Low-Dose Epinephrine Boluses for Acute Hypotension in the PICU*

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Objectives: To describe the use of low-dose bolus epinephrine in critically ill children during an acute hypotensive episode or prearrest condition.

Design: Institutional Review Board approved, single-center, retrospective medical chart review.

Setting: Large medical-surgical PICU within a freestanding, tertiary care children's hospital.

Patients: Patients admitted to the PICU between June 1, 2015, and June 1, 2016, who received low-dose (≤ 5 µg/kg) IV bolus epinephrine.

Interventions: None.

Measurement and Main Results: Twenty-four resuscitation episodes (63 doses; 19 patients) were analyzed. Median age and weight of patients were 9 years (interquartile range, 1–15 yr) and 38.5 kg (interquartile range, 12–54.8 kg). Median Pediatric Risk of Mortality III score was 17 (interquartile range, 10–27). Mean epinephrine dose was 1.3 ± 1.1 µg/kg. Median number of doses per patient was two. If more than one dose was provided, median dosing interval was 6.5 minutes. Heart rate and mean arterial blood pressure were compared at the time of epinephrine administration and 1–4 minutes (median = 1 min) following administration. Heart rate changed from 130 ± 41 to 150 ± 33 beats/min ($p < 0.05$), and mean arterial blood pressure changed from 51 ± 17 to 75 ± 27 mm Hg ($p < 0.001$). Variability in mean arterial blood pressure response was observed; nonresponders required extracorporeal membrane oxygenation; 66% of doses resulted in up to 100% mean arterial blood pressure increase, and 21% of doses resulted in greater than 100% mean arterial blood pressure increase. Doses below 1 µg/kg were associated with a lower mean arterial blood pressure increase than doses between 1 and 5 µg/kg (mean percent change in mean arterial blood pressure = 6.6% vs 60%, respectively). Children less than or equal to 2 years old had the greatest percentage increase in heart rate and mean arterial blood pressure.

Conclusions: Provision of low-dose bolus epinephrine during periods of acute hypotension can result in a significant increase in mean arterial blood pressure and heart rate. This dosing strategy may provide temporary stabilization while other therapies are added or adjusted, but further research is needed. (*Pediatr Crit Care Med* 2018; 19:281–286)

Key Words: bolus; children; epinephrine; hypotension; intensive care

Acute systemic hypotension is a common physiologic finding in critically ill children with sepsis, trauma, severe dehydration, blood loss, and heart disease. Additional causes of hypotension include toxin ingestion, adverse effects of medications (e.g., sedation, analgesia, and anesthesia), and anaphylaxis. Epinephrine, due to its alpha-1 and beta-adrenergic effects, is considered an important part of the management of children with hypotension. Epinephrine is typically used as a continuous infusion (0.02–0.5 µg/kg/min) for severe sustained hypotension and as a bolus (0.01 mg/kg, maximum dose = 1 mg) for bradycardia, asystole, or pulseless arrest (1, 2).

There are, however, clinical conditions that may benefit from smaller doses of bolus epinephrine. For example, brief periods of hypotension during medical procedures, intermittent hemodynamic instability, and augmentation of low blood pressure in a prearrest condition. While a resuscitation (or code) dose of epinephrine would be inappropriate (as it would cause an unacceptable large increase in blood pressure and heart rate [HR]), a smaller dose (sometimes referred to as "dwindle dose" or "push-dose pressor" at typically 1/10th the code dose) may be particularly useful.

Low-dose bolus vasopressors have been used for decades by anesthesiologists to prevent postreperfusion injury after solid

*See also p. 372.

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organ transplant, control cerebral oxygenation during anesthesia and manage acute hypotension during spinal surgery (3–9). Recently, use of bolus dose phenylephrine has been described in the emergency department setting to augment blood pressure during periods of hypotension surrounding intubation (10, 11). Finally, free open access medical publications have provided some insight into using bolus dose pressors for acute hypotensive episodes in adults (12–15). However, there is no published data describing the use of low-dose vasopressor boluses in children.

Despite a paucity of data supporting the use of low-dose bolus epinephrine in the PICU, many providers, including those at our institution, will prescribe it in certain clinical scenarios. The specific aim of this study is to characterize current practice related to low-dose epinephrine boluses (defined as ≤ 5 μg/kg/dose) in a large tertiary care children's hospital.

METHODS

This was a single-center retrospective chart review of children admitted to a 32-bed medical/surgical PICU in a freestanding tertiary care pediatric hospital during a 1-year study period (June 1, 2015, to June 1, 2016) who received low-dose (≤ 5 μg/kg) IV bolus epinephrine. Children with known cardiac disease are admitted to a separate ICU and were not considered for enrollment. Eligible patients were identified using unit-based drug cabinet dispense reports and resuscitation records. This study protocol was reviewed and approved by the Colorado Multiple Institutional Review Board with a waiver of informed parent/subject consent.

The primary outcome measure was change in HR (beats/min) and mean arterial blood pressure (MAP, mm Hg) from baseline (immediately predose) to 1 minute post dose. Because both HR and MAP are influenced by age, we also report outcomes as "percent change" and categorized patients into three age groups (≤ 2, 2–12, and > 12 yr). Secondary outcome measures included the number of children requiring full code dose epinephrine and/or chest compressions; exploration of any relationship between HR and MAP response with epinephrine dose, age, or concomitant use of vasopressor infusions; and overall survival from the PICU.

Outcome measures and patient variables were extracted from resources using a standardized data collection form. The resources included 1) the resuscitation record—a hand written form detailing interventions and completed by an ICU nurse during a resuscitation event and then scanned into the electronic health record (EHR) following completion; 2) the vital sign archive—an electronic database that captures minute-by-minute reports of HR, blood pressure, oxygen saturation, respiratory rate, central venous pressure, and intracranial pressure (if pertinent); 3) the unit-based drug dispensing cabinet report which captures all transactions involving low-dose bolus—epinephrine kits (which contain medication and equipment necessary to rapidly prepare a 10 μg/mL solution); 4) the EHR which contains all medical management and patient characteristics; and 5) the Virtual Pediatric Systems, LLC database (VPS data were provided from the Virtual Pediatric Systems, LLC. No endorsement or editorial restriction of the interpretation of these data or opinions of the authors has been implied or stated.). The following data were collected and reviewed: 1) patient information: sex, age, weight, Pediatric Risk of Mortality (PRISM) III score, primary PICU diagnosis, respiratory support, and relevant procedure or clinical event preceding epinephrine administration; 2) medication information: dose of bolus epinephrine administered (μg/kg), interval of administration, total number of doses provided, additional resuscitation therapies administered; and 3) outcomes: HR and blood pressure, requirement of chest compressions, and survival from PICU. All patients receiving concomitant cardiovascular support with dopamine, milrinone, dobutamine, epinephrine, norepinephrine, vasopressin, and/or phenylephrine had a Vasoactive-Inotropic Score calculated per previously described methods (16, 17). To improve accuracy and minimize inconsistencies, all patients underwent a second data abstraction by a different investigator. Any disputes in chart coding were resolved after agreement by investigators. A descriptive analysis was first performed on each variable in the dataset. Skewness and kurtosis tests were performed to determine distribution of data. Results are presented as mean ± SD, median with interquartile ranges (IQRs), or percentage. A two-tailed paired Student *t* test, Wilcoxon rank-sum test with continuity correction, one-way analysis of variance, or Kruskal-Wallis test was then performed on the outcome variables. Statistical significance was set at an α level of less than 0.05. All statistical analyses were performed using GraphPad Prism Version 7.00 for Windows (GraphPad Software, La Jolla, CA).

RESULTS

More than 100 low-dose bolus epinephrine kits were removed from the unit-based drug cabinet during the 1-year study period. Actual administration occurred 63 times during 24 resuscitation episodes in 19 patients. The median age and weight of patients who received epinephrine were 9 years (IQR, 1–15 yr) and 38.5 kg (IQR, 12–54.8 kg), respectively. There were seven males and 12 females. The median PRISM III score was 17 (IQR, 10–27). The most common PICU admission diagnosis was septic shock (27%), followed by respiratory failure (21%), trauma (12%), and oncologic (11%). Identifiable reasons for acute deterioration immediately before epinephrine administration, during the 24 resuscitation events, are outlined in **Table 1**.

Although most children received low-dose bolus epinephrine during a single resuscitation episode ($n = 15$), some children experienced more than one resuscitation episode during their PICU stay. Specifically, three patients experienced two distinct events, and one patient experienced three events. The mean dose of epinephrine administered was 1.3 ± 1.1 μg/kg (range, 0.2–5 μg/kg) with a median number of doses per patient was two (range, 1–7). Fourteen of the 24 events (58%) included provision of multiple doses of bolus epinephrine. If more than one dose was provided, the median dosing interval was 6 minutes (IQR, 3–10 min).

TABLE 1. Comparison of Change in Mean Arterial Blood Pressure (mm Hg) Following Low-Dose Bolus Epinephrine When Categorized by Identifiable Etiology of Acute Decompensation During 24 Episodes

Identifiable Reason for Acute Deterioration	No. of Resuscitation Episodes	No. of Doses	Percent Change in Mean Arterial Blood Pressure, Mean ± SD
Shock	11	30	57.2 ± 53.6
Distributive	8		
Septic	7		
Nonseptic	1		
Hemorrhagic	2		
Obstructive	1		
Tracheal intubation	7	14	70.7 ± 74.1
Hypoxia (saturation < 80%)	6		
Sedative related	1		
Postarrest hypotension	5	12	69.3 ± 65.6
Unclear etiology	1	7	13.4 ± 17.3

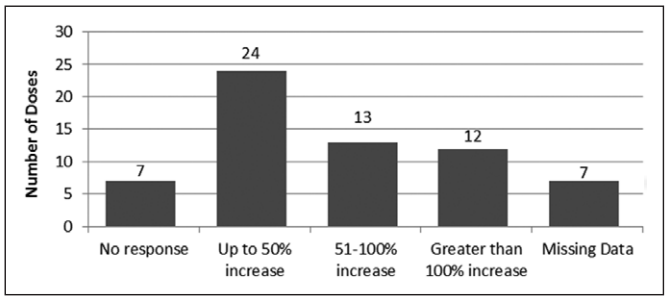

Figure 1. Distribution of percent change in mean arterial blood pressure (MAP) following 63 low-dose epinephrine injections. Percent change in MAP was calculated as: ([MAP post dose − MAP pre dose]/MAP pre dose) × 100.

Twenty-one (of 24) resuscitation events involved the provision of supplemental therapies (e.g., fluid bolus, calcium, vasoactive infusions, blood) prior to (or concomitant with) administration of low-dose bolus epinephrine. The majority of these resuscitation episodes (n = 14/21 and 42/63 doses) included the use of continuous vasoactive support (median number of vasoactive infusions per patient = 2; range = 1–4). During eight (of these 14) resuscitation episodes, there were multiple low-dose epinephrine doses administered. In these events, we calculated the change in vasoactive score from the first dose to the last dose of epinephrine. The mean score changed from 39 to 70.

HR and MAP, compared at the time of epinephrine administration and 1–4 minutes (median = 1 min) following administration, changed from 130 ± 41 to 150 ± 33 beats/min ($p < 0.05$) and 51 ± 17 to 75 ± 27 mm Hg ($p < 0.001$), respectively. There was, however, variability in blood pressure response within the group (**Fig. 1**). Whereas many doses (n = 24/63) were associated with an increase in MAP (from pre-dose values) of up to 50%, some doses (n = 7/63) were associated with no (or negative) change in blood pressure. This variability was observed not only between patients but also within patients who received more than one dose. In the 14 episodes (52 doses) where multiple epinephrine doses were administered, there was a variable MAP response ranging from no response to greater than 100% increase. The responses in MAP did not appear to be related to timing of low-dose bolus epinephrine, specifically; we did not identify any pattern of a "first-dose" effect among those children receiving multiple doses. In addition, response in MAP did not differ between the three identifiable reasons for acute deterioration (shock, tracheal intubation, and postarrest hypotension) Table 1. Overall, the majority of doses (42/63; 67%) were associated with achievement of systolic blood pressures at or above the definition of hypotension (per Pediatric Advanced Life Support definition).

There was some association between age and percent change in MAP. Patients 2 years old and younger tended to demonstrate a more robust change in MAP compared with those 2–12 years old and those more than 12 years old, **Table 2**. Although percent change in HR was different between age groups, it did not reach statistical significance. We did not detect any difference in percent change in MAP when low-dose epinephrine was administered with vasoactive infusions (n = 42 doses) versus without

TABLE 2. Comparison of Percent Change in Mean Arterial Blood Pressure (mm Hg) and Heart Rate (beats/min) When Categorized by Age Among 19 Children Receiving 63 Low-Dose Epinephrine Injections

Age Category (yr)	No. of Patients	No. of Low-Dose Epinephrine Boluses	Percent Change in Mean Arterial Blood Pressure, Mean ± SD ($p < 0.05$)	Percent Change in Heart Rate, Median (IQR) ($p = 0.2$)
≤ 2	5	13	92 ± 70	10.9 (2–50.8)
2.1–12	5	22	56.8 ± 57	5.9 (0–20.5)
> 12	9	28	39.2 ± 48.8	1.7 (0–9)

IQR = interquartile range.

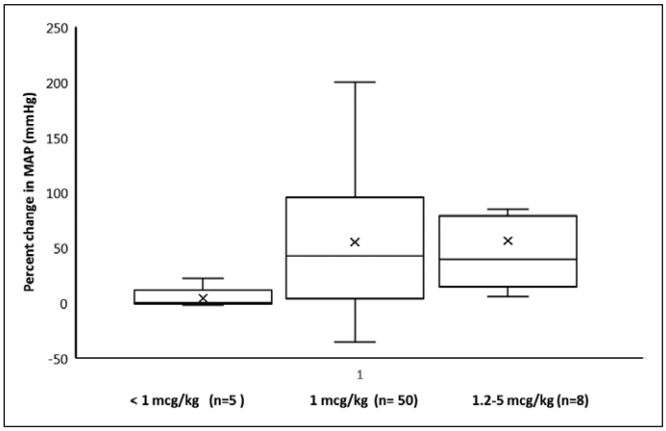

Figure 2. Comparison of percent change in mean arterial blood pressure (MAP) mm Hg following low-dose epinephrine injections, categorized by dosage. *Boxes* represent 25–75th percentile, *line within box* is median, and × represents mean.

(n = 21 doses); p value equals to 0.39. There did, however, appear to be some dose-effect relationship observed (**Fig. 2**). Although the majority of doses (n = 50) were at 1 µg/kg, five doses were below 1 µg/kg and eight doses were 1.2–5 µg/kg. Doses less than 1 µg/kg were associated with a lower percent change in MAP.

Three patients experienced episodes in which some (but not all) doses resulted in either no change in MAP or a slight decrease in MAP. The PICU admission diagnosis of these patients included polypharmacy ingestion (n = 1) and presumed septic shock (n = 2). All three patients eventually required cannulation to veno-arterial extracorporeal membrane oxygenation and survived to PICU discharge. Progression to full arrest and requirement of code dose epinephrine (with chest compressions) following the provision of low-dose epinephrine were observed in three patients; two of those patients did not survive the arrest event. All of these patients received multiple doses of low-dose epinephrine. The time interval between administration of the last low-dose of epinephrine and initiation of chest compressions in these three patients was 6, 8, and 14 minutes. MAP response to the low-dose epinephrine that preceded chest compressions was robust in two patients (50–100% increase) and absent in one. All three patients were on concomitant vasoactive infusions at the time of cardiac arrest. In total, seven patients died. The relevant diagnoses of these patients included trauma (n = 1), septic shock (n = 3), liver failure (n = 1), accidental asphyxiation with severe hypoxic ischemic encephalopathy (n = 1), and obstructive shock due to massive pulmonary embolus (n = 1). This resulted in an overall survival to PICU discharge rate of 63% (12/19 patients).

The occurrence rate of hypertension, defined as systolic blood pressure greater than the 99th percentile for age and gender, following a dose of epinephrine was 19% (n = 12/63 doses). Most doses associated with hypertension were 1 µg/kg (10 doses; 77%), with two doses above 1 µg/kg. Although severe tachycardia, defined as a HR above the 99th percentile for age (18, 19), following epinephrine was common (51/63 doses; 81%), tachycardia was present before epinephrine administration in most patients (43/51; 84%).

DISCUSSION

The primary finding of this study was that low-dose bolus epinephrine (mean dose 1.3 µg/kg), in critically ill children with acute hypotension at high risk of mortality, was associated with a significant increase in MAP and HR at 1 minute following administration. The smallest dose administered was 0.2 µg/kg, and the largest dose was 5 µg/kg. When epinephrine dosage was divided into three categories, doses less than 1 µg/kg were associated with a smaller change in MAP than those greater than or equal to 1 µg/kg (mean percent change in MAP = 6.6% vs 60%, respectively). Nineteen percent of doses, however, were associated with a SBP considered high for age. This highlights the variability in blood pressure response following similar doses of epinephrine and is an area for further investigation. Children less than or equal to 2 years old appeared to have the most robust response.

Most previous studies exploring the influence of low-dose bolus vasopressors on hemodynamics were performed using ephedrine or phenylephrine in adults to either prevent or treat anesthesia-related hypotension associated with excessive vasodilation (3, 4, 6–9). Additional work has been published in adults undergoing elective lumbar spine surgery with general anesthesia in the prone position (9). Patients were randomly assigned to receive either phenylephrine or ephedrine during the operative procedure. Results suggested that the ephedrine group experienced a more sustained blood pressure response than the phenylephrine group. Although speculative, there is a mechanistic advantage of ephedrine over phenylephrine that may explain this observation. Namely, since phenylephrine is a pure alpha-adrenergic agonist, MAP is increased only by increasing systemic vascular resistance (SVR), whereas ephedrine releases stored catecholamines and increases the activity of norepinephrine at the postsynaptic α and β receptors. This indirect mechanism of action improves cardiac contractility, provided that stored norepinephrine in sympathetic nerve terminals has not been depleted. In a separate study, ephedrine also appeared to have the added benefit of preserving cardiac output and cerebral oxygenation compared with phenylephrine (6).

The use of bolus dose phenylephrine (100–200 µg) for acute hypotension within the emergency department setting was reported in two single-center retrospective trials (10, 11). The predominate reason for bolus phenylephrine was for the management of acute hypotension surrounding intubation. Both studies observed an increase in systolic and diastolic blood pressure, but HR was not significantly affected. These studies were limited by their retrospective design, concomitant vasopressor infusion usage, and treatment time variability.

The published use of low-dose bolus epinephrine is not as common as phenylephrine or ephedrine. Linton et al (20) describe the hemodynamic response to low-dose epinephrine boluses (5 µg) in 10 adult patients, before and during cardiopulmonary bypass surgery. Compared with predose values, low-dose epinephrine boluses (off bypass) produced an initial increase in SVR of 129% ± 15%, followed by a more sustained (albeit lower) increase of 57% ± 13%. During

cardiopulmonary bypass, the increase in SVR was appreciated but less pronounced. The authors speculate that this was due to hemodilution. In another investigation among adult liver transplantation recipients, low-dose bolus epinephrine and phenylephrine boluses were used to mitigate postreperfusion injury and vasopressor requirements following transplantation surgery (5). This prospective, double-blind, randomized, placebo-controlled trial concluded that pretreatment with either 10 μg of epinephrine or 100 μg of phenylephrine (at the time of liver reperfusion) significantly reduced the occurrence of reperfusion injury and the need for vasopressor support, compared with placebo. Blood pressure (1–10 min after vasopressor administration) was significantly increased but without an appreciable influence on HR.

There are important pharmacokinetic, pharmacodynamic, and dose differences between the aforementioned vasopressors. Whereas all three agents have an onset of action within 1 minute, epinephrine has a shorter duration of action (3–8 min), compared with phenylephrine (15–20 min) or ephedrine (20–60 min). The short duration of effect seen with epinephrine should alert providers to anticipate additional doses and/or alternative therapies within 5–10 minutes following a dose. Since epinephrine acts directly on α, β_1, and β_2 receptors, increases in myocardial contraction, coronary blow flow, HR, and SVR should be expected. Therefore, it is important to identify children who may be harmed by the provision of bolus epinephrine—particularly those with underlying cardiac disease or myocarditis for which a lethal arrhythmia may be triggered. In contrast, phenylephrine will selectively increase SVR without a direct effect on HR and may be preferred in those patients with existing tachycardia. Finally, there are dosing differences between agents. The dose of epinephrine commonly endorsed for temporary treatment of hypotension in adults is 5–20 μg (or 1 μg/kg in children), compared with 40–200 μg for phenylephrine and 5–10 mg for ephedrine (5, 6, 8, 10, 11, 20).

The current report has similar findings to previously published reports, with an increase in blood pressure following low-dose vasopressor injections. Although the bulk of previous work has described the influence of single low-dose bolus vasopressor injections on hemodynamics, we provide some insight into multiple doses of epinephrine injections and describe the association of age and dose on outcomes. The dose of bolus epinephrine used in previous adult studies was only 5–10 μg—or 0.5–1% of a code dose. This is substantially lower than the current study using ~10% of a calculated code dose. Although the majority of patients in this cohort received 1 μg/kg per dose, there were some deviations. The rationale for these deviations, however, was not readily discernable during chart review.

Although the precise place in therapy for low-dose bolus epinephrine within the PICU remains somewhat elusive, the current study provides some evidence of blood pressure and HR augmentation with epinephrine doses approximating 1 μg/kg, yet there remains a subset of patients who have variable hemodynamic response. If a provider elects to use this strategy for management of hypotension, we advocate provider education surrounding correct patient selection and drug preparation. In addition, we reinforce that the use of low-dose epinephrine is a temporizing measure, and all efforts should be directed toward managing the underlying cause of hypotension (e.g., sepsis, oversedation, etc).

There are limitations to our work that must be acknowledged and are inherent to any retrospective chart review. First, we were not able to control for factors that may have impacted outcomes. In particular, the use of concomitant vasoactive infusions and other therapies that may have influenced blood pressure and/or HR was completely at the discretion of the prescribing provider. We attempted to account for the influence of vasoactive therapy by calculating individual Vasoactive-Inotropic Scores in children who received multiple low-dose epinephrine doses. Not unexpectedly, we noted an increase in vasoactive score. We speculate that this represents the need for ongoing support in a clinically unstable patient, but we cannot exclude that the use of more vasoactive infusion therapy may have affected outcomes. Second, this study reflects the experience of a single center with medical and surgical patients that excluded critically ill cardiac patients. Nevertheless, this report adds to the small body of work that describes the use of low-dose bolus epinephrine during periods of acute hypotension.

CONCLUSIONS

In this pediatric patient population, provision of low-dose bolus epinephrine (mean dose = 1.3 μg/kg) during an acute systemic hypotensive or prearrest condition was associated with an increase in MAP and HR in most patients. There was considerable variability in the degree of blood pressure change associated with these epinephrine doses, with some patients illustrating no response and other exhibiting an exaggerated response. Children less than or equal to 2 years old tended to exhibit the greatest physiologic response. This dosing strategy may provide temporary stabilization of the hypotensive child while other therapies are added or adjusted, but further research involving dose-response is needed.

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