A Graded Approach to Intravenous Dextrose for Neonatal Hypoglycemia Decreases Blood Glucose Variability, Time in the Neonatal Intensive Care Unit, and Cost of Stay

Sarbattama Sen, MD[1,2], Sara Cherkerzian, ScD[1,2], Daria Turner, BA[1], Carmen Monthé-Drèze, MD[1,2], Elisa Abdulhayoglu, MD[1,2], and John A. F. Zupancic, MD, ScD[2,3]

Objective To determine associations between a graded approach to intravenous (IV) dextrose treatment for neonatal hypoglycemia and changes in blood glucose (BG), length of stay (LOS), and cost of care.

Study design Retrospective cohort study of 277 infants born at ≥35 weeks of gestation in an urban academic delivery hospital, comparing the change in BG after IV dextrose initiation, neonatal intensive care unit (NICU) LOS, and cost of care in epochs before and after a hospital protocol change. During epoch 1, all infants who needed IV dextrose for hypoglycemia were given a bolus and started on IV dextrose at 60 mL/kg/day. During epoch 2, infants received IV dextrose at 30 or 60 mL/kg/day based on the degree of hypoglycemia. Differences in BG outcomes, LOS, and cost of hospital care between epochs were compared using adjusted median regression.

Results In epoch 2, the median (IQR) rise in BG after initiating IV dextrose (19 [10, 31] mg/dL) was significantly lower than in epoch 1 (24 [14,37] mg/dL; adjusted β = -6.0 mg/dL, 95% CI -11.2, -0.8). Time to normoglycemia did not differ significantly between epochs. NICU days decreased from a median (IQR) of 4.5 (2.1, 11.0) to 3.0 (1.5, 6.5) (adjusted β = -1.9, 95% CI -3.0, -0.7). Costs associated with NICU hospitalization decreased from a median (IQR) $14 030 ($5847, $30 753) to $8470 ($5650, $19 019) (adjusted β = -$4417, 95% CI -$571, -$8263) after guideline implementation.

Conclusions A graded approach to IV dextrose was associated with decreased BG lability and length and cost of NICU stay for infants with neonatal hypoglycemia. *(J Pediatr 2021;231:74-80)*.

Neonatal hypoglycemia is estimated to affect 15%-30% of newborn infants and is associated with neurodevelopmental sequelae.[1-3] Recent evidence suggests that both neonatal hypoglycemia and a rapid rise in blood glucose (BG) after treatment with intravenous (IV) dextrose are associated with adverse neurodevelopmental outcomes.[3,4] The 2011 American Academy of Pediatrics guidelines recommend treatment of neonatal hypoglycemia in asymptomatic infants with "refeeding or IV glucose as needed."[5] However, these guidelines were composed prior to the emergence of data suggesting that a rapid rise in BG may be associated with adverse neurodevelopmental outcomes,[3] and do not specify parameters for providing IV dextrose.

A common approach to IV dextrose administration for hypoglycemia for infants with persistent hypoglycemia after enteral management is to provide a bolus of 10% IV dextrose (2 mL/kg) followed by an infusion of 10% IV dextrose at 60 mL/kg/day for infants, regardless of the degree of hypoglycemia. There are minimal data regarding how this practice impacts BG concentrations and whether providing lower rates of IV dextrose may be adequate in achieving normoglycemia. In most hospitals, infants are separated from their mothers and admitted to the neonatal intensive care unit (NICU) to provide IV dextrose. This practice impacts bonding and breastfeeding outcomes and is associated with a higher cost of care. Therefore, initiating IV dextrose at a lower rate may facilitate quicker weaning from IV dextrose and a shorter NICU length of stay (LOS).

We implemented a clinical practice guideline in November 2017 that provided a graded approach to IV dextrose administration based on baseline BG in asymptomatic newborns at-risk for hypoglycemia at a single, academic, high-volume birth hospital in the US. We sought to examine the impact of this change in practice on the rise in BG after first IV dextrose administration; the length of NICU stay; and the cost of hospital admission. We also quantified time to normoglycemia, to understand whether this protocol would change the length of time that infants were exposed to hypoglycemia.

NICU	Neonatal intensive care unit
IV	Intravenous
BG	Blood glucose
LOS	Length of stay

From the [1]Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, [2]Harvard Medical School, and [3]Department of Neonatology, Beth Israel Deaconess Medical Center, Boston, MA

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Methods

This was a retrospective study of 277 asymptomatic infants receiving IV dextrose for hypoglycemia treatment at ≤48 hours after birth per institutional hypoglycemia screening protocol from January 2016 to December 2018 at Brigham and Women's Hospital in Boston, Massachusetts. Using a data extract report from the electronic health record, we identified all infants born during this period who had a BG measurement within 48 hours of birth, developed hypoglycemia, failed oral dextrose gel and feeding, and required IV dextrose for management of hypoglycemia. Timing of all variables, including when infants were transferred between care units (nursery to NICU and NICU to nursery), was provided with a date and time stamp in the data extract report. Infants were excluded from this analysis if they had a gestational age of <35 weeks, were a multiple gestation, or developed hypoglycemia after 48 hours of life**.** This project was undertaken and approved, per The Brigham and Women's Hospital Institutional Review Board policy, as a quality improvement initiative and was not formally supervised by the Institutional Review Board.

Summary of Clinical Guidelines

Asymptomatic infants were screened after a feeding at 1 hour of age based on established risk factors infant of a mother with diabetes, birth weight small or large for gestational age, maternal beta blocker or terbutaline administration, prematurity (<37 weeks), post-term gestation, perinatal stress (Apgar score <7 at 5 minutes of life, respiratory distress >1 hour), family history of hypoglycemia, or a midline congenital anomaly. Point-of-care BG was measured with the Abbott Precision Xceed Pro Point-of-Care System. The goal BG concentration for infants <48 hours of age was ≥45 mg/dL. If an infant's BG concentration was below the treatment threshold, the infant was fed and provided dextrose gel up to 3 times. If hypoglycemia persisted, the infant was admitted to the NICU for IV dextrose administration.

In epoch 1 (December 2016-October 2017), infants with a BG <45 mg/dL after dextrose gel and feeding received a 2 mL/kg IV bolus of 10% dextrose followed by a continuous infusion of 10% IV dextrose at 60 mL/kg/day. During epoch 2 (November 2017 - December 2018), infants who failed dextrose gel and feeding were treated based on the baseline BG preceding the initiation of IV dextrose. If the baseline BG was <20 mg/dL, the infant received a 2 mL/kg bolus of 10% IV dextrose followed by a continuous infusion of 10% IV dextrose at 60 mL/kg/day. If the baseline BG was 20-30 mg/dL, the infant received a continuous infusion of 10% IV dextrose at 60 mL/kg/day (without a bolus). If the baseline BG was 31-44 mg/dL, the infant received a continuous infusion of 10% IV dextrose at 30 mL/kg/day. The follow-up BG was evaluated 30 minutes after initiating IV dextrose. Three BG measurements in the normal range were required after IV dextrose was discontinued. The change in BG was defined as the difference between the baseline and follow-up glucose.

Costs of Hypoglycemia-Related Care

Cost of care was calculated based on the acuity of care infants received, which was provided on a patient-level from the data extract report. Institutional charges for hospital care were retrieved from hospital financial records. These were converted to costs using the hospital-level cost-to-charge ratio from the Center for Medicare and Medicaid Services.[6] Professional fees were also based on the Metropolitan Boston facility price from the Center for Medicare and Medicaid Services Physician Fee Schedule, based on the relevant Healthcare Common Procedure Coding System code.[6]

A sum of the following components was used to estimate the total cost of hospital admission on a per-patient basis: dextrose gel ($12.60/gel), nursery care (initial-$475, technical-$2694/day, professional-$285/day after day 1), NICU triage admission ($539), NICU care (initial-$1392, technical-$9898/day, professional-$554/day after day 1). For infants admitted to the NICU after initial admission to the nursery, only the NICU costs (ie, not initial nursery costs) were included. Infants who were persistently hypoglycemic, or who required a venous blood draw for BG, were sent to the NICU triage area for a brief admission (<6 hours). If infants returned to the nursery after a triage admission, then the additional cost of NICU triage admission ($539) was added to their level 1 care. If they were subsequently admitted to the NICU, only their NICU admission cost was applied. Costs for infants who were admitted to the NICU and returned to the nursery were calculated using NICU and subsequent nursery expenditures for the number of days they were admitted to each. Costs for BG measurement supplies (glucometer strips, lancets, alcohol) were negligible and not included. NICU total charges were adjusted using the United States Bureau of Economic Analysis Personal Health Care Index (personal consumption expenditures-health) to express costs in 2018 US dollars.[7]

Statistical Analyses

Descriptive statistics of the mother/infant dyad demographic and clinical characteristics were calculated for the overall sample and by epoch. Differences by epoch were assessed using $\chi 2$ or Wilcoxon rank-sum tests, as appropriate. Comparison of the distributions of BG concentration (mg/dL) after IV dextrose, total hospital and NICU LOS (days), and total hospital and NICU costs by epoch were evaluated using an overlay of epoch-specific distribution histograms with corresponding kernel density curves followed by modeling of the associations of interest using median regression unadjusted and adjusted for potential confounding, an approach selected given the skew of the variable distributions. Adjusted models included control for baseline covariates that differed ($P < .10$) between the 2 epochs. Similar analyses were conducted by maximum IV flow rate (≥60 vs 30 mL/kg/day) among infants with a pre-IV BG 30-44 mg/dL (n = 210) to further isolate the associations of IV dextrose rate on outcomes within the subset of infants who were most impacted by this practice change. The time to normoglycemia (≥45 mg/dL) after IV dextrose initiation by epoch status was evaluated using

median regression. The longitudinal sequences of the total NICU costs and LOS over the duration of the study period were graphed using run charts of the median value for each annual quarter. Because the protocol change occurred during the fourth quarter of 2017, the quarter was divided by epoch—epoch 1 (October 1, 2017 to November 1, 2017) and epoch 2 (November 1, 2017 to January 1, 2018). Overall and epoch-specific measures were calculated as weighted medians given the variation in sample size by annual quarter. All analyses were performed using SAS software v 9.4 (SAS Institute).

Results

There were n = 277 infants in the analytic sample, 144 (52%) in epoch 1 and 133 (48%) in epoch 2. Demographic and clinical characteristics among infants of the 2 epochs were similar except there were more female and small for gestational age infants, but fewer large for gestational age infants, in epoch 2 than in epoch 1 (Table I). As expected, more infants in the postimplementation period had a maximum IV dextrose rate of 30 mL/kg/day compared with the preimplementation period (post: 48.9% vs pre: 4.9%, $P < .0001$).

BG Concentrations

The median (IQR) change in BG after initiation of IV dextrose decreased in epoch 2 (epoch 1: 24 (14, 37) mg/dL vs epoch 2: 19 (10, 31) mg/dL; Figure 1, A), driven by the lower rise in BG concentration among infants who received a maximum IV dextrose rate of 30 mL/kg/day. In an analysis adjusted for sex and birth weight percentile, infants in epoch 1 had a median 6 mg/dL higher rise in BG after initiation of IV dextrose compared with infants in epoch 2 (95% CI 0.8, 11.2; Table II). In analyses adjusted for sex, birth weight percentile, and maternal body mass index,

Table I. Demographic and clinical characteristics

Maternal or infant characteristics	All (N = 277)		Epoch 1 Admitted to NICU pre implementation (n = 144)		Epoch 2 Admitted to NICU post implementation (n = 133)		*P* value*
Maternal characteristics							
Parity: n (%)							.309
Primiparity	160	57.8%	79	54.9%	81	60.9%	
Multiparity	117	42.2%	65	45.1%	52	39.1%	
Race: n (%)							.956
White	150	54.2%	76	52.8%	74	55.6%	
Asian	17	6.1%	9	6.3%	8	6.0%	
Black/African American	47	17.0%	25	17.4%	22	16.5%	
Hispanic/Latino	20	7.2%	12	8.3%	8	6.0%	
Other	43	15.5%	22	15.3%	21	15.8%	
Delivery body mass index							.315
<30 kg/m^2	99	35.7%	45	31.3%	54	40.6%	
≥30 kg/m^2	158	57.0%	82	56.9%	76	57.1%	
Preeclampsia: n (%)							.725
Yes	16	5.8%	9	6.3%	7	5.3%	
No	261	94.2%	135	93.8%	126	94.7%	
Gestational diabetes: n (%)							.768
Yes	46	16.6%	23	16.0%	23	17.3%	
No	231	83.4%	121	84.0%	110	82.7%	
Mode of delivery: n (%)							.162
Vaginal delivery	135	48.7%	76	52.8%	59	44.4%	
Cesarean delivery	142	51.3%	68	47.2%	74	55.6%	
Infant characteristics							
Birth weight: mean (SD)	3186.4	772.5	3200.7	799.7	3170.8	744.5	.831
Sex: n (%)							.058†
Female	113	40.8%	51	35.4%	62	46.6%	
Male	164	59.2%	93	64.6%	71	53.4%	
Gestational age, wk: n (%)							.621
Late preterm (35-36.9)	68	24.5%	32	22.2%	36	27.1%	
Term (37-41)	195	70.4%	105	72.9%	90	67.7%	
Post dates (>41)	14	5.1%	7	4.9%	7	5.3%	
Birth weight percentile: n (%)							.015‡
Small for gestational age (<10%)	146	52.7%	64	44.4%	82	61.7%	
Appropriate for gestational age	68	24.5%	39	27.1%	29	21.8%	
Large for gestational age (>10%)	63	22.7%	41	28.5%	22	16.5%	
Proportion of infants with maximum IV dextrose rate: n (%)							<.0001‡
30 mL/kg/d	72	65.0%	7	4.9%	65	48.9%	
≥60 mL/kg/d	205	65.0%	137	95.1%	68	51.1%	

*Comparisons by epoch (1 vs 2) among categorical and binary variables analyzed using $\chi 2$ test, among continuous variables nonparametric Wilcoxon rank-sum test.
†$P < .10$.
‡$P < .05$.

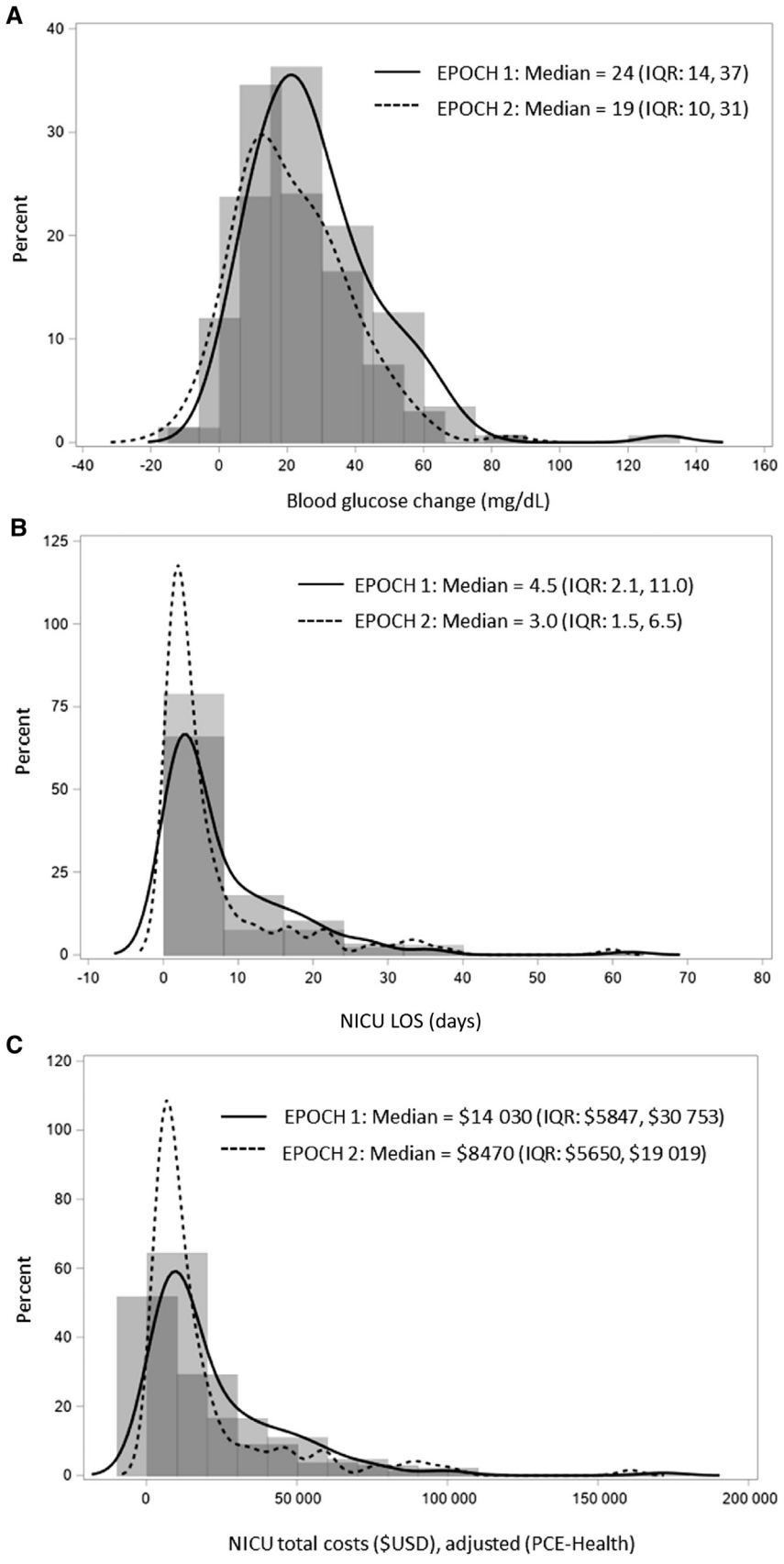


Figure 1. **A, B, and C,** Histograms of quality improvement measures: Comparisons by epoch.

Table II. Median differences in outcomes by epoch*: unadjusted and adjusted quantile regression models

Outcomes (N = 277)	β†	95% CI		P value
BG concentration change (mg/dL), after IV dextrose initiation				
Unadjusted	5.0	−0.2	10.2	.06‡
Adjusted§	6.0	.8	11.2	.02¶
NICU LOS (d)				
Unadjusted	1.5	.1	2.9	.04¶
Adjusted§	1.9	.7	3.0	.002¶
NICU total costs (US dollars)				
Unadjusted	$5441	$1111	$9772	.001¶
Adjusted§	$4417	$571	$8263	.03¶
Time to normoglycemia (min)				
Unadjusted	1.0	−12.1	14.1	.9
Adjusted§	.0	−13.3	13.3	1.0

*Epoch 1 (January 2016 - October 2017), n = 144; epoch 2 (November 2017 - December 2018), n = 133.
†Reference group: epoch 2.
‡$P < .10$.
§Analyses adjusted for potential confounding by sex and birth weight percentile.
¶$P < .05$

infants with a baseline BG 30-44 mg/dL who received IV dextrose at a minimum rate of 60 mg/kg/day had a median 13 mg/dL higher rise in BG after initiation of IV dextrose compared with infants with a maximum IV dextrose rate of 30 ml/kg/day (95% CI 8.7, 17.3). Among the subset of infants whose BG after IV dextrose initiation was >45 mg/dL, infants who received a maximum rate of 30 mL/kg/day had a median BG of 54 (IQR 50, 61), whereas infants whose minimum rate was 60 mL/kg/day had a median BG after IV dextrose initiation of 66 mg/dL (IQR: 56, 74).

Length of NICU Stay

The median LOS for infants admitted to the NICU for hypoglycemia decreased after implementation from 4.5 (95% CI 2.1, 11.0) days to 3.0 (1.5, 6.5) days (Figure 1, B) (adjusted β: 1.9, 95% CI 0.7, 3.0; Table II). Figure 2, A illustrates the gradual longitudinal change in the median NICU LOS across annual quarters from the start of epoch 1 (weighted median: 4.3 days [IQR: 3.7, 6.4]) to the end of epoch 2 (weighted median: 2.6 days [IQR: 2.4, 2.6]). Given the high median LOS in the first quarter of 2016, we conducted an adjusted sensitivity analysis excluding this quarter that did not alter these findings.

Cost of Care

In line with the decrease observed in NICU LOS from epoch 1 to epoch 2, there was a decrease in NICU total costs from epoch 1 (median: $14 030; IQR: $5847, $30 753) to epoch 2 (median: $8470; IQR: $5650, $19 019; Figure 1, C) by an adjusted median difference of $4417 (95% CI $571, $8263; Table II). The longitudinal change in the median NICU total costs across annual quarters from the start of epoch 1 (weighted median: $14,149 [IQR $11 191, $19 353]) to the end of epoch 2 (weighted median: $8324 [IQR $8,324, $13 671], Figure 2, B) followed a similar pattern observed for NICU LOS. Given the high median cost of NICU care in the first quarter of 2016, we conducted an adjusted sensitivity analysis excluding this quarter, which did not alter these findings. The median cost of the newborn hospitalizations overall did not change between epochs, because only 5% of infants from the overall population of screened infants were admitted to the NICU for hypoglycemia and thus, costs were driven by the large number of infants who did not require NICU care (data not shown).

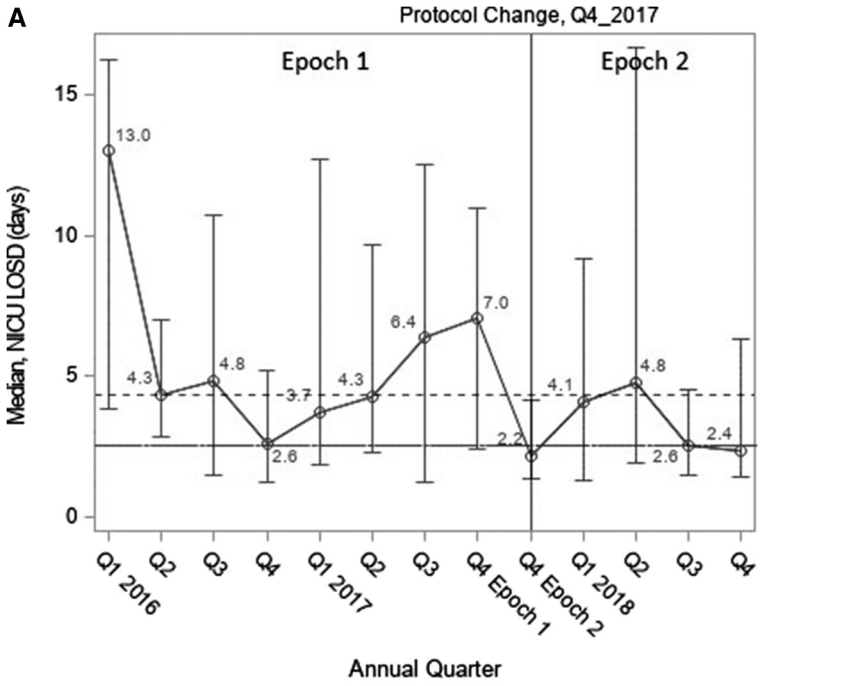
Time to Achieve Normoglycemia

We compared the time to achieve normoglycemia after IV dextrose initiation by epoch. Time to achieve normoglycemia was similar between epochs (median [IQR] epoch 1: 60 [37, 89] minutes vs epoch 2: 59 [40, 106] minutes, $P = .4$). Similarly, in adjusted analysis, time to normoglycemia did not differ between epochs (Table II). After instituting the graded approach (epoch 2), 21% (14 of 68) of infants with a pre-IV BG 30-44 mg/dL required escalation of IV dextrose above 30 mL/kg/day.

Discussion

The results of our study suggest that infants with hypoglycemia who require IV dextrose may benefit from a graded approach to providing IV dextrose. In our study cohort, after a graded approach was adopted, infants had a less steep rise in BG, shorter NICU stays, and lower cost of NICU care. This change in practice was not associated with a longer time to achieve normoglycemia, which was a potential concern when initiating this practice change. Thus, providing graded IV dextrose for infants who have failed enteral treatment for hypoglycemia appears to achieve normoglycemia within an equivalent time-frame as the "one-size-fits-all" approach, but with less steep BG flux and a shorter time to wean off of IV dextrose. This was associated with a shorter NICU admission, less separation of mother and infant, and lower NICU-associated costs of care.

There is no standard, nationally recommended guideline for administering IV dextrose to infants with hypoglycemia. Historically, infants who failed enteral options, such as feeding and dextrose gel would all receive the same treatment: a bolus of 2 mL/kg 10% dextrose in water followed by initiation of 10% dextrose in water at 60 mL/kg/day. Based on recent data that a rapid flux or rise in BG may be associated with neurodevelopmental harm[3] and the biologically plausible concern that rapid rises may stimulate subsequent insulin production and further prolong the need for IV dextrose for hypoglycemia, we instituted a practice change to provide a graded approach based on pre-IV dextrose BG concentration. As hypothesized, infants who received lower rates of IV dextrose had a less steep rise in BG and did not require more time to achieve normoglycemia. We also observed that receiving a higher IV dextrose rate was associated with achieving a BG in excess of the goal BG. Historically, this practice may have stemmed from a perception that



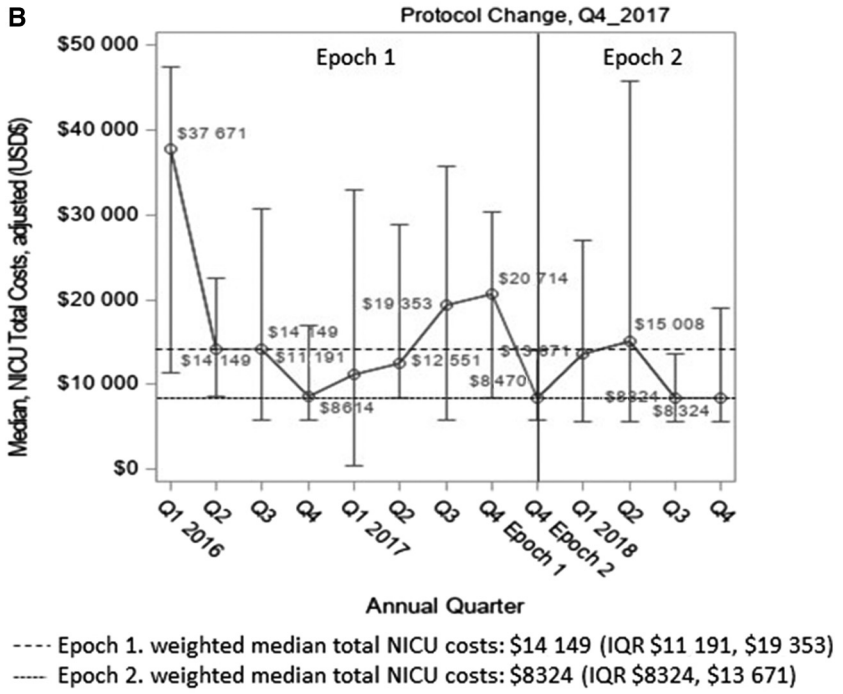


Figure 2. **A,** Median NICU LOS (days) by annual quarters from January 2016 to December 2018 among n = 277 infants treated for hypoglycemia with IV dextrose: differences before and after the November 2017 protocol change. Data from epoch 1 are represented in blue and epoch 2 in red. **B,** Median NICU total costs by annual quarters from January 2016 to December 2018 among n = 277 infants treated for hypoglycemia with IV dextrose: differences before and after the November 2017 protocol change. Data from epoch 1 are represented in blue and epoch 2 in red.

only hypoglycemia, not rapid glucose flux or hyperglycemia, is associated with harm. Here we suggest that given contemporary data, new approaches to providing IV dextrose, such as those we have proposed here, may adequately treat hypoglycemia and minimize potential harm associated with rapid glucose fluxes. This study was not able to address whether this practice change was associated with improvement in neurodevelopmental outcome, which should be addressed in future studies.

We found that few infants with moderate hypoglycemia required escalation of IV dextrose rate above 30 mL/kg/day and instituting a graded approach to IV dextrose allowed infants to wean from IV dextrose more quickly. At our institution, IV dextrose is administered only in the NICU, so this practice change resulted in fewer days of maternal-infant separation. Separation of mother and infant is associated with lower breastfeeding success, higher maternal and infant stress, higher rates of postpartum depression and anxiety, and lower parental satisfaction with postpartum hospitalization.[8-10] We did not measure the impact of this practice change on these specific outcomes in this study but can conclude that this practice aligns with the goals of the "baby-friendly" initiatives to minimize mother-infant separation by decreasing length of NICU admissions.

We estimated the costs associated with this change in practice and found a considerable cost-savings attributable to the decreased NICU LOS. Neonatal hypoglycemia ranks in the top 5 indications in the US for NICU admission of infants with gestational ages of >37 weeks, accounting for 4%-5.8% of all NICU diagnoses.[11] The proportion of NICU admissions of infants >2500 g birthweight increased by 23% between 2007 and 2012, mirroring the rising rates of maternal dysmetabolism.[12] We estimate, using a NICU admission rate of 43 per 1000 live births with 5% of those admissions for hypoglycemia, that if widely implemented in the US, a similar practice change would result in an annual cost savings of $36 million.[12]

Limitations of this study include that it was conducted at a single, academic, high delivery-volume center, which may limit the generalizability to other settings. Further, infants who require IV dextrose are treated in the NICU, not a special care or step-down unit, which may impact the cost of care. This study is inherently limited by its retrospective design, comparing time periods, although there were no other relevant practice changes that occurred over the study time-period that may have impacted results. These findings lay the foundation for a randomized controlled trial evaluating the effect of graded IV dextrose vs the standard approach on hypoglycemia outcomes, which would address potential confounding by known and unknown factors. We applied a top-down costing approach that relied on summing daily costs and stratified by illness acuity. Although this approach does not have the granularity of patient-level daily itemized costs, it has been used in multiple formal economic evaluations and should reflect cost differences driven by LOS changes. Finally, the impact of this practice change on longer term outcomes was not within the scope of this study but bears further examination.

In summary, we found that a graded approach to IV dextrose for hypoglycemia in infants who failed enteral measures led to a less steep rise in BG concentrations, shorter length of NICU stay, and lower cost of NICU care without lengthening the duration of exposure to low BG concentrations. Further research on this practice change may hold promise as we optimize care for the increasing numbers of infants at-risk for hypoglycemia. ■

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Reprint requests: Sarbattama Sen, MD, Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail: ssen2@bwh.harvard.edu

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