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Neurologic Outcomes in Neonates Following the Introduction of a Restrictive Transfusion Guideline

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ABSTRACT

Objective: *To evaluate the neurodevelopmental outcomes of very low birthweight (VLBW) infants before and after the introduction of a restrictive transfusion guideline.*

Study design: *This is a large retrospective study comparing neurodevelopmental outcomes before and after a restrictive transfusion guideline (RTG) was established for VLBW infants admitted to a large single neonatal intensive care unit (NICU). Bayley-III scores obtained from routine NICU follow up appointments at pediatric neurodevelopmental clinics were evaluated. The mean age of obtaining the Bayley-III score was 20.3 months with a standard deviation of +/- 5.2 months.*

Results: *Neurodevelopmental outcomes measured by Bayley-III scores, were similar for cognitive, language, and motor testing in the RTG versus LTG groups. In addition, the subcategories for normal, mild delay, moderate delay and severely delayed were also similar.*

Conclusion: *RTG is safe in the neonatal VLBW population. RTG when compared to liberal transfusion guideline (LTG) is associated with similar neurodevelopmental outcomes as defined by Bayley-III scores.*

Introduction

Anemia is common in premature infants, especially in those born at less than 30 weeks of gestation. An inverse relationship exists between gestational age and receipt of packed red blood cell (PRBC) transfusions: the lower the gestational age at birth, the greater the number of PRBC transfusions received [1]. Nearly 85% of extremely low birth weight (ELBW) infants receive at least one PRBC transfusion before discharge from the neonatal intensive care unit (NICU) [2]. While anemia is expected in premature infants, a debated question remains: At what hemoglobin or hematocrit level should providers transfuse an infant? In our previous study we found RTG is safe in the very low birthweight

(VLBW) neonatal population [3]. RTG when compared to liberal transfusion guidelines (LTG) is associated with similar mortality and chronic lung disease (CLD) rates. We found that RTG appears to be protective regarding retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), sepsis and necrotizing enterocolitis (NEC) [3]. With our subsequent study, we have taken this further to examine the neurodevelopmental outcomes of VLBW infants before and after the change to RTG.

The purpose of our study was to assess neurodevelopmental outcomes in VLBW infants before and after changing to RTG.

Materials/Subjects and Methods

We performed a retrospective study of VLBW infants (birth weight less than 1500 g) admitted to the Gerber Foundation Neonatal Center at Helen DeVos Children's Hospital (HDVCH) of Spectrum Health Hospital from January 1, 2012 to December 31, 2015. The 108-bed NICU at HDVCH is the only level 4 NICU in West Michigan and cares for infants born both within and outside of the institution. The Institutional Review Board at Spectrum Health approved both the original and follow-up research.

Study Population

Eligible infants were those with birth weights less than 1500 grams and either born at HDVCH or transported to HDVCH within the first 2 weeks of life. All included infants had to have been transported to HDVCH prior to receiving a PRBC transfusion. Infants were excluded if they were diagnosed with congenital heart disease, genetic anomalies, major malformations, or if they died within 48 hours of birth. Infants with red blood cell alloimmunization were not excluded. There were approximately 860 infants born during the study time period that were potentially eligible for inclusion. If an infant had repeated admissions, only the data from the initial admission was included. Of these, 99 infants were excluded from initial data analysis. Of the 766 patients included in the study, a total of 470 had Bayley-III testing completed at a routine outpatient neurodevelopmental clinic appointment.

Bayley Scales of Infant and Toddler Development is used by the neurodevelopmental clinic at HDVCH. The third edition, Bayley-III, was used during this time frame. Children between the ages of 1 to 42 months can be developmentally assessed across five domains by this tool, including cognitive, language, and motor skills. Bayley Scales can be used to identify patients with a neurodevelopmental delay, provide identification of children needing early intervention as well as scoring to monitor progress once intervention has been initiated.[6] Criteria for referral to the neurodevelopmental clinic include, but are not limited to, infants born at less than 31 weeks gestation and/or birth weight less than 1500 grams. For this study, the composite scores of 85 and above are considered normal; scores of 71 to 84 are associated with mild delay; scores of 70 and below are considered a significant delay.

Intervention

Infants received PRBC transfusions (leukocyte-depleted and CMV negative) according to our NICU's transfusion guidelines. Whether to suspend or continue enteral feeding during the time of transfusion was at the discretion of the neonatologist; however, the standard was to continue the infant's current feeding plan during and after transfusion. During the study time period, the standard infusion time for a single PRBC transfusion was three hours. Neonatologists may have transfused infants outside the guidelines depending on clinical indications. The PRBC liberal transfusion guidelines (LTG) were used during 2012-2013 and RTG were used during 2014-2015 (Table 1). The platelet transfusion guideline remained unchanged during the study time. The RTG were distributed to residents, neonatal nurse practitioners and registered nurses practicing in the NICU.

Data Collection

All data, excluding the Bayley-III scores, were collected by review of HDVCH's electronic medical records (PowerChart Organizer,

Table 1: Transfusion Guidelines 2012-2013 & 2014-2015.

Hematocrit Parameter	Action per 2012-2013 Guideline (LTG)	Action per 2014-2015 Guideline (RTG)
If Hct < 40% and on > 35% oxygen via ventilator, NCPAP or NIPPV	Transfuse 15 mL/kg PRBC	Not applicable
If Hct < 30%	Transfuse 15 mL/kg PRBC if on any respiratory support	Transfuse 15-20 mL/kg of PRBC if on > 40% oxygen via ventilator/NIPPV/ NCPAP (MAP > 7)
If Hct ≤ 25%	Not applicable	Transfuse 20 mL/kg of PRBC if on <40% oxygen via ventilator/NIPPV/ NCPAP (MAP>7)
If Hct < 20%	Transfuse 15 mL/kg PRBC	Transfuse 20 mL/kg of PRBC if on supplemental oxygen or NCPAP/ ventilator/NIPPV MAP < 7 and symptomatic
If Hct < 18% and absolute reticulocyte counts < 100,000 cells/microL	Not applicable	Transfuse 20 mL/kg of PRBC

PRBC: Packed red blood cells; Hct: Hematocrit; NCPAP: Nasal continuous positive airway pressure; NIPPV: Nasal intermittent positive pressure ventilation; MAP: Mean arterial pressure

Symptoms - > 24 hours of tachycardia (>180 beats/min) or tachypnea (>60 breaths/min)

A doubling of the oxygen requirement form the previous 48 hours

Lactate >=2.5 or an acute metabolic acidosis

Weight gain < 10 g/kg/day over the previous 4 days while receiving >=120 kcal/kg/day

Undergoing surgery within 24 hours

Cerner Corporation, North Kansas City, MO). All Bayley-III scores were collected by review of HDVCH's electronic medical records (EPIC, 1979 Milky Way Verona, WI 53593).

Statistical methods

Summary statistics were calculated. Quantitative, normally distributed data are expressed as the mean ± standard deviation, while non-normally distributed data are expressed as the median, with the range (25th percentile – 75th percentile) in brackets. Nominal data are expressed as a percentage. Comparisons between groups for quantitative variables were performed using the t-test, with the exception of length of stay, which was analyzed using negative binomial regression. With regards to the t-test, those comparisons were performed using the 2-tailed t-test for equal variances, with the exception of the analysis comparing the transformed data for the PRBC, which was performed using the 2-tailed t-test for unequal variances. Prior to analysis, non-normally distributed quantitative data were either log-transformed or transformed using the inverse hyperbolic sine function. Nominal variables were evaluated using the chi-square test. Bayley-III score data was analyzed as normal for age (yes vs. no), as well as severe delay (yes vs. no). Significance for demographic and hematologic data was assessed at $p<0.05$, while significance for the Bayley-III score data was assessed at $p < 0.025$. Data was analyzed using Stata v.16.1 (StataCorp, College Station, TX).

Results

Study Population

A total of 865 infants met the gestational age, birthweight, and birth date criteria for our initial study reviewing RTG vs LTG outcomes. Of these, 99 infants were excluded from initial data analysis. Of the 766 patients included in the study, a total of 465 patients had Bayley-III Scales testing completed at the neurodevelopmental clinic at HDVCH for a follow-up rate of 60.7 percent. The mean age of obtaining the Bayley-III score was 20.3 months with a standard deviation of +/- 5.2 months.

Of those patients with Bayley-III scores, a total of 226 were in the LTG group, and a total of 239 were in the RTG group. The LTG group was significantly younger, had a lower birthweight and had fewer females (Table 2). There was no significant difference in median hospital length of stay (LOS) between the RTG and LTG groups (67 days and 71 days, respectively; p=0.086).

Table 2: General demographic data.

	LTG	RTG	P value
Gestational age	27.3 ± 2.6	28.0 ± 2.7	0.005
Birthweight	1023 ± 278	1077 ± 263	0.032
Sex, % female	(96/223) 43.1%	(126/238) 52.9%	0.034

LTG: Liberal transfusion guidelines; RTG: Restrictive transfusion guidelines.

Transfusion

The numbers of PRBC transfusions were significantly different in the two groups (Table 3). Significantly more subjects were transfused in the LTG group than in the RTG group. The difference in transfusion rates between RTG and LTG groups was fairly consistent across infants of various gestational ages (Figure 1). The median number of PRBC transfusions received per infant was also significantly less in the RTG group compared to the LTG group. Although the RTG group received fewer PRBC transfusions, the RTG group had significantly higher discharge hematocrit levels compared to the LTG group.

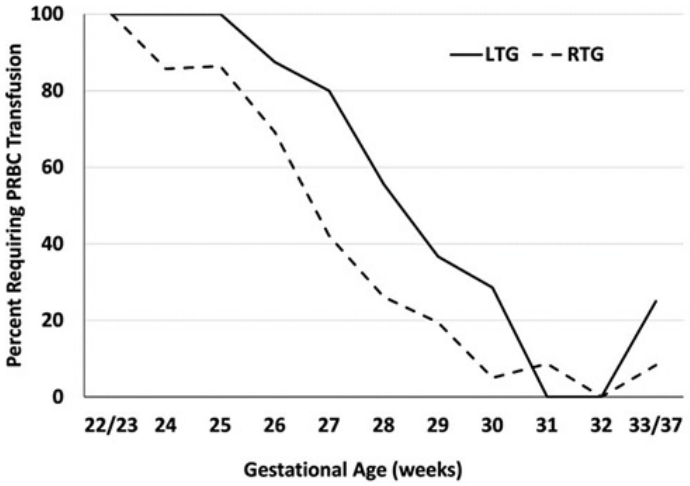

Figure 1: Gestational Age vs. PRBC Transfusions.

Table 3: Hematologic data [1].

	LTG	RTG	P value
Lowest hematocrit (%)	25.8±4.5	25.7±6.1	0.762
Discharge hematocrit (%)	30.3±5.2	31.4±5.4	0.022
PRBC transfusion given	148/226 (65.5%)	93/239 (38.9%)	< 0.001
PRBC transfusions per patient[2]	2 (0-6)	1 (0-2)	< 0.001
Platelet transfusions per patient[2]	0 (0-0)	0 (0-0)	0.680
PRBC transfusions per patient if transfused PRBC[3]	5 (2-8)	3 (1-5)	< 0.001

LTG: Liberal transfusion guidelines; RTG = restrictive transfusion guidelines; PRBC: Packed red blood cells

[1]Quantitative data expressed as either the mean+SD, or as the median (25^{th}% ile – 75^{th} %ile).

[2]All patients in the LTG and RTG groups regardless of transfusion history.

[3]Patients who received at least 1 transfusion.

Table 4: Bayley score outcome data for the LTG and RTG groups, and for different gestational ages.

		LTG	RTG	P value
Cognitive				
Normal		177/226 (78.3%)	183/239 (76.6%)	0.652
Severe delay		19/226 (8.4%)	18/239 (7.5%)	0.727
Language				
Normal		131/226 (58.0%)	147/239 (61.5%)	0.436
Severe delay		34/226 (15.0%)	28/239 (11.7%)	0.291
Motor				
Normal		158/226 (69.9%)	174/239 (72.8%)	0.490
Severe delay		31/226 (13.7%)	26/239 (10.9%)	0.351
	GA 22-25 wk	**GA 26-28 wk**	**GA > 28 wk**	**P value**
Cognitive				
Normal	63/109 (57.8%)	137/177 (77.4%)	159/178 (89.3%)	< 0.001
Severe delay	17/109 (15.6%)	16/177 (9.0%)	4/178 (2.3%)	< 0.001

Language				
Normal	42/109 (38.5%)	112/177 (63.3%)	123/178 (69.1%)	< 0.001
Severe delay	30/109 (27.5%)	21/177 (11.9%)	11/178 (6.2%)	< 0.001
Motor				
Normal	52/109 (47.7%)	128/177 (72.3%)	152/178 (85.4%)	< 0.001
Severe delay	33/109 (30.3%)	15/177 (8.5%)	9/178 (5.1%)	< 0.001

LTG: Liberal transfusion guidelines; RTG = restrictive transfusion guidelines; GA: Gestational age.

Primary Outcome

Our primary outcome, neurodevelopmental outcomes measured by Bayley-III scores, were similar for cognitive, language, and motor testing in the RTG versus LTG groups. The two groups were also similar for normal, mild delay, moderate delay and severely delayed subcategories (Table 4).

Secondary Outcomes

Our secondary outcomes were the Bayley-III scores for infants with specific prematurity morbidities and/or gestational ages. Lower gestational ages were associated with significantly less subjects achieving normal for age results for cognitive, language and motor (Table 4). PVL and ROP (any category) were associated with fewer subjects achieving normal for age results for all categories of the Bayley Scales (Table 5). Sepsis at any time was associated with fewer subjects achieving normal for age results for cognitive, language and motor (Table 6). In the motor category, the number of severely delayed was also significantly higher in the infants with sepsis. NEC was associated with higher rates of severe motor delays (Table 6). IVH of any grade (grades 1, 2, or 3) was associated with lower Bayley-III scores for cognitive and severe delay for motor skills (Table 7). Severe IVH (grade 3) was associated with fewer subjects achieving normal for age results for all categories.

Discussion

As PRBC transfusion is a common occurrence in VLBW infants, it is paramount to determine the optimal threshold for transfusing and whether avoidable transfusions are associated with improved or impaired neurological outcomes which often have lifelong consequences. Our primary outcome, neurodevelopmental outcomes measured by Bayley-III Scales, showed no significant difference in the RTG vs LTG for cognitive, motor or language categories.

The gestational age at which parents are offered resuscitation varies by location and is an ongoing discussion at our center. At 22 weeks estimated gestational age (EGA), our current protocol is to provide prenatal consultation to the family and to recommend comfort care but are willing to provide resuscitation at 22 weeks if the parents request resuscitation. At 23 weeks EGA, the parents are counseled by a neonatologist prior to birth, if time allows, and are given the option of resuscitation or comfort care. As the gestational age decreased, the percentage of normal scores for cognitive, language and motor Bayley-III scores also declined. Our data was divided into age categories of 22 and 23 weeks EGA infants, 24 and 25 weeks EGA, 26 to 28 weeks EGA, and greater than 28 weeks EGA infants. Not surprisingly, a normal Bayley-

Table 5: Bayley score outcome data for subjects with PVL or any level of ROP.

	PVL			ROP		
	No	Yes	P value	No	Yes	P value
Cognitive						
Normal	320/397 (80.6)	6/15 (40.0%)	<0.001	182/214 (85.1%)	161/229 (70.3%)	< 0.001
Severe delay	23/397 (5.8%)	5/15 (33.3%)	<0.001	4/214 (1.9%)	30/229 (13.1%)	< 0.001
Language						
Normal	247/397 (62.2%)	4/15 (26.7%)	0.006	147/214 (68.7%)	117/229 (51.1%)	< 0.001
Severe delay	42/397 (10.6%)	8/15 (53.3%)	<0.001	16/214 (7.5%)	42/229 (18.3%)	0.001
Motor						
Normal	299/397(75.3%)	65/15(33.3%)	<0.001	181/214 (84.6%)	136/229(59.4%)	< 0.001
Severe delay	36/397 (9.1%)	7/15 (46.7%)	<0.001	10/214 (4.7%)	42/229 (18.3%)	< 0.001

PVL: Periventricular leukomalacia; ROP: Retinopathy of prematurity

Table 6: Bayley score outcome data for subjects with sepsis or NEC.

	Sepsis			NEC		
	No	Yes	P value	No	Yes	P value
Cognitive						
Normal	280/345(81.2%)	60/87(69.0%)	0.013	304/383(79.4%)	29/39(74.4%)	0.465
Severe delay	21/345 (6.1%)	11/87(12.6%)	0.037	26/383 (6.8%)	4/39 (10.3%)	0.422
Language						
Normal	218/345 (63.2%)	43/87(49.4%)	0.019	236/383(61.6%)	22/39(56.4%)	0.525
Severe delay	38/345 (11.0%)	17/87(19.5%)	0.033	47/383 (12.3%)	5/39 (12.8%)	0.921
Motor						
Normal	269/345 (78.0%)	45/87(51.7%)	<0.001	285/383(74.4%)	25/39(64.1%)	0.165
Severe delay	30/345 (8.7%)	18/87(20.7%)	0.001	35/383 (9.1%)	11/39(28.2%)	< 0.001

NEC: Necrotizing enterocolitis.

Table 7: Bayley score outcome data for subjects with IVH or severe IVH.

	IVH[1]			Severe IVH[2]		
	No	Yes	P value	No	Yes	P value
Cognitive						
Normal	265/330 (80.3%)	66/96 (68.8%)	0.017	314/392 (80.1%)	17/34 (50.0%)	< 0.001
Severe delay	21/330 (6.4%)	13/96 (38.2%)	0.022	27/392 (6.9%)	7/34 (20.6%)	0.005
Language						
Normal	207/330 (62.7%)	48/96 (50.0%)	0.025	244/392 (62.2%)	11/34 (32.4%)	0.001
Severe delay	37/330 (11.2%)	19/96(19.8%)	0.029	47/392 (12.0%)	9/34 (26.5%)	0.017
Motor						
Normal	250/330 (75.8%)	60/96 (62.5%)	0.010	297/392 (75.8%)	13/34 (38.2%)	< 0.001
Severe delay	26/330 (7.9%)	23/96 (24.0%)	<0.001	32/392 (8.2%)	17/34 (50.0%)	< 0.001

IVH: Intraventricular hemorrhage
[1]IVH Grade 1, Grade 2, or Grade 3
[2]IVH Grade 3

III score more frequently correlated with a higher gestational age. Inversely, the younger the gestational age, the higher percentage of infants had a severely delayed Bayley-III score (Table 4).

Neurologic and ophthalmologic morbidities including IVH, PVL and ROP have lifelong consequences. All these neurologic morbidities were associated with lower Bayley-III scores in our study. Although not commonly found in our patients, PVL was found to have a significant impact on Bayley-III scores. The presence of PVL correlated with significantly lower scores for cognitive, language and motor testing. The fifteen infants with PVL who had neurodevelopmental follow-up were all in the LTG group. Our previous study had found a significantly lower rate of PVL and ROP in the RTG compared to the LTG[3]. Retinopathy of prematurity had a significant negative affect on the Bayley-III scores. The effect was present when looking at any ROP vs no ROP. The lowering of the Bayley-III score was most pronounced in the severe ROP (stage 3 or 4) ROP rather than the less severe ROP (stage 1 or 2). Sixty five percent of the infants with stage 3 ROP had normal cognitive scores. Only 33 percent of infants with stage 4 ROP vs 73 percent of the infants with stage 1 ROP had a normal cognitive score. No infant with stage 4 ROP had a normal language comprehension score.

Similar to ROP, the more severe IVH was associated with a more severe decrease in Bayley-III scores. Infants with any IVH had lower normal Bayley-III scores for cognitive and motor scores compared to infants without an IVH. A significant difference was present in the infants with a grade 1 IVH vs grade 3 IVH. (Table 7) While we did not record which day of life PRBC transfusions were given in our study, it is highly likely that infants received PRBC transfusions well after the third day of life, which is when the majority of IVH occurs. Interestingly, the PVL rates in our previous study were much lower in the RTG group.[3] In contrast to IVH and hemorrhagic venous infarct (HVI), PVL is thought to be a consequence of ischemia or inflammation. PVL is not present at birth and is often not detectable early in an infant's hospital course. Infants exposed to repetitive PRBC transfusions are exposed to repetitive episodes of inflammation[7], and we theorize that these repeated inflammatory episodes are a factor causing an increase in PVL and ultimately a risk factor in lower Bayley-III scores.

Sepsis as defined by seven days of antibiotic treatment with or without a positive bacterial culture result was associated with lower Bayley-III scores compared to those without the diagnosis of sepsis. We theorize that the prolonged inflammatory episode present with sepsis is a factor in causing damage to the brain matter which, in turn, increases the risk of developmental delays, which is identified through the formal Bayley Scales testing.

Necrotizing enterocolitis (NEC) continues to be a leading cause of death in extremely premature infants, with extreme prematurity defined as birth between 22 0/7 weeks to 28 6/7 weeks gestation. In 2000-2011, death rates in extremely premature infants due to infectious and pulmonary causes decreased, whereas death rates due to NEC increased.[8] We anticipated NEC causing a significant lowering of Bayley-III scores, however, the normal score category for cognitive, language and motor were not significantly different. An increased percentage of infants with severely delayed and moderately delayed motor category scores were noted in those who had NEC compared to those who did not. For the purposes of our study, NEC was defined by a clinical diagnosis of NEC by a neonatologist and treated for a minimum of 7 days of bowel rest and antibiotics.

There are two recent multicenter randomized studies that were both published in 2020; Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth Weight Infants [ETTNO] [4] and the Transfusion of Prematures [TOP] Trial [5]. Both studies randomized infants under 1000 grams to a low or high transfusion criteria and neurodevelopmental follow up between 18 to 26 months of age. There are several differences between the ETTNO and TOP study and our study. For our study we reviewed all babies under 1500 grams, regardless of gestational age. In contrast, both the TOP and ETTNO studies weight limit was 1000 grams and a maximum gestational age limit of 28+6 weeks [4,5]. We used transfusion criteria based on respiratory support only, not a tiered guideline dependent on chronological age. Our restrictive transfusion criteria used a lower hemoglobin during for 4 out of 5 of their categories. Our criteria were approximately 4 grams/

dL lower during the first week of life, 3 grams/dL lower for the second week of life and approximately 1.5 grams/dL lower for the third and greater week of life. Only in the category of mechanical ventilation was our criteria similar (our criteria were 1 gram/dL lower during the first week, the same level during the second week, and 1 gram/dL higher during the third and greater week). The difference in transfusion criteria may partially account for the difference in the number of transfusions given and discharge hematocrit/hemoglobin levels. For the TOP's higher transfusion group, infants received 6.2 transfusions [5] where our liberal transfusion group received 2 (Table 3). Our discharge hematocrit levels were higher in the restrictive transfusion group compared to the liberal transfusion group. Whereas, in the TOP study the lower transfusion group had a lower discharge hemoglobin compared to the higher transfusion group. The difference in average gestational ages between the studies is likely a major contributor to higher impairment rates in the TOP and ETTNO studies compared to our study. ETTNO and TOP studies had higher percent of infants with <70 score for composite cognitive, composite language, and composite motor compared to our study [5] (Table 4).

We acknowledge that both our current study has several limitations. The primary concern is the retrospective nature of our original study. It is possible that during the time frame of our study, other changes in hospital protocols could have accounted for some of the effects seen. For example, our unit opened a small baby unit (SBU) during the study. The SBU opened nine months prior to the end of the RTG portion of the study. In our original study, we statistically evaluated the SBU data separate from the other 15 months of RTG data and found no significant differences; therefore, the RTG data was included as a single 24-month time period [3]. Another change that occurred during the study was that our neonatology staff had two new hires for the second 12 months of the RTG study timeframe. A randomized study would better address changing transfusion criteria without timing differences between the groups. Another possible limitation is with reviewing documentation. We relied on the attending neonatologist diagnoses of NEC as well as pneumonia and sepsis (culture negative) without standardized diagnoses criteria. Again, randomized studies with clear diagnosis criteria would better address these secondary outcomes. Bayley-III scoring may have been the gold standard for assessment at the time but is not without its limitations and shortcomings [6]. Scores may also be affected by factors outside our control including the disposition of the child being tested on a particular day. Parents are strongly encouraged, but not required, to complete neurodevelopmental clinic follow-up. The Bayley Scales testing was performed by several different licensed providers. Of our study subjects, approximately 61 percent had neurodevelopmental clinic follow up, leaving some margin of disparity due to not having 100 percent follow up. A final concern is that our results are from a single institution.

RTG is safe in the neonatal VLBW population. RTG when compared to LTG is associated with similar neurodevelopmental outcomes as defined by Bayley Scores at 20.3 +/- 5.2 months. The two major recent studies (ETTNO and TOP) have similar results to our study and agree with the safety of using restrictive transfusion guidelines. Studies looking at transfusion guidelines with and without both respiratory support criteria and age criteria are needed.

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