Efficacy of Low-Dose Epinephrine Continuous Infusion in Neonatal Intensive Care Unit Patients

Gloria Lee, PharmD; Jeffrey R. Kaiser, MD, MA; Brady S. Moffett, PharmD, MPH; Emily Rodman, PharmD; Cynthia Toy, PharmD; and Danielle R. Rios, MD, MS

OBJECTIVES Although epinephrine is used in the neonatal intensive care unit, few data exist on efficacy of doses <0.05 mcg/kg/min. This study evaluates the efficacy and safety of low-dose epinephrine continuous infusion at doses <0.05 mcg/kg/min in infants.

METHODS Single-center, retrospective review of hypotensive infants from 2011–2018. Charts were reviewed for initial and maximum epinephrine doses, additional vasoactive agents, short-term efficacy, and adverse effects. The primary outcome was percentage of patients initiated on low-dose epinephrine whose dose did not require titration to ≥ 0.05 mcg/kg/min.

RESULTS A total of 115 patients met study criteria with 131 distinct occurrences of low-dose epinephrine initiation. Most patients were unresponsive to other vasopressors at the time of epinephrine initiation. The median (IQR) starting dose of low-dose epinephrine was 0.01 (0.01–0.04) mcg/kg/min and median (IQR) maximum dose was 0.04 (0.02–0.08) mcg/kg/min. Fifty-five percent were responders. Patients in this cohort demonstrated significant improvement of blood pressure and urine output ($p < 0.001$) without adverse effects.

CONCLUSIONS Low-dose epinephrine infusion may be considered as an alternative treatment to standard starting doses in hypotensive neonatal intensive care unit patients.

ABBREVIATIONS BP, blood pressure; IV, intravenous; NICU, neonatal intensive care unit; UOP, urine output

KEYWORDS blood pressure; epinephrine; hypotension; infants; preterm; vasopressors

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Introduction

Hypotension is common in patients admitted to the neonatal intensive care unit (NICU). Adequate cardiovascular support is crucial to prevent negative outcomes, such as long-term neurological deficit, brain injury, and death.^{1–5} One of many difficulties to managing hypotension in this patient population is the lack of a consensus definition of hypotension;¹ consequently, wide variations in practice styles and approaches to management of hypotension exist.

Epinephrine is an inotrope used in the treatment of hypotension in the NICU.⁶ In adults, it stimulates both α -1, α -2, and β -1, β -2 receptors. Known effects include positive inotropy, positive chronotropy, and vasoconstriction.⁷ Dose-related β -receptor effects in adults are seen at doses 0.01 to 0.1 mcg/kg/min; α -receptor effects begin at doses >0.1 mcg/kg/min. Dose-related thresholds have not been established in neonates. Using the standard dosing regimen for infants (≥ 0.1 mcg/kg/min), epinephrine has been shown to be as efficacious as dopamine in raising blood pressure (BP), but with higher lactate levels and base deficit, lower bicarbonate, and hyperglycemia requiring insulin therapy.^{8,9} Metabolic effects of epinephrine, including glycogenolysis, glu-

coneogenesis, and decreased insulin secretion, are known to result in hyperglycemia and lactic acidosis especially with higher doses.¹⁰ These doses have also been shown previously to decrease plasma bicarbonate.¹¹ There is a paucity of data regarding the optimal and safest initial dose of epinephrine continuous infusions in neonates and premature infants <44 weeks' postmenstrual age.^{12,13}

Although the lowest reported epinephrine dosing found in the literature for neonatal patients is 0.05 mcg/kg/min,¹⁴ current practice at our institution is to initiate continuous infusion epinephrine at 0.01 mcg/kg/min and titrate to the lowest effective dose. This study will report the efficacy and adverse effects of low-dose epinephrine continuous infusion in neonates and premature infants at a single institution.

Materials and Methods

Patient demographics, primary underlying diagnoses, vasoactive medication use, and administration times were collected from the electronic medical record (EPIC, Hyperspace EPIC 2014, Madison, WI). The electronic medical record historical database was queried for patients admitted to the NICU between January 1,

Table 1. Patient Demographics (N = 115)

Demographic	Result
Sex, n (%), male	66 (57)
Gestational age at birth, mean $\pm$ SD, wk	31.4 $\pm$ 6.0
Prematurity, n (%)	85 (74)
Birth weight, mean $\pm$ SD, g	1739 $\pm$ 107

2011, and December 31, 2018, who received a continuous intravenous epinephrine infusion during their initial hospitalization. Included patients were those who were <44 weeks' postmenstrual age upon initiation of low-dose epinephrine continuous infusion (<0.05 mcg/kg/min). Exclusion criteria included initiation of epinephrine prior to admission to the NICU, unknown epinephrine starting dose, receipt of epinephrine through any route other than intravenous, receipt of bolus epinephrine during newborn resuscitation, infusion time of <3 hours, and incomplete documentation of BP values. The primary objective for this study was to determine the percentage of infants initiated on low-dose epinephrine whose doses were not titrated to ≥ 0.05 mcg/kg/min for the desired effect (i.e., responders). The secondary objective was to assess the efficacy of low-dose epinephrine infusion, which was defined as a significant increase in urine output (UOP; by approximately 1 mL/kg/hr) or BP measurements (systolic, diastolic, and/or mean BP) that increased by >20% after drug initiation. Urine output was collected in 4-hour increments prior to and after epinephrine initiation and described in mL/kg/hr. Blood pressure measurements were obtained via invasive arterial catheters or BP cuffs when arterial access was not available. To assess efficacy during epinephrine infusion, BP values as close to maximum dose of epinephrine as possible or after 2 hours if maximum dose equaled initial dose were used. To evaluate side effects noted historically with higher dosing regimens, lactate, base deficit, and glucose levels were also compared prior to and after low-dose epinephrine initiation. Values were assessed as close as possible before initiation and after the maximum

effective dose was achieved.

For those with >1 epinephrine infusion during the hospitalization, a washout period of 12 hours between administrations was used to ensure that more than enough time was allowed for complete elimination of the drug with BP stability demonstrated before reinitiation. Administration of fluid boluses (within 1 hour before epinephrine administration) included normal saline or blood products, such as packed red blood cells, albumin, or fresh frozen plasma. Maximum dose of epinephrine was defined as the highest dose of epinephrine received within that 1 administration. Additional vasoactive drugs that were used included dopamine, dobutamine, vasopressin, milrinone, and hydrocortisone. Although there is not a standard practice for management of hypotension at this institution, most commonly, dopamine was started at 5 mcg/kg/min and titrated up to 20 mcg/kg/min, and then hydrocortisone and/or epinephrine were used as second- and third-line agents at the discretion of attending neonatologists. Moreover, epinephrine was initiated at the lowest possible dose of 0.01 mg/kg/min and titrated to the lowest effective dose.

Statistical analyses were performed using PSPP (GNU, version 3, Boston, MA). Descriptive statistical methods were used to characterize the patient population (mean and SD, median and IQR, and frequency [%]). Related-samples Wilcoxon signed rank test was used for continuous variables to evaluate change prior to and after epinephrine initiation.

Results

A total of 115 patients (57% male) met study criteria with 131 distinct low-dose epinephrine administrations. Mean estimated birth gestational age and weight were 31.4 $\pm$ 6.0 weeks and 1739 $\pm$ 107 g, respectively. Epinephrine initiation was begun about 2 weeks after birth. Table 1 summarizes patient demographics, and Table 2 shows characteristics of medication administration. Median (IQR) starting dose of low-dose epinephrine was 0.01 (0.01–0.04) mcg/kg/min; median (IQR) maximum dose was 0.04 (0.02–0.08) mcg/kg/min.

Table 2. Characteristics of Medication Administration (N = 131)

Characteristic	Results
Responded to low-dose epinephrine, n (%)	72 (55)
Gestational age at epinephrine initiation, mean $\pm$ SD, wk	33.5 $\pm$ 5.9
Time to epinephrine infusion, mean $\pm$ SD, wk	2.1 $\pm$ 2.7
Fluid bolus prior to epinephrine infusion, n (%)	25 (19)
Dopamine prior to epinephrine, n (%)	98 (75)
Dobutamine prior to epinephrine, n (%)	2 (2)
Hydrocortisone prior to epinephrine, n (%)	54 (41)
Milrinone prior to epinephrine, n (%)	9 (7)
Vasopressin prior to epinephrine, n (%)	14 (11)

Table 3. Analysis of Efficacy (N = 131)

Variable	Baseline	After Epinephrine	p value
Systolic BP, median (IQR), mm Hg	44 (32-54)	52 (42-64)	<0.001
Diastolic BP, median (IQR), mm Hg	26 (18-34)	32 (24-40)	<0.001
Mean BP, median (IQR), mm Hg	34 (24-42)	40.5 (32-50)	<0.001
UOP; mean $\pm$ SD, mL/kg/hr	1.8 $\pm$ 2.5	2.8 $\pm$ 3.3	<0.001

UOP, urine output

Twenty (15%) patients received epinephrine as the first-line agent; most patients (75%), however, were already receiving dopamine when epinephrine was initiated. In this cohort, 55% of patients were considered responders to low-dose epinephrine and did not require doses ≥ 0.05 mcg/kg/min. Low-dose epinephrine was efficacious in this cohort because systolic, diastolic, and mean BP values increased significantly after medication initiation ($p < 0.001$). In addition, significant improvement was seen in UOP after initiation ($p < 0.001$; Table 3). Glucose ($p = 0.17$), lactate ($p = 0.98$), and base deficit ($p = 0.74$) were not different before epinephrine initiation and after the maximum dose of epinephrine was achieved (Table 4).

Discussion

We examined the use of low-dose (<0.05 mcg/kg/min) epinephrine infusions in a single-center level IV NICU and observed that this lower than standard dosing rate was efficacious without metabolic or clinical adverse effects in more than half of the patients.

The data on the cardiovascular effects of epinephrine and other vasoactive drugs in infants are limited.^{12,13} Baske et al¹⁵ evaluated epinephrine initiated at 0.2 mcg/kg/min as a first-line agent in neonatal septic shock and compared it with dopamine. They concluded that epinephrine dosed at 0.2 to 0.4 mcg/kg/min had similar efficacy and safety to dopamine at 10 to 20 mcg/kg/min. Valverde et al⁸ compared epinephrine (0.125–0.5 mcg/kg/min) to dopamine as first-line treatment in hypotensive very low birth weight infants, and found that epinephrine was as effective as dopamine in raising BP. However, infants receiving epinephrine had higher lactate levels irrespective of improved hemodynamics, higher heart rate, and hyperglycemia requiring insulin therapy.⁹ The current study evaluated the effect of low-dose epinephrine on glucose control and lactate levels and found no difference between values prior to and after low-dose epinephrine initiation. Heckmann et al¹⁴ reported the use of epinephrine infusion (0.05–2.6 mcg/kg/min) in very low birth weight infants, which is the lowest reported dosing described, although all infants received 0.2 mcg/kg/min at initiation. In the current study, epinephrine was begun at lower doses (starting at 0.01 mcg/kg/min) and titrated up to the most effective dose, unlike the Heckmann et al¹⁴ study. Rai and Singh¹⁶ concluded epinephrine infusions beginning at 0.3 mcg/

kg/min were safe and effective in neonates with birth asphyxia and shock refractory to dopamine and dobutamine. The current study also found that low-dose epinephrine could safely be used in combination with dopamine. To our knowledge, there are no previous studies, prospective or retrospective, evaluating the use, efficacy, and side effects of low-dose epinephrine infusions in NICU patients.

We previously reported that epinephrine usage in hypotensive neonates (16.6%) and extremely low birth weight infants (32.8%) remained constant between 2001 and 2012.⁶ In addition, a survey of clinical practice reported that Canadian neonatologists use epinephrine with variable starting infusion rates ranging from 0.01 to 0.1 mcg/kg/min (median 0.05 mcg/kg/min) though there have been no studies evaluating the efficacy of initiation rates < 0.05 mcg/kg/min.¹⁷ There are limited data available about the pharmacokinetic profile of epinephrine in children,¹⁸ and what is available does not include information on neonates and infants who exhibit different pharmacokinetics than older children.¹⁹ Infants receiving treatment for hypotension have high rates of short-term and long-term morbidities¹ in addition to increased mortality correlated to the number of medications used.⁶ NICU patients receiving higher dosage epinephrine have decreased survival.²⁰ All of this illustrates the importance of gaining more information about the practice patterns, dosages, and efficacy data for epinephrine usage in NICU patients.

Increased UOP and BP were chosen as secondary data points in this study, but lactate monitoring also plays an important role in neonatal hemodynamic assessment. Studies have confirmed that low BP and high lactate are the most prevalent biomarkers guiding cardiovascular treatment with early elevated lactate associated with higher risk of death.^{21,22} In clinical practice, UOP is used as a surrogate for renal perfusion, so this marker was chosen to evaluate renal tissue perfusion in this study. Both UOP and BP were analyzed as a comparison change from prior to epinephrine administration to after. In general, there was at least a 20% increase in BP in mm Hg and approximately 1 mL/kg/hr increase in UOP in this cohort, which these authors consider a significant clinical change.

There are limitations to this study. First, due to its retrospective nature, it is unknown why clinicians began low-dose epinephrine and the reasons why epinephrine

Table 4. Analysis of Safety (N = 131)

Variable	Baseline*	After Epinephrine*	p value
Glucose, mg/dL	135 ± 79	139 ± 76	0.17
Lactate, mg/dL	3.9 ± 4.4	3.8 ± 4.4	0.98
Base deficit, mEq/L	8.9 ± 6.4	8.5 ± 5.9	0.74

* all data presented as mean ± SD

doses were or were not up-titrated. Second, the retrospective nature of this paper did not allow for clinical and adverse effect parameters to be obtained prior to and after initiation of epinephrine in all cases. Third, confounding therapies, such as fluid boluses or other vasoactive medications, were unable to be controlled. The frequency of fluid boluses was assessed within 1 hour of epinephrine administration and only 19% of patients received any fluid bolus. These fluid boluses, however, likely did not play a significant role in our analyses. The simultaneous administration of other vasoactive agents prior to and after epinephrine infusion were also recorded. Although we noted a median (IQR) increase from 1 (1–2) vasoactive medication prior to epinephrine to 2 (1.75–2) 24 hours afterward, the most significant increase was the addition of hydrocortisone, which increased from 41% before to 76% 24 hours after epinephrine infusion. As hydrocortisone requires time to take effect, it is likely the increased use of hydrocortisone did not significantly affect the results. The use of dopamine, milrinone, and vasopressin increased by 4%, 3%, and 14%, respectively, whereas the use of dobutamine decreased 24 hours after epinephrine initiation. Commonly, at this institution, practitioners tend to titrate 1 vasoactive medication at a time. Though this study was unable to verify if doses of concurrently administered medications remained unchanged due to the retrospective nature and nonstandard charting, we evaluated effects of epinephrine shortly after initiation in order to minimize confounding factors. Another limitation to this study is the long study period. Clinical practice evolves and a study period of 7 years lends itself to enduring potential practice changes that may have been introduced in an institution; however, using the 7-year time frame allowed an evaluation of a large number of infants exposed to low-dose epinephrine infusion.

Conclusion

Low-dose (0.01–0.04 mcg/kg/min) epinephrine was efficacious without increased adverse effects in this cohort. Based on the historical association of adverse effects with epinephrine infusions at higher dosing rates and potential increased morbidity and mortality, perhaps, epinephrine infusions could be initiated at these lower rates and titrated up to the lowest effective dose to limit potentially harmful effects. This low-

dose strategy may be especially beneficial in high-risk populations, such as extremely premature infants or infants of diabetic mothers with cardiac hypertrophy, where metabolic and chronotropic effects may be contraindicated.

Article Information

Affiliations. Department of Pharmacy (GL, BSM, ER), Texas Children's Hospital, Houston, TX, Departments of Pediatrics and Obstetrics and Gynecology, Division of Neonatal-Perinatal Medicine (JRK), Penn State Health Children's Hospital, Hershey, PA, Department of Pharmacy (CT), Phoenix Children's Hospital, Phoenix, AZ, Department of Pediatrics, Division of Neonatology (DRR), Stead Family Children's Hospital, Iowa City, IA

Correspondence. Danielle R. Rios, MD, MS, FAAP; danielle-r-rios@uiowa.edu

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