# A Prospective, Randomized Double-blind Study in Children Comparing Two Doses of Nebulized L-epinephrine in Postintubation Croup

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***Objective:*** *To compare the effectiveness and side effects of nebulized l-epinephrine (NLE) at a dose of 0.05 mL/kg versus 0.5 mL/kg in the treatment of postintubation croup in children.*
***Material and Method:*** *Thirty-nine children, who developed signs and symptoms of upper airway obstruction (UAO) after extubation, were randomized to receive either 0.05 mL/kg or 0.5 mL/kg of NLE. UAO scores, vital signs (VS) and possible side effects were recorded before and at 20 and 40 minutes after the treatment.*
***Results:*** *Twenty-one and 18 patients were allocated to the 0.05 and 0.5 mL/kg groups, respectively. Both groups showed improvements in UAO scores over time. There were no significant differences in UAO scores and VS between the groups at all time points. Side effects of epinephrine were not observed.*
***Conclusion:*** *In children with postintubation croup, the administration of NLE at the dose of 0.05 mL/kg results in similar improvements in the UAO scores, compared with the dose of 0.5 mL/kg. No complications were seen in either dose.*

***Keywords:*** *Aerosol, Children, Croup, Epinephrine, Intubation, Upper airway obstruction*

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Postintubation croup, or postextubation subglottic edema, has been a well-recognized entity since airways were first secured by intubation. Children are more prone to develop croup following intubation than adults because of differences in airway anatomy. Children have narrower laryngeal and tracheal lumens that are obstructed more readily by mucosal edema. In addition, the narrowest portion of the child's airway is at the level of the cricoid cartilage and not at the level of the larynx, which invites internal tracheal injury because an endotracheal tube that can easily pass through the vocal cords may become wedged in the narrower subglottic area. The incidence of postintubation croup has been reported to be 1 to 6% in all endotracheally intubated children[1].

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The medical treatment of postintubation croup is the same as that for infectious croup, including corticosteroids and nebulized epinephrine. The vasoconstrictive effect of epinephrine could attenuate the degree of subglottic edema, resulting in clinical improvement. Initial studies employed nebulized racemic epinephrine [a mixture of dextro (d)-isomers and levo (l)-isomers] because of fears regarding cardiotoxicity from l-isomers[2], but subsequent trials have shown the l-epinephrine (the usual form available for resuscitation) to be as safe and effective in both infectious and postintubation croup[3,4]. It was noted that the doses of l-epinephrine used in those trials were 2.5 and 5 mL of 1:1000 solution for all recruited children, regardless of weight. As a result, the dose of l-epinephrine in the treatment of croup has been suggested to be 0.5 mL/kg, with a maximum dose of 2.5 mL and 5 mL for children younger and older than 4

years, respectively[5]. In Thailand, since racemic epinephrine has never been available, nebulized l-epinephrine has long been routinely prescribed for patients with croup. However, the recommended dose of nebulized l-epinephrine in Thailand, surprisingly, is much less than that in the Western world. The dose of 0.05 mL/kg, with a maximum of 0.5 mL, together with systemic corticosteroids, was found to be effective in the treatment of infectious croup in Thai children[6]. Because of this controversy, the authors therefore conducted this study in a prospective, randomized double-blind fashion to compare the efficacy and safety of these two different doses of nebulized l-epinephrine in the treatment of postintubation croup.

## Material and Method

The present study was performed in the Pediatric Intensive Care Unit of Ramathibodi Hospital, Mahidol University. Patients were eligible for enrollment in the study if they were under 15 years of age and demonstrated hoarseness, barking cough or inspiratory stridor after extubation. Patients with a previous history of laryngomalacia, subglottic stenosis, infectious croup or foreign body aspiration were excluded from enrollment. The study was approved by the Institutional Review Board, and written consent was obtained from a parent or guardian of each child.

Eligible patients were randomized, using a block randomization, to receive nebulized l-epinephrine (1:1000 solution) of either 0.05 or 0.5 mL/kg per dose, up to a maximum dose of 2.5 mL for patients $\leq$ 4 years old and 5.0 mL for patients > 4 years old. One nurse prepared the l-epinephrine with the dose according to the block randomization. If the amount of l-epinephrine was less than 5 mL, isotonic saline was added until the volume achieved 5 mL. Another nurse gave the nebulized l-epinephrine formulation to the patient via a facemask, with a continuous flow of 100% oxygen at 7 liters/minute. The treatment was blinded to both the patient and the investigator. The blinded randomization code was broken only after the last patient completed the study.

The principal outcome measure was the change in the upper airway obstruction score. Secondary outcome measures included changes in respiratory rate, heart rate, blood pressure and oxygen saturation. The upper airway obstruction score as shown in Table 1 was evaluated by a single investigator before aerosol administration (time 0), and at 20 and 40 minutes after aerosol administration was initiated. Supplemental humidified 40% oxygen was given to all patients after the aerosol treatment. For better objective accuracy, the parameter of cyanosis was modified and defined as oxygen saturation < 95%. The respiratory rate, heart rate, blood pressure (Dinamap, Critikon, Tampa, FL) and arterial oxygen saturation (Nellcor, Inc, Hayward, CA) were recorded for each patient at time 0 and at 20 and 40 minutes. The presence of arrhythmia, pallor or tremor was also recorded to determine other possible side effects of epinephrine. If, during the study, a patient demonstrated recurrent signs and symptoms of upper airway obstruction, additional interventions were administered as clinically indicated.

### *Statistical analysis*

Differences between patient characteristics of the two groups were assessed by the unpaired t-test or Mann-Whitney U test for numerical variables, the chi-square test for categorical variables or Fisher exact test if one expected cell value was < 5. Repeated-measures analysis of variance (ANOVA) was used to compare changes in the upper airway obstruction score, respiratory rate, heart rate, blood pressure and oxygen saturation over the course of the study. Physiologic measurements were examined first for change over time, then for differences in change over time between the two groups. Differences were considered statistically significant at $p \leq 0.05$.

**Table 1.** Upper airway obstruction score[9]

| Score | 0 | 1 | 2 |
|---|---|---|---|
| Cough | None | Hoarse cry | Bark |
| Stridor | None | Inspiratory | Inspiratory + expiratory |
| Retraction | None | Suprasternal | Suprasternal + substernal + intercostal |
| Inspiratory breath sound | Normal | Harsh with rhonchi | Delayed |
| Cyanosis* | None | In room air | In 40% oxygen |

* Cyanosis was modified and defined as oxygen saturation < 95%

## Results

A total of 46 patients were enrolled in the present study, with 23 patients randomized to receive 0.05 mL/kg and 23 patients randomized to receive 0.5 mL/kg of l-epinephrine. The oral route was used for intubation in all patients in both groups. Before the study was completed, 2 patients in the 0.05 mL/kg group and 1 patient in the 0.5 mL/kg group had developed worsening signs and symptoms of upper airway obstruction and required rescue doses of l-epinephrine. Moreover, in the 0.5 mL/kg group, there were 2 patients reintubated due to central nervous system problems associated with respiratory fatigue; 1 patient due to upper airway obstruction and 1 patient due to sudden cyanosis of unknown etiology. No patient in the 0.05 mL/kg group required reintubation. As a result, 7 patients were deleted from the statistical analysis, so there were 21 and 18 patients who remained in the 0.05 mL/kg and 0.5 mL/kg groups, respectively. Both groups were similar in baseline characteristics (Table 2). The majority of the patients in both groups had initial upper airway obstruction scores between 4-7, which were classified as moderate obstruction.

As shown in Table 3, patients in both groups demonstrated a significant reduction in upper airway obstruction scores at 20 and 40 minutes, compared to time 0. No significant differences were observed between the two groups in the rate and overall extent of improvement in upper airway obstruction scores. At 20 minutes, 7 of 21 patients in the 0.05 mL/kg group and 8 of 18 patients in the 0.5 mL/kg group demon-

**Table 2.** Patient characteristics of study groups

| | 0.05 mL/kg | 0.5 mL/kg |
|---|---|---|
| Number of patients | 21 | 18 |
| Age (months) | 2-131* | 2-136* |
| Gender (M/F) | 10/11 | 8/10 |
| Indications for intubation, n (%) | | |
| Respiratory failure | 14 (66.7) | 10 (55.6) |
| Heart failure | 1 (4.8) | 2 (11.1) |
| Central nervous system problems | 2 (9.5) | 4 (22.2) |
| Postsurgical | 4 (19.0) | 2 (11.1) |
| Duration of intubation (days) | 1-30* | 1-40* |
| > 7 days, n (%) | 9 (42.9) | 6 (33.3) |
| Corticosteroid administration | | |
| Before extubation, n (%) | 10 (83) | 13 (93) |
| After extubation, n (%) | 2 (17) | 1 (7) |
| Upper airway obstruction score immediately after extubation | 3.71±1.62** | 3.56±1.46** |
| < 4, n (%) | 8 (38.1) | 7 (38.9) |
| 4-7, n (%) | 12 (57.1) | 11 (61.1) |
| >7, n (%) | 1 (4.8) | 0 (0) |

No significant differences exist between the two treatment groups for any variable
* range, ** mean ± SD, n = number

**Table 3.** Outcome variables

| | Time 0 | | 20 Minutes | | 40 Minutes | |
|---|---|---|---|---|---|---|
| | 0.05 mL/kg (n = 21) | 0.5 mL/kg (n = 18) | 0.05 mL/kg (n = 21) | 0.5 mL/kg (n = 18) | 0.05 mL/kg (n = 21) | 0.5 mL/kg (n = 18) |
| Upper airway obstruction score* | 4 (1-8) | 4 (1-6) | 3 (0-5)** | 2 (0-5)** | 2 (0-8)** | 1.5 (0-5)** |
| Respiratory rate*** (per min) | 35.1±8.7 | 35.2±9.4 | 38.3±8.8 | 38.1±8.4 | 36.4±7.8 | 38.0±10.3 |
| Heart rate*** (bpm) | 128.1±17.7 | 127.2±13.3 | 137.5±19.0 | 127.2±16.0 | 130.2±18.8 | 124.4±17.8 |
| Systolic blood pressure*** (mmHg) | 97.4±13.0 | 104.2±19.6 | 103.1±15.2 | 106.6±20.3 | 97.0±13.7 | 104.4±22.1 |
| Diastolic blood pressure*** (mmHg) | 56.0±12.8 | 62.8±14.1 | 59.8±11.9 | 62.6±16.3 | 54.5±14.0 | 62.2±15.9 |
| Oxygen saturation*** (%) | 95.5±7.1 | 97.8±2.4 | 96.1±6.3 | 98.6±2.2 | 96.6±4.8 | 98.1±3.5 |

* Values are expressed as median (range), ** Significant change from time 0, $p < .05$ (ANOVA with repeated-measurement), *** Values are expressed as mean ± SD

strated a clinically significant reduction in upper airway obstruction scores $\geq$ 2 points. At 40 minutes, compared to time 0, 9 of 21 patients in the 0.05 mL/kg group and 11 of 18 patients in the 0.5 mL/kg group demonstrated a clinically significant reduction in upper airway obstruction scores $\geq$ 2 points. The patients' vital signs were unchanged at 20 and 40 minutes in either group (Table 3). Neither arrhythmia, pallor nor tremor was observed in both groups. The minimum sample size of 18 patients in each group yielded an 80% power to detect a difference of change in upper airway obstruction scores of $\geq$ 1.7 points, between groups.

**Discussion**

The present results suggest that nebulized l-epinephrine, at a minimal dose of 0.05 mL/kg, is at least as effective as the dose of 0.5 mL/kg in the treatment of postintubation croup. Both doses temporarily alleviated airway obstruction without undesirable side effects. The dose of 0.05 mL/kg is much less expensive. The authors would suggest that the dose of 0.05 mL/kg is also efficacious in the treatment of children with postintubation croup. This dose may be adequate to diminish mucosal edema of the upper airway by stimulating alpha-adrenergic receptors and producing vasoconstriction[7].

Sumboonnanonda[6] used nebulized l-epinephrine at the dose of 0.05 mL/kg (maximum 0.5 mL) in the treatment of infectious croup. They found a clinically significant reduction in upper airway obstruction scores at 24 and 48 hours after admission, even in the placebo group without dexamethasone treatment. The present study found a similar effect at 20 and 40 minutes in the patients with postintubation croup. The maximum dose in the present study was set at 2.5 mL for patients $\leq$ 4 years old and 5.0 mL for patients > 4 years old. Therefore, some of the presented patients weighing more than 10 kg received a greater amount of l-epinephrine than the dose regimen used in the study by Sumboonnanonda.

The present results confirm previous observations regarding the beneficial effects and safety of nebulized l-epinephrine in the treatment of postintubation croup[4] and infectious croup[3]. Nutman[4] used 0.25 mL of 1% l-epinephrine (2.5 mg), regardless of weight, for children with postintubation croup. Nutman found a significant reduction in stridor score within 20 minutes, similarly to the present study. They also demonstrated that the improvement continued over the next 8 hours. Waisman[3] used 5 mL of 1:1000 l-epinephrine (5 mg), regardless of weight, in children with infectious croup. Waisman found a significant reduction of the croup score, reaching a maximal effect at 30 minutes, but the croup score at the 2-hour-posttreatment was not different from the pretreatment, suggesting the potential risk of rebound phenomenon. It was noted that the dose used in Waisman's study was double the dose used in Nutman's study. Whether the rebound phenomenon depends on the amount of l-epinephrine is unknown. In addition, epinephrine side effects, including changes in heart rate, blood pressure and the presence of anxiety or jitteriness, were not noticed in either study, which is consistent with the present findings.

The upper airway obstruction score is a helpful research tool used to standardize disease severity at an arbitrary point, and a decreasing score provides an objective measure of clinical improvement. A variety of the upper airway obstruction scores have been devised. However, none has been universally accepted as the gold standard[8]. The disadvantages of Downes and Raphaely's score[9], which was chosen to be used in the present study, were the lack of a parameter for alterations in mental status, which are sometimes seen in patients with moderate to severe croup, and the lack of an objective parameter, such as the respiratory rate. However, other clinical parameters, such as stridor and retractions, which have been demonstrated to correlate well with radiological measurements of tracheal diameter in croup[10], are represented.

Several study limitations merit discussion. The present study was designed to assess only the maximal effect of nebulized l-epinephrine, which most likely occurred within the first 40 minutes. The duration of action of nebulized l-epinephrine, which may be longer than 40 minutes, could not be ascertained and was beyond the scope of the present study. It is our clinical practice guideline to give humidified oxygen to all patients after extubation. The score of cyanosis in room air, therefore, could not be evaluated. Since the present study had a relatively small number of participants, it might not be powered to detect small differences between groups. Finally, it is possible that observer bias influenced the reporting of upper airway obstruction scores. However, previously mentioned measures to ensure blinding were adhered to meticulously.

In conclusion, the presented data suggest that aerosolized l-epinephrine, at the dose of 0.05 mL/kg, results in a similar reduction in upper airway

obstruction scores, compared with the dose of 0.5 mL/kg, in children with postintubation croup. Neither dose was associated with any adverse side effects. Given the comparable efficacy of both doses, the use of a minimal dose in clinical practice would save the medication expense and, theoretically, have a lower risk of developing side effects that are mostly dose dependent. Future studies should consider the use of l-epinephrine at the dose of 0.05 mL/kg in children with infectious croup, which has a pathophysiology resembling postintubation croup. Further studies examining the optimal dose and frequency of nebulized l-epinephrine in children with croup seem warranted.

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## *การศึกษาเปรียบเทียบประสิทธิภาพของยาอีพิเนฟรินแบบพ่นสองขนาดในการรักษาการบวมที่เกิดขึ้นภายหลังการถอดท่อหลอดลมคอ*

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***วัตถุประสงค์****: เพื่อเปรียบเทียบประสิทธิภาพและผลข้างเคียงของการใช้ยาพ่นอีพิเนฟรินในขนาด 0.05 มล./กก. กับ 0.5 มล./กก. ในการรักษาการบวมที่เกิดขึ้นภายหลังการถอดท่อหลอดลมคอ*

***วัสดุและวิธีการ****: สุ่มผู้ป่วยเด็กจำนวน 39 ราย ที่มีอาการแสดงของการบวมของทางเดินหายใจส่วนต้นภายหลังการถอดท่อหลอดลมคอออกเป็น 2 กลุ่ม กลุ่มแรกให้พ่นอีพิเนฟรินขนาด 0.05 มล./กก. กลุ่มที่สองให้พ่นขนาด 0.5 มล./กก. แล้วประเมินประสิทธิภาพการรักษาโดยใช้คะแนนสะสมของอาการแสดงที่บ่งชี้ภาวะอุดกั้นทางเดินหายใจส่วนต้นร่วมกับการประเมินสัญญาณชีพและผลข้างเคียง ก่อนพ่นยา และที่ 20 และ 40 นาทีหลังพ่นยาตามลำดับ*

***ผลการศึกษา****: มีผู้ป่วย 21 และ 18 รายอยู่ในกลุ่ม 0.05 มล./กก. และ 0.5 มล./กก. ตามลำดับ ผู้ป่วยทั้ง 2 กลุ่มมีการลดลงของอาการแสดงที่บ่งชี้ภาวะอุดกั้นทางเดินหายใจส่วนต้นที่เวลา 20 และ 40 นาทีพอ ๆ กัน โดยไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างทั้ง 2 กลุ่ม นอกจากนี้ยังไม่พบผลข้างเคียงใด ๆ ที่เกิดจากยาพ่นทั้ง 2 ขนาด*

***สรุป****: ยาอีพิเนฟรินพ่นในขนาด 0.05 มล./กก. มีประสิทธิภาพไม่แตกต่างจากขนาด 0.5 มล./กก. ในการรักษาการบวมที่เกิดขึ้นภายหลังการถอดท่อหลอดลมคอ ไม่พบผลข้างเคียงที่เป็นอันตรายจากยาทั้ง 2 ขนาด*