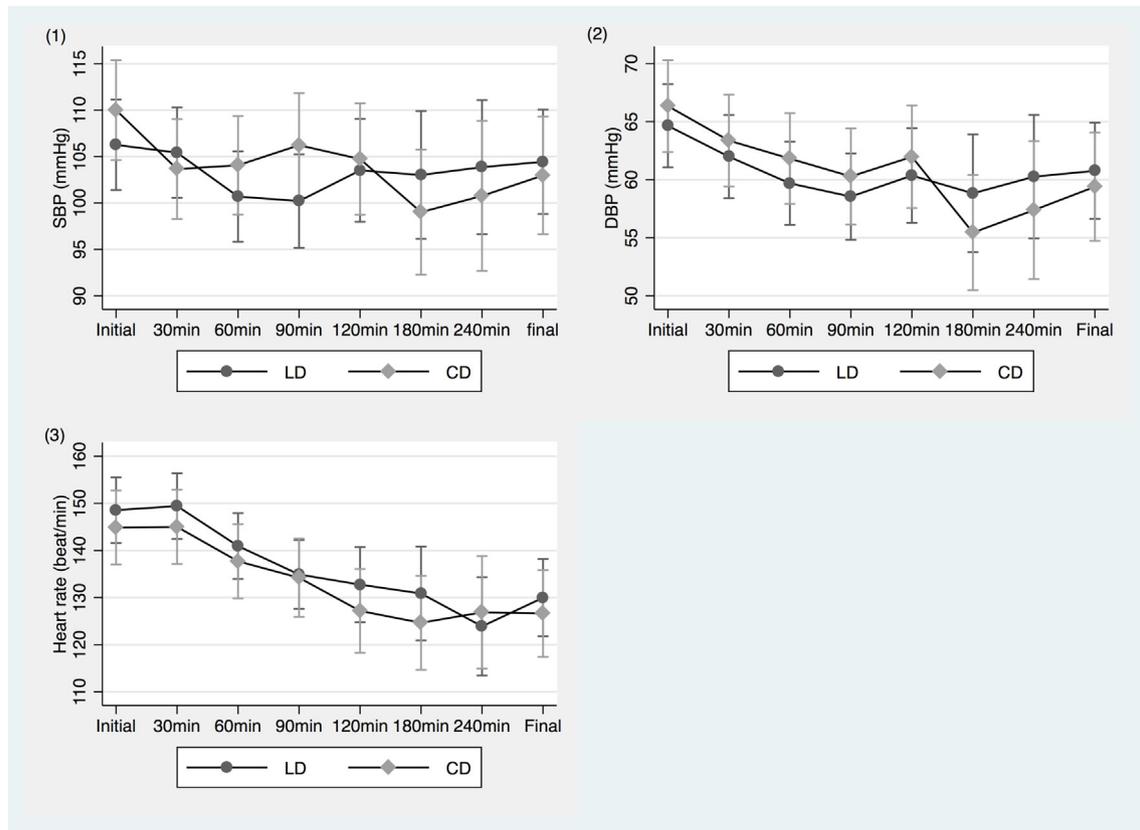


Fig. 4. Changes in vital signs. SBP, DBP, and HR did not differ between the two groups, and we encountered no clinically significant hypertension or tachycardia. LD: low-dose group: 0.1 mg/kg of 1:1000 ι -epinephrine. CD: conventional dose group: 0.5 mg/kg of 1:1000 ι -epinephrine. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. HR: Heart rate.

sample size was attained prior to the 10% dropout, this did not greatly affect the results. Second, the mean initial croup score was significantly different between the groups, suggesting that the croup score of the CD group was particularly high. However, there were no significant differences between the two groups when comparing the median rather than the mean. Repeated-measures ANOVA revealed no significant differences in changes in croup score between the two groups. Third, secondary outcomes such as hospital admission and revisit rates may have been statistically nonsignificant due to the small sample size. This should be verified by further additional large-scale studies. Finally, the severity of the patients enrolled in the study was relatively mild. We recruited moderate to severe patients but were able to include only a limited number of severe patients due to the nature of the disease. To overcome this limitation, future research should include stratification according to severity.

5. Discussion

We performed a randomized controlled double-blind non-inferiority trial in pediatric patients with moderate to severe croup and found that LD (0.1 mg/kg) 1:1000 nebulized ι -epinephrine therapy was not inferior with regard to croup score reduction compared to CD (0.5 mg/kg) therapy. To our knowledge, this is the first study to explore the effects of different epinephrine doses in croup patients.

Using the Westley croup score system, a score difference of 1–2 points greatly reflects the difference in the patient's clinical condition. If the medication causes a score of 1–2 points to be reduced it

is considered to be of clinical importance, and if the difference between the two doses is <1 point it is regarded as a criterion for not overlooking the effect difference.

Viral croup usually commences as an upper respiratory tract-like infection, with low-grade fever and coryza followed by barking cough and shortness of breath to various degrees. Although croup is a benign condition with a low mortality rate, many children with croup present to the ED because the symptoms commence suddenly. Several treatments have been used to manage croup in children, but only supportive care, steroids, and nebulized epinephrine have proven effective [5].

Nebulized epinephrine has become part of the standard management of moderate and severe croup. Initially, nebulized epinephrine was delivered in the form of 2.25% racemic epinephrine. One study explored whether 1:1000 ι -epinephrine could be used instead of racemic epinephrine; 5 mg of 1:1000 ι -epinephrine was equivalent to 0.5 mL of 2.25% racemic epinephrine. A comparison revealed no between-group difference in croup score reduction [2]. They suggested that the ι -form of the racemic mixture is the active isomer, and that there is no reason to believe that a given amount of the ι -isomer, when mixed with the D-form (RE), is less likely to produce adverse effects [2]. A recent meta-analysis concluded that nebulized epinephrine significantly reduces the croup score at 30 min and significantly shortens the hospital stay compared to placebo; racemic epinephrine and ι -epinephrine show no difference in efficacy after 30 min, although ι -epinephrine shows a significant reduction over racemic epinephrine after 2 h [8]. The production and use of racemic epinephr-

ine is limited, and all recent studies have been conducted using ι -epinephrine; thus, the significance of this study is much greater [9,10].

Although some studies evaluated the utility of nebulized ι -epinephrine in patients with croup, studies comparing different doses have been performed only in patients with post-extubation stridor. In one such study, 0.5, 2.5, and 5 mg nebulized ι -epinephrine were equally effective [3]. In another study, 0.05 mg/kg and 0.5 mg/kg 1:1000 ι -epinephrine were also equally effective [11]. We compared epinephrine at 0.1 mg/kg and 0.5 mg/kg in croup patients. The croup score fell significantly and to the same extent in the two groups.

Consistent with our results, no side effects have been reported following administration of any form of epinephrine to patients with croup [8]. We did not encounter any hypertension or tachycardia, which may be clinically problematic at higher epinephrine doses.

Medication errors are common when pediatric populations are treated, with a rate threefold higher than for adult patients [12]. Such errors include dosing errors and the use of incorrect administration routes. One study indicated that 16% of treatments featured drug administration errors [13]. In Korea, a 2012 analysis of the Korea Adverse Event Reporting System database showed that medication errors associated with erroneous drug administration routes (21.2%) and accidental overdoses (24.6%) were 2.73-fold more common in pediatric patients than in adults [14]. Medication errors may be even more frequent in busy EDs. If a physician prescribes nebulized epinephrine for a croup patient and a nurse then erroneously gives the drug intravenously, the side effects may be fatal. Multifocal atrial tachycardia following an iatrogenic overdose of epinephrine has been reported after incidental intravenous administration [15]. Higher epinephrine dose is associated with poorer outcome. Therefore, the lowest possible dose of epinephrine should be used.

Our randomized controlled double-blind non-inferiority trial in pediatric patients with moderate to severe croup showed that LD (0.1 mg/kg) 1:1000 ι -epinephrine inhalation was not inferior to the CD (0.5 mg/kg). The results suggest that low-dose nebulized ι -epinephrine can be used safely in treatment of moderate to severe croup.

Contributor's statement

Jin Hee Lee, Jae Yun Jung: Dr. Lee and Dr. Jung equally conceptualized and designed the study, and drafted the initial manuscript, and approved the final manuscript as submitted.

Do Kyun Kim: Dr. Kim coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

Hyunjung Lee, Young Ho Kwak, Ikwan Chang, Hyuksool Kwon, Yoo Jin Choi, Joong Wan Park, So Hyun Paek, Jun Hwi Cho carried out the data collection, the initial analyses, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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References

- [1] Cherry JD. Clinical practice. Croup. *N Engl J Med* 2008;358(4):384–91.
- [2] Waisman Y, Klein BL, Boenning DA, Young GM, Chamberlain JM, O'Donnell R, et al. Prospective randomized double-blind study comparing ι -epinephrine and racemic epinephrine aerosols in the treatment of laryngotracheitis (croup). *Pediatrics* 1992;89(2):302–6.
- [3] Abir M, Davis MM, Sankar P, Wong AC, Wang SC. Design of a model to predict surge capacity bottlenecks for burn mass casualties at a large academic medical center. *Prehosp Disaster Med* 2013;28(1):23–32.
- [4] Rajapaksa S, Starr M. Croup—assessment and management. *Aust Fam Physician* 2010;39(5):280–2.
- [5] Zoorob R, Sidani M, Murray J. Croup: an overview. *Am Fam Physician* 2011;83(9):1067–73.
- [6] Moreira ME, Hernandez C, Stevens AD, Jones S, Sande M, Blumen JR, et al. Color-coded prefilled medication syringes decrease time to delivery and dosing error in simulated emergency department pediatric resuscitations. *Ann Emerg Med* 2015;66(2):97–106 e3.
- [7] Westley CR, Cotton EK, Brooks JG. Nebulized racemic epinephrine by IPPB for the treatment of croup: a double-blind study. *Am J Dis Child* 1978;132(5):484–7.
- [8] Bjornson C, Russell K, Vandermeer B, Klassen TP, Johnson DW. Nebulized epinephrine for croup in children. *Cochrane Database Syst Rev* 2013(10):Cd006619.
- [9] Duman M, Ozdemir D, Atasever S. Nebulised ι -epinephrine and steroid combination in the treatment of moderate to severe croup. *Clin Drug Investig* 2005;25(3):183–9.
- [10] Eghbali A, Sabbagh A, Bagheri B, Taherahmadi H, Kahbazi M. Efficacy of nebulized ι -epinephrine for treatment of croup: a randomized, double-blind study. *Fundam Clin Pharmacol* 2016;30(1):70–5.
- [11] Preutthipan A, Poomthavorn P, Sumanapisan A, Chinrat B, Thasuntia S, Plitponkarnpim A, et al. A prospective, randomized double-blind study in children comparing two doses of nebulized ι -epinephrine in postintubation croup. *J Med Assoc Thai* 2005;88(4):508–12.
- [12] Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001;285(16):2114–20.
- [13] Marino BL, Reinhardt K, Eichelberger WJ, Steingard R. Prevalence of errors in a pediatric hospital medication system: implications for error proofing. *Outcomes Manag Nurs Pract* 2000;4(3):129–35.
- [14] Woo Y, Kim HE, Chung S, Park BJ. Pediatric medication error reports in Korea adverse event reporting system database, 1989–2012: comparing with adult reports. *J Korean Med Sci* 2015;30(4):371–7.
- [15] Aburawi EH, Narchi H, Soudi AK. Persistent wandering atrial pacemaker after epinephrine overdosing—a case report. *BMC Pediatr* 2013;13(1).