

# Volume Versus Mass Dosing of Epinephrine for Neonatal Resuscitation: A Randomized Trial

Kate D. Brune, DO,<sup>a</sup> Varsha Bhatt-Mehta, PharmD, MS,<sup>a,b</sup> Deborah M. Rooney, PhD,<sup>c</sup> Gary M. Weiner, MD<sup>d</sup>

## ABSTRACT

**BACKGROUND:** Intravenous epinephrine for neonatal resuscitation requires weight-based calculations. Epinephrine is available in 2 different concentrations, increasing the risk of dosing errors. Expert panels have conflicting recommendations for the ordering method. The Neonatal Resuscitation Program recommends the volume (milliliters per kilogram) method, whereas the Institute for Safe Medication Practices recommends the mass (milligrams per kilogram) method. In this study, we aim to determine if the mass method is more accurate and efficient than the volume method.

**METHODS:** In a randomized crossover simulation study, 70 NICU and pediatric emergency department nurses calculated the intended dose then prepared epinephrine using both the mass and volume methods. Both epinephrine concentrations were available. Scenarios were video recorded and timed. The primary outcome was the proportion of epinephrine doses prepared correctly. Variables associated with correct dosing were analyzed by using logistic regression.

**RESULTS:** Of 136 total doses, 77 (57%) were prepared correctly. The correct intended dose was calculated more frequently by using the mass method (82% vs 68%; risk difference 15%; 95% confidence interval 3% to 26%), but there was no difference in the proportion of doses that were actually prepared correctly (53% of mass method doses versus 60% of volume method doses; risk difference -7%; 95% confidence interval -24% to 9%). There was no difference between methods in the time required to prepare the dose. Selecting the correct epinephrine concentration was the only variable associated with correct dosing.

**CONCLUSIONS:** The mass method was neither more accurate nor more efficient. Nurses made frequent errors when using both methods. This is a serious patient safety risk. Additional educational and medication safety interventions are urgently needed.

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Address correspondence to Kate D. Brune, DO, Department of Neonatal-Perinatal Medicine, C.S. Mott Children's Hospital, 1540 E Hospital Dr, Ann Arbor, MI 48109. E-mail: [kdkarp@med.umich.edu](mailto:kdkarp@med.umich.edu)

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<sup>a</sup>Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Michigan Medicine,  
<sup>b</sup>Department of Clinical Pharmacy, College of Pharmacy, and  
<sup>c</sup>Department of Learning Health Sciences, University of Michigan, Ann Arbor, Michigan

Medication errors frequently cause adverse events in the hospital, and newborns receiving intensive care have a significantly greater risk of errors compared with other patients.<sup>1,2</sup> Within the NICU, the most common cause of medication error is related to dose calculation.<sup>3</sup> During the stress of a delivery room resuscitation, noise, time pressure, and the use of unfamiliar medications increase the risk of dosing errors.<sup>4,5</sup>

Epinephrine is used infrequently during neonatal resuscitation. Timely administration of the correct dose may be lifesaving.<sup>6</sup> The International Liaison Committee on Resuscitation and Neonatal Resuscitation Program (NRP) algorithms recommend intravenous epinephrine administration for bradycardia (<60 beats per minute) that persists after ventilation and chest compressions.<sup>7,8</sup> Epinephrine has been identified by the Institute for Safe Medication Practices (ISMP) as a medication associated with a high risk of harm if errors occur during administration.<sup>9</sup> It is commercially available in multiple concentrations and preparations, including a dilute solution (1 mg/10 mL) in a 10-mL glass syringe that requires assembly (ABBOJECT; Pfizer Inc, New York, NY), a concentrated solution (1 mg/mL) in a 1-mL glass vial, and a concentrated solution (1 mg/mL) in a 30-mL multidose glass bottle. The NRP recommends that providers use only the dilute solution, and in the NRP textbook, the dose for the volume (milliliters per kilogram) method is described.<sup>8</sup> In contrast, the Pediatric Advanced Life Support (PALS) program includes both the dilute and concentrated solutions, depending on the route of administration, and only the dose for the mass (milligrams per kilogram) method is described.<sup>10</sup> Errors may occur with either method. The volume method requires a single calculation; however, there is a risk of preparing a 10-fold overdose if the provider inadvertently uses the concentrated solution. The mass method requires providers to convert the dose between milligrams and milliliters; however, it would result in the correct dose if the concentrated solution was selected inadvertently as long as the provider correctly performs the calculation.

Highlighting this controversy, the ISMP released a safety alert about the risk of a 10-fold error from using the volume method and recommended that providers use only the mass method.<sup>11</sup> In response, the NRP Steering Committee released a statement in which it expressed the opinion that the volume method reduced the risk of error by simplifying the calculations performed in a stressful environment.<sup>12</sup> The methods have not been directly compared during neonatal resuscitation in previous studies. In this study, we aimed to determine if ordering emergency epinephrine for neonatal resuscitation by using the mass dosing method was safer and more efficient than by using the volume method, which is currently recommended by the NRP. We hypothesized that mass ordering would lead to a 20% difference in the proportion of doses prepared correctly.

## METHODS

### Study Design

In this prospective, randomized, crossover trial, we compared the accuracy and efficiency of nurses preparing intravenous epinephrine after receiving a mass (milligrams per kilogram) and a volume (milliliters per kilogram) order during simulated neonatal resuscitations. We recruited volunteer nurses from the University of Michigan (Ann Arbor, MI) C.S. Mott Children's Hospital NICU ( $n = 35$ ) and Pediatric Emergency Department ( $n = 35$ ) during regular work hours. Nurses were recruited from all shifts without exclusions. To limit the potential for experience bias, we used a matched-pair design, in which each participant served as their own control and sequentially prepared 1 dose of epinephrine using each ordering method.

### Randomization

Using an online randomization tool,<sup>13</sup> we assigned participants to receive either the mass order or the volume order first. After preparing the first dose, each participant crossed over to the alternate ordering method. Randomization was stratified by primary work setting (NICU versus pediatric emergency department). Group allocation was concealed in sequentially numbered opaque envelopes.

### Study Intervention

Each participant was directed to a quiet room with a sweep second-hand clock, paper, pencil, calculator, 3 labeled preparations of epinephrine (1 mg/10 mL in a glass 10-mL ABBOJECT syringe, 1 mg/mL in a glass 1-mL vial, and 1 mg/mL in a glass 30-mL bottle), syringes (1, 3, and 5 mL), 2 needles, and 2 3-way stopcocks. Although the concentrated solution is the only preparation typically available in our emergency carts, all 3 preparations were provided specifically to investigate the ISMP safety concern about settings where both concentrations are available. Participants were allowed to orient themselves to the supplies provided, which were the same supplies used during an NRP course and during an actual resuscitation at our hospital. An on-site investigator explained that they would calculate and prepare 2 doses of epinephrine on the basis of scenarios that would be read aloud. To simulate the resuscitation environment and assist with washout between orders, participants calculated a simulated heart rate from an audible rhythm (40 beats per minute) and wrote their estimate on a data collection form. Afterward, the investigator requested the first dose, either 0.1 mL/kg or 0.01 mg/kg, with the 1 mg/10 mL epinephrine solution for intravenous administration to a 3-kg newborn. Participants could have the order repeated but could not receive assistance with calculating or preparing the dose. On the basis of their calculation, participants wrote the intended dose on the data collection form. The correct units (milligrams or milliliters) for the requested order were provided on the form. Next, participants prepared the dose using the supplies provided and handed the prepared syringe to the investigator. After preparing the first dose, the participant listened to the simulated heart rhythm again, calculated the heart rate, and wrote their second estimate on the data collection form before receiving the next order. The investigator read the second order for the alternate ordering method, either 0.3 mL/kg or 0.03 mg/kg, with the 1 mg/10 mL epinephrine solution for intravenous administration to a 3-kg newborn.

After preparing both doses, participants completed a written questionnaire in which they were asked about their resuscitation training, the interval since their last NRP or PALS course, their self-perceived comfort with math (5-point rating scale), and their anxiety level during the study (5-point rating scale). The on-site investigator determined if the written and prepared doses were correct. Written doses were considered correct if calculated exactly and correctly with the correct units (milliliters or milligrams). Prepared doses were considered correct if they were within 20% of the correct mass of epinephrine. All encounters were video recorded for time analysis by a second investigator. Preparation time (seconds) was calculated from completion of the verbal order until the prepared dose was handed to the on-site investigator.

### Statistical Analysis

The primary outcome was the proportion of doses correctly prepared by using each method. On the basis of a pilot group of pediatric residents ( $n = 15$ ), we estimated that 45 participants would be required to identify a 20% difference in the proportion of doses correctly prepared using the McNemar paired proportion test ( $\alpha = .05$ ,  $\beta = .8$ ,  $P_{01} = 0.2$ , and  $P_{10} = 0.01$ ). The first 45 participants demonstrated a significantly higher error rate than anticipated on the basis of our pilot study. To maintain the desired power, the sample size was increased to 70 participants. Categorical data were compared by using McNemar's test for paired proportions or Fisher's exact test for independent proportions. Continuous and ordinal data were compared by using the Wilcoxon rank test for paired samples or the Mann-Whitney test for independent samples. Stepwise logistic regression was used to assess whether years of experience, NRP training, sequence of order method, comfort with math, anxiety, or selection of the correct epinephrine bottle predicted correct preparation of the ordered dose. Analyses were completed by using MedCalc statistical software (version 18.10.2; Ostend, Belgium).  $P < .05$  was considered statistically significant.

The University of Michigan Institutional Review Board determined the study was

exempt from review, and all participants gave written informed consent.

### RESULTS

Seventy nurses were randomly assigned to receive either the mass order first ( $n = 34$ ) or the volume order first ( $n = 36$ ). After random assignment, 1 participant from each group was excluded because they were interrupted by patient care responsibilities during the study. Demographic characteristics were similar between randomly assigned groups (Table 1). Participants in both groups were experienced nurses who had completed NRP, PALS, or advanced cardiac life support training. Some participants had completed multiple training courses. Nurses in both groups described a moderate degree of comfort with math and a moderate level of study-related anxiety.

More participants calculated and wrote the correct intended dose on the data collection form after receiving a mass order versus a volume order (Table 2). Of the 136 epinephrine doses evaluated, 77 (57%) were prepared in the syringe correctly. Only 32% of participants correctly prepared both doses. There was no difference in the probability of participants correctly preparing the epinephrine dose after receiving a mass order versus a volume order (Table 2). There was no difference in the probability of participants choosing the correct epinephrine concentration or in the median time required to prepare the dose. If the participant chose the incorrect

epinephrine solution, there was no difference in the probability of preparing the correct dose between the mass and volume ordering methods (18% for the mass method versus 7% for the volume method; risk ratio [RR] 2.5; 95% confidence interval [CI] 0.37 to 18.10;  $P = .56$ ).

In total, the mass order method resulted in 32 errors, including twofold to 10-fold overdoses ( $n = 7$ ), twofold to 10-fold underdoses ( $n = 21$ ), and >10-fold underdoses ( $n = 4$ ). The volume order method resulted in 27 errors, including twofold to 10-fold overdoses ( $n = 17$ ), less than twofold underdoses ( $n = 2$ ), twofold to 10-fold underdoses ( $n = 7$ ), and >10-fold underdoses ( $n = 1$ ). In exploratory post hoc analyses, the mass method was more likely to result in underdosing (RR 2.1; 95% CI 1.3 to 3.7;  $P < .01$ ), and the volume method was more likely to result in overdosing (RR 2.7; 95% CI 1.4 to 5.6;  $P < .01$ ). After reviewing the video recordings, we found that 14 participants (20%) had difficulty in using the ABBOJECT dispensing syringe, and it appeared to contribute to 7 (12%) of the dosing errors.

In the regression analysis, the only variable significantly associated with correct preparation of the requested dose was choosing the correct epinephrine concentration (odds ratio 14.7; 95% CI 4.1 to 52.2).

### DISCUSSION

In this study, we investigated whether ordering emergency intravenous

**TABLE 1** Participant Characteristics

	Mass Order First ( $n = 33$ ) <sup>a</sup>	Volume Order First ( $n = 35$ ) <sup>a</sup>	<i>P</i>
Primary work location <i>n</i> (%)			
NICU	18 (55)	16 (46)	.64
ED	15 (45)	19 (54)	—
Experience, y, median (IQR)	10 (5–16.5)	8 (6–13)	.48
Anxiety score, 1 (low) to 5 (high), median (IQR)	4 (3–5)	3 (3–4)	.30
Math comfort score, 1 (low) to 5 (high), median (IQR)	4 (3–4.5)	3 (3–4)	.25
NRP trained, <i>n</i> (%)	18 (55)	15 (43)	.47
PALS trained, <i>n</i> (%)	18 (55)	19 (54)	1.0

IQR, interquartile range; —, not applicable.

<sup>a</sup> There was 1 postrandomization exclusion from each group secondary to patient care interruptions during the study.

**TABLE 2** Outcome by Dosing Method

	Mass Order ( <i>n</i> = 68)	Volume Order ( <i>n</i> = 68)	<i>P</i>	Difference (95% CI)
Correct dose written, <i>n</i> (%)	56 (82)	46 (68)	.03	14.7% (2.99 to 26.42)
Correct concentration selected, <i>n</i> (%)	57 (84)	54 (79)	.38	4.4% (−1.95 to 10.77)
Correct dose prepared, <i>n</i> (%)	36 (53)	41 (60)	.49	−7.4% (−23.8 to 9.1)
Time to prepare dose, <i>s</i> , median (IQR)	110 (79–178)	123 (73.5–179)	.90	1.3 (−14.4 to 15.7)

IQR, interquartile range.

epinephrine for neonatal resuscitation by using the mass dosing method (milligrams per kilogram) was safer than by using the volume method (milliliters per kilogram), which is currently recommended by the NRP. In low-fidelity simulations, our results revealed no difference in either accuracy or efficiency between the 2 methods. The ISMP warns that the volume method results in a 10-fold overdose if the provider inadvertently uses the concentrated epinephrine solution; therefore, it recommends that providers only use the mass ordering method.<sup>11</sup> Although the mass method could result in the correct dose in this situation, we found no benefit from the mass method because participants frequently misinterpreted the concentration on the epinephrine label or made calculation errors. When controlling for other potential confounders, selecting the correct epinephrine concentration was the only variable significantly associated with correct preparation of the requested dose. We found that calculation and dispensing errors were common with using either ordering method. The most common errors resulted in twofold to 10-fold underdoses with the mass method and twofold to 10-fold overdoses with the volume method. During medication administration for newborns, decimal-point errors are particularly common. Krzyzaniak and Bajorek<sup>14</sup> reviewed neonatal medication errors and found that a  $\geq 10$ -fold overdose accounted for 47% of administration errors. In the context of resuscitation, both of these errors have the potential to result in serious harm. During neonatal resuscitation, epinephrine is beneficial because it increases peripheral vascular resistance and improves coronary artery perfusion pressure.<sup>6</sup> An underdose is likely to result in a delayed or ineffective response.<sup>15</sup> Although a higher than recommended dose of epinephrine may

increase the likelihood of return of spontaneous circulation, it may increase the risk of postresuscitation morbidity and mortality.<sup>16,17</sup>

The incidence and nature of medication errors during neonatal resuscitations have not previously been described. Investigators have demonstrated that dosing errors are common during pediatric resuscitations in the emergency department. In a series of simulated pediatric resuscitations, Porter et al<sup>18</sup> found errors in 41% of initial medication orders given by residents. Although many were identified by other participants before the drugs were administered, 26% of medications administered during the simulations had dosing errors. Kozer et al<sup>19</sup> studied medication errors during simulated pediatric emergencies and found significant deviations from the intended dose in 16% of analyzed medication syringes. In a simulation study involving pediatric seizures, Morgan et al<sup>20</sup> found an error rate as high as 27% when nurses were required to convert the prescribed medication between milligrams and milliliters. In 33% of the 150 medications administered during the simulations, the dose measured in the syringe was not consistent with the intended dose. In the current study, we found more errors of preparing the medication dose than in these emergency department studies. In part, this reflects differences in the study protocols. Participants in the studies by Porter et al<sup>18</sup> and Kozer et al<sup>19</sup> were allowed to use cognitive aids and received assistance from other team members. In addition, the difference may reflect the increased complexity of preparing epinephrine for neonatal resuscitation.

Cognitive load refers to the complexity of a given task. It varies with the number of

components involved in the task and the learner's experience.<sup>21</sup> Cognitive load is an important factor in pediatric resuscitation, with increased load associated with increased risk of error.<sup>5</sup> Because epinephrine for neonatal resuscitation is not commercially available in unit-dose syringes, preparing the dose imposes a significant cognitive load. The provider must select between multiple preparations, interpret the concentration ratio on the label, perform calculations and decimal-point adjustments, and use an unfamiliar delivery device in a stressful environment. During the post hoc video review, we noted that participants frequently started with the correct preparation but became confused while trying to assemble the ABBOJECT syringe and ultimately decided to use the simpler glass bottle or vial without recognizing that they contained a more concentrated solution. This occurred although our institution's NRP course requires all participants to assemble and use an ABBOJECT syringe. Others appeared confused by the scripted prescribing order that specified the medication concentration, which was immediately followed by the dose, resulting in the nurse hearing 2 consecutive ratios (0.1 mg/1 mL and 0.01 mL/kg) in series. Previous studies have revealed that health care professionals have difficulty interpreting the concentration of solutions, understanding ratios, and performing simple math calculations.<sup>22,23</sup> Moreover, math anxiety is common among nurses and significantly increases the risk of medication calculation errors.<sup>24</sup> Although the calculations required to prepare epinephrine add to cognitive load, we did not find an association between years of experience, self-described comfort with math, or self-described anxiety and the probability of a dosing error.

Our study reveals opportunities to improve the safety of emergency medication administration during neonatal resuscitation. To prevent inadvertent use of concentrated epinephrine, hospitals should maintain designated neonatal emergency boxes that contain only the medications and concentrations appropriate for newborns.<sup>25,26</sup> Removing the concentrated epinephrine solutions may have prevented

many of the dosing errors in our study. Cognitive aids, such as preprinted weight-based guidelines, are helpful but still require providers to prepare the dose from an unfamiliar delivery device.<sup>18,27</sup>

Photographs of the correct epinephrine concentration with illustrated instructions for assembling the ABBOJECT syringe may be effective.<sup>25</sup> Standardized pediatric dosing systems, such as the Broselow-Luten tape,<sup>28</sup> and color-coded prefilled syringes<sup>29</sup> have been shown to reduce drug errors; however, there is currently no similar device for the neonatal weight range. Effective teamwork, read-back of medication orders, and improved communication may decrease the risk of medication errors.<sup>27,30</sup> In particular, addition of a clinical pharmacist to the resuscitation team has been shown to significantly reduce the risk of medication errors during resuscitations.<sup>18,26</sup>

The current study has several limitations. First, we used a low-fidelity simulation environment, where participants prepared the medication in a quiet room with an audible heart rate but without the noise and pressure of an actual resuscitation. We chose this setting because it allowed us to control the environment and carefully assess each step of drug preparation. As a result, our study may underestimate the risk of drug errors during neonatal resuscitations. Second, our original sample size was based on a pilot study in which pediatric residents prepared a simulated medication using the volume ordering method. The residents obtained the simulated medication from a 10-mL bottle, not the ABBOJECT syringe. We speculate that using a bottle rather than the ABBOJECT syringe may have resulted in fewer errors and may have led to an underestimate of the baseline dosing error rate. In addition, they may have better math skills or may have experienced less stress during testing than our study participants. Finally, in our crossover design, participants were their own controls and prepared epinephrine using both ordering methods. Although this design decreased the potential for experience bias, it may have led to learning bias, in which participants prepare the second dose quicker and with greater accuracy. We controlled for potential

learning bias by randomizing the sequence of order methods, and we found no evidence of a learning effect based on sequence order in our logistic regression analysis.

## CONCLUSIONS

In simulated resuscitations, the mass method was neither more accurate nor more efficient than the volume method. Nurses made frequent errors when using both methods. Our results do not support the ISMP suggestion that changing to the mass ordering method would reduce the risk of epinephrine dosing errors during neonatal resuscitation. Selecting the wrong epinephrine solution is likely to result in a dosing error regardless of the ordering method used. This is a serious patient safety problem and reveals that only the dilute epinephrine solution (1 mg/10 mL) should be available where newborns are resuscitated. Additional medication safety interventions are urgently needed.

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