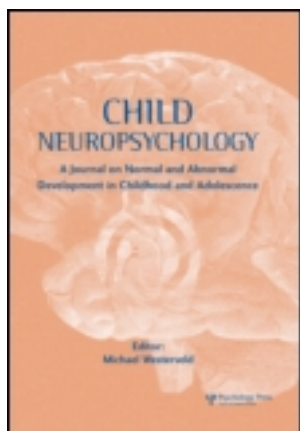


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Neurocognitive profiles of preterm infants randomly assigned to lower or higher hematocrit thresholds for transfusion

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CE Neurocognitive profiles of preterm infants randomly assigned to lower or higher hematocrit thresholds for transfusion

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Objective: Preterm infants are frequently transfused with red blood cells based on standardized guidelines or clinical concerns that anemia taxes infants' physiological compensatory mechanisms and thereby threatens their health and well-being. The impact of various transfusion guidelines on long-term neurocognitive outcome is not known. The purpose of this study is to evaluate long-term neurocognitive outcome on children born prematurely and treated at birth with different transfusion guidelines.

Methods: Neurocognitive outcomes were examined at school age for 56 preterm infants randomly assigned to a liberal ($n=33$) or restrictive ($n=23$) transfusion strategy. Tests of intelligence, achievement, language, visual-spatial/motor, and memory skills were administered. Between-group differences were assessed.

Results: Those in the liberal transfusion group performed more poorly than those in the restrictive group on measures of associative verbal fluency, visual memory, and reading.

Conclusions: Findings highlight possible long-term neurodevelopmental consequences of maintaining higher hematocrit levels.

Keywords: Preterm; Neuropsychology; Red blood cell transfusion; Hematocrit; Longitudinal.

The high incidence of anemia in preterm, very low birth weight (VLBW; <1500 grams) infants mandates frequent red blood cell (RBC) transfusions during the first few weeks after birth. Though all infants experience decreased hemoglobin (i.e., physiologic

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anemia) during the first months after birth, anemia of prematurity is common in infants weighing less than 1 kg (< 32 weeks gestation), and is essentially low endogenous erythropoietin (EPO; a hormone that stimulates RBC production in response to low-oxygen saturation) production and exaggeration of physiologic anemia in which hemoglobin levels fall 7–10 g/dl more than in term infants and remain lower for longer periods of time (Bain & Blackburn, 2004). Concern regarding the preterm infant's capacity to tolerate anemia as well as the potential consequences (e.g., increased risk of death), have resulted in routine RBC transfusions among preterm infants (Hébert, Tinmouth, & Corwin, 2007; Straus, 1995). Views on the risks of anemia and the effectiveness of RBC transfusion in addressing these risks, however, are varied, while the clinical signs of anemia are nonspecific and require significant physician interpretation (Maier et al., 2000; Strauss, 1995). Information has begun to emerge about the impact of transfusion strategy on the outcome of anemic preterm infants, but the outcomes analyzed to date have been limited to the neonatal period and later infancy (i.e., up to 18 to 21 months of corrected age) (Whyte et al., 2009). Evaluating long-term neurodevelopmental outcomes associated with different transfusion thresholds is critical for assessing the safety of current transfusion practice especially in terms of potential cognitive and behavioral morbidity.

The Impact of Preterm Birth on Neurocognitive Outcomes

The survival rate of preterm infants has improved in recent decades as a result of advances in neonatal intensive care. Although rates of mortality and severe morbidity have decreased, children and adolescents who were born prematurely are nevertheless at risk for problems in psychosocial, behavioral, and cognitive functioning (Hoff, Hansen, Munck, & Mortensen, 2004; Litt, Taylor, Klein, & Hack, 2005; Miceli et al., 2000; Nadeau, Tessier, Boivin, Lefebvre, & Robaey, 2003; Taylor, Hack, & Klein, 1998, 2000). It has been estimated that preterm children, as a group, perform an average of 10 points lower than full-term children on standardized intellectual assessments (Goyen, Lui, & Woods, 1998). Preterm birth is also associated with increased risk for high-prevalence, low-severity deficits in many functions, including memory, language/vocabulary, concept formation, executive functioning, perceptual, visuomotor, and gross motor (e.g., balance, gait, and coordination) abilities (Aylward, 1997, 2002, 2005; Breslau, 1995; Hack et al., 1994; Taylor et al., 1998). These deficits are considered "high prevalence" because of the elevated rates at which they have been found to occur in children born preterm as compared to the general population. In addition, studies suggest that these deficits result in learning, attention, and behavior problems in approximately 50%–70% of children born with very low birth weight (VLBW; Aylward, 1997, 2002; Taylor et al., 1998). These deficits have been termed "low severity" because they are not necessarily associated with global deficits in intellectual or psychomotor functioning (e.g., intellectual disability, cerebral palsy) and often go unrecognized in early development.

Preterm birth is associated with increased risk of problems in executive functioning (or the processes of planning, initiating, and sustaining goal-directed behavior and self-directing behavior and emotion), including attention, working memory, and inhibitory control in school-age children and adolescents (Anderson, Doyle, & the Victorian Infant Collaborative Study Group, 2004; Aylward, 2005; Bhutta, Cleeves, Casey, Craddock, & Anand, 2002; Harvey, O'Callaghan, & Mohay, 1999; Luciana, Lindeke, Mills, & Nelson, 1999; Stephens & Vohr, 2009; Taylor et al., 1998). A global dysexecutive pattern has been

found among preterm groups with average intellectual abilities (Waber & McCormick, 1995), while others have found that differences between preterm and full-term groups remain after controlling for general cognitive abilities (IQ) (Taylor, Minich, Klein, & Hack, 2004) and after excluding children with neurosensory impairment (Anderson et al., 2004).

Overall, research on achievement outcomes of premature and low birth weight (LBW) infants at school age indicates poor general academic functioning in addition to more specific areas of weakness in reading, arithmetic, and spelling (Hack et al., 1994; Hagen, Palta, Albanese, & Sadek-Badawi, 2006; Litt et al., 2005; O'Callaghan, Burns, Gray, & Harvey, 1996). Some research suggests that deficits in the academic skills of decoding, problem solving, and calculation not only persist but also become more pronounced over the course of preterm children's development (Espy, Fang, Charak, Minich, & Taylor, 2009). Within preterm groups, males perform more poorly in school than females (Saigal, Hoult, Streiner, Stroskopf, & Rosenbaum, 2000) and are more likely than females to be identified as learning disabled (Whitfield, Eckstein Grunau, & Holsti, 1997). Evidence suggests that specific neurocognitive weaknesses can interfere with learning, academic performance, and social-emotional/behavioral functioning of former preterm children and adolescents. For example, Mulder, Pitchford, and Marlow (2010) recently found deficits in processing speed and working memory predicted overall academic achievement in very preterm (i.e., < 31 weeks) children at 9–10 years of age. The level of LBW has been associated with math, but not reading, performance (i.e., < 1500 g infants perform more poorly than heavier LBW infants in math) in a longitudinal study of a stratified sample of LBW and non-low birth weight (NBW; Breslau, Johnson, & Lucia, 2001) infants from diverse family and environmental backgrounds (i.e., inner city/low income and suburban/middle class). Breslau et al. further demonstrated that while approximately 80% of the difference in reading and math between LBW and NBW groups at age 11 was accounted for by intellectual ability at age six, a subset of VLBW infants had significantly poorer math achievement independent of IQ. In the Breslau et al. study, phonological awareness and visual-motor integration measures predicted reading performances at 11 independent of IQ. Furthermore, social-environmental factors were more highly predictive of achievement than LBW, with low maternal education and single-mother status predicted reading performance at age 11. An interaction between academic area assessed and inner city versus the suburbs was observed, whereby inner city placement continued to adversely affect math performance above and beyond the initial effects on cognitive ability affecting performance at school entry.

Red Blood Cell Transfusion

It is estimated that 80% (out of approximately 38,000) of preterm infants with birth weights less than 1500 grams who are born annually receive multiple red blood cell (RBC) transfusions during the first few weeks of life due to phlebotomy blood losses secondary to severe respiratory disease and to physiologic factors resulting in decreased circulating RBC mass (Levy et al., 1993; Strauss, 1991, 1995). Traditionally, transfusions have been small to modest in volume (5 to 15 mL of RBC per kg bodyweight per dose). Transfusions are often repeated, with mean donors per neonate estimated between 8 to 10 (Strauss, 1991; Strauss et al., 1990).

Decisions about when and how much to transfuse preterm neonates are made based upon a clinical approach in which the hematocrit level is maintained according to what is thought to be most advantageous for each infant's clinical status (Strauss, 1995). Though

definitions of liberal and restrictive transfusion strategies vary by study, they generally refer to RBC transfusion criteria in which hemoglobin concentration or hematocrit are maintained at higher (for liberal) and lower (for restrictive) levels in order to better understand the way in which different transfusion practices may affect the developing brain. In restrictive approaches, the timing of RBC transfusions is intentionally delayed (i.e., the hemoglobin or hematocrit threshold at which transfusions were performed was allowed to fall to lower levels) in order to reduce transfusion numbers, donor exposures, and total blood volume transfused (Beeram, Krauss, & Riggs, 2001; Brooks et al., 1999; Franz & Pohlandt, 2001; Maier et al., 2000; Widness et al., 1996). Little is known about what, if any, role medical interventions such as antenatal corticosteroid treatment, surfactant replacement therapy, and RBC transfusion play in reducing the risk of neurocognitive, academic, and behavioral problems in preterm infants. However, it is clear that such practices have significantly decreased rates of mortality in the postnatal period. Faster weight gain, less severe apnea, and increased oxygenation of the blood as a result of transfusion (Hudson et al., 1990; Murray & Roberts, 2004; Ross et al., 1989) are thought to play important roles in the immediate survival of small, critically ill neonates. Transfusion is also thought to protect against brain damage that may occur as a result of oxygen deprivation or brain hemorrhage that results from the body's natural attempts to increase blood supply to the brain (Bell et al., 2005).

Comparing Liberal and Restrictive Transfusion Strategies

As with any medical procedure, the benefits and protective factors associated with RBC transfusion must be carefully weighed in light of potential risks. In addition to being costly (Murray & Roberts, 2004), transfusions are associated with a number of well-documented risks associated with blood incompatibility, immunosuppression, or immune activation (Bordin, Hedde, & Blajchman, 1994; Jeschke et al., 2007; Marik, 2009; van de Watering et al., 1998), and transfusion reactions or infections such as viral hepatitis and cytomegalovirus (Szekely et al., 2009). Studies have also shown that the risks of transfusion complications may be more pronounced for the most critically ill infants and as the amount of blood transfused increases (Jeschke et al., 2007).

No consensus exists regarding the optimal point at which to transfuse preterm infants. Recent investigations have begun to address whether restrictive approaches to transfusion would result in poorer outcomes compared to more liberal approaches. The primary concern with performing transfusions in a more restrictive manner is greater risk for brain injury, as higher hemoglobin levels assure higher cerebral oxygen delivery and, in addition, are thought to help prevent apnea episodes that may both result from and contribute to hypoxia-ischemia in critically ill preterm infants (Bell, 2006).

A number of studies have compared liberal transfusion strategies with more restrictive approaches (Beeram et al., 2001; Brooks et al., 1999; Franz & Pohlandt, 2001; Maier et al., 2000; Widness et al., 1996). These studies have failed to document increased risks of morbidity and mortality in restrictive transfusion groups compared to liberal strategies. In comparison to liberal transfusion groups, restrictive groups did not show increased risk for primary outcomes (e.g., death or presence of a major developmental defect such as cerebral palsy; cognitive delay; severe visual or hearing impairment; retinopathy of prematurity [ROP]; intraventricular hemorrhage [IVH]; necrotizing enterocolitis; chronic lung disease; or sepsis) or secondary outcomes (e.g., poorer weight gain, increased length of hospital stay, or increased need for respiratory support and oxygen therapy) (Beeram et al., 2001;

Brooks et al., 1999; Franz & Pohlandt, 2001; Kirpalani et al., 2006; Lacroix et al., 2007; Maier et al., 2000; Whyte et al., 2009; Widness et al., 1996). Moreover, there has even been some indication that restrictive strategies may be superior. For example, Venancio et al. (2006) found that stricter guidelines reduced the need for RBC transfusions in VLBW preterm infants and reduced the volume of blood transfused without adversely affecting clinical outcomes. These authors also found that infants in the liberal group were more likely to have retinopathy and hypothesized that increased transfusions may increase the risk of diseases related to the release of free radicals (Venancio et al., 2006).

Limitations to Existing Research

Despite emerging evidence suggesting that restrictive strategies may be equivalent or superior to liberal strategies, transfusion practices are inconsistent (Hume, 1997; Levy et al., 1993; Murray & Roberts, 2004). In addition, there is limited understanding of the effects of different RBC transfusion strategies on neurocognitive functioning. Even less is known with regard to the potential benefits and risks of transfusions at the upper and lower hemoglobin limits (Bell, 2008). The Iowa trial set a higher hemoglobin threshold than previous studies in order to better compare the effects of significant differences in mean hemoglobin levels (Bell, 2008; Bell et al., 2005). In the Iowa trial, 100 preterm infants were stratified by birth weight (500–750 g, 751–1000 g, 1001–1300 g) and randomly assigned to either restrictive or liberal transfusion groups. Infants received 15 mg/kg RBC when hematocrit fell below prescribed thresholds. For mechanically ventilated infants, the thresholds were hematocrit 46% for the liberal group and 34% for the restrictive group.

Liberal infants received more RBC transfusions ($M = 4.2$; $SD = 4.5$) than restrictive infants ($M = 3.3$; $SD = 2.9$). The number of donors per infant ($Mdn = 2$ for both groups) was not statistically significant between groups. The median age at first transfusion was 8 days in the restrictive group and 3 days in the liberal group; though this difference was not statistically significant. No differences in survival or risk of patent ductus arteriosus (PDA), ROP, or bronchopulmonary dysplasia were found between transfusion groups. Liberal and restrictive groups did not differ in length of hospitalization, time on assisted ventilation, time on supplemental oxygen, time to regain birth weight, or time to double birth weight. Initial results of the Iowa trial (Bell et al., 2005) also indicated a higher incidence of adverse neurological events such as intraparenchymal brain hemorrhage, periventricular leukomalacia or both, and more frequent episodes of apnea in the restrictive group (Bell et al., 2005). Given these findings and the worse neurocognitive outcomes at 18–21 months of the restrictive group in the Premature Infants in Need of Transfusion (PINT) trial (Whyte et al., 2009), further examination of the neurocognitive outcomes of these preterm infants in late childhood and adolescence is warranted.

Aims of the Current Study

The current study was designed to fill an important void in the literature by evaluating the long-term neurocognitive outcomes of differing transfusion practices in anemic preterm infants. The infants from the Iowa trial were evaluated at school age (8–15 years old) to compare the neurocognitive impact of liberal and restrictive transfusion strategies.

METHODS

Participants

This study was approved by the university's institutional review board. Participants were recruited from the 100 infants who participated in the Iowa transfusion trial (Bell et al., 2005). For the original study, eligible participants had birth weights between 500 and 1300 g and received neonatal care at the University of Iowa Children's Hospital between December 1992 and June 1997. Infants were excluded if they had alloimmune hemolytic disease, congenital heart disease, other major birth defects requiring surgery, or a chromosomal abnormality; if their parents had strong philosophical or religious objections to transfusion; if they were thought to face imminent death; if they had received more than two transfusions prior to enrollment in the study; or if they were already enrolled in a clinical study that might interfere with the conduct or outcome of this study.

The follow-up study began in 2005—13 years after the initial study began. The parents were contacted by research nurses and asked if they would be interested in having their child participate in a study on the effects of RBC transfusion on brain structure and function in children born prematurely, as a follow-up to the original transfusion study. (Given the large nature of this study, the neuroimaging data have not been analyzed and will be analyzed separately.) Parents who expressed interest were asked screening questions. None of the children who could be located met any of the exclusion criteria: significant hearing loss or history of epilepsy, brain tumor, or head injury resulting in unconsciousness or concussion. A total of 44 preterm subjects from the original 100 did not participate in the follow-up study: 3 were deceased, 12 declined to participate, and 29 were unable to be contacted. A death index search was conducted on those children who were lost to follow-up. These children did not match any death records through 2007. A complete flow chart of participants and nonparticipants by transfusion group and gender is presented in Table 1. Because the original study found differences with rates of Periventricular Leukomalacia (PVL) between groups, two chi-square analyses were run to determine if incidence of IVH and PVL were different between those tested; both were nonsignificant for differences between participating Restrictive and Liberal children, IVH: $\chi^2(100) = 0.097$, $p = .333$ and PVL: $\chi^2(100) = -0.025$, $p = .805$.

The Score for Neonatal Acute Physiology (SNAP; Richardson, Gray, McCormick, Workman, & Goldmann, 1993) was recorded on the day of birth and once daily through the

Table 1 Flow Chart of Participants and Nonparticipants by Transfusion Group and Gender with Frequency of IVH and PLV and Death.

Participant	Total ($N = 100$)							
	Liberal ($n = 51$)				Restrictive ($n = 49$)			
	Male ($n = 21$)		Female ($n = 30$)		Male ($n = 30$)		Female ($n = 19$)	
	Yes = 12	No = 9	Yes = 21	No = 9	Yes = 19	No = 11	Yes = 4	No = 15
IVH = 1–4	50%	44%	29%	11%	32%	36%	25%	13%
IVH = 4	–	–	–	–	5%	9%	–	7%
PVL	–	–	–	–	5%	9%	25%	7%
Deceased	–	–	–	11%	–	–	–	13%

Note. Intraventricular Hemorrhage (IVH); Periventricular Leukomalacia (PVL).

Table 2 Means, Standard Deviations, and the Results of MANOVA Analyses on Neonatal and Demographic Characteristics of Participants and Nonparticipants.

	Participant		Nonparticipant		<i>F</i>	<i>df</i>	<i>p</i> value	Effect Size
	<i>(n</i> = 56)		<i>(n</i> = 44)					
	Mean	<i>SD</i>	Mean	<i>SD</i>				
BW	944.57	198.12	970.55	185.79	0.447	98	.505	.005
GA	27.79	2.03	27.73	1.83	0.025	98	.876	<.001
IVH Grade	0.71	1.14	0.61	1.20	0.183	98	.670	.002
HCT Mean	41.26	5.22	38.94	4.55	5.439	98	.022	.053
Vent	22.32	23.70	23.45	28.61	0.047	98	.829	<.001
Apnea	30.18	31.64	26.25	27.37	0.427	98	.515	.004
SNAP1	14.33	8.32	13.89	7.42	0.076	97	.784	.001
SNAP2	10.20	6.61	10.23	6.70	<.001	97	.984	<.001

Note. Birth weight (BW), Gestational Age (GA), Intraventricular Hemorrhage (IVH), Vent (Days on Ventilator), Apnea (Number of Apnea episodes requiring stimulation), Score for Neonatal Acute Physiology Day of Life 0 (SNAP1), Score for Neonatal Acute Physiology Week 1 Average (SNAP2). Effect sizes are generated Partial Eta Squared values.

first week of life. Multivariate analyses of variance (ANOVAs) were conducted to examine differences in neonatal characteristics of participants ($n = 56$) and nonparticipants ($n = 44$). After correction for multiple comparisons, results indicate no significant difference in birth weight, gestational age, grade of IVH, days on ventilator, number of apnea episodes requiring stimulation, or SNAP on the day of birth or averaged over the first week of life (Table 2; SNAP data were not available for one infant). Although the multivariate analysis demonstrated no overall effect between groups, $F(6, 93) = 1.358$, $p = .240$, mean Hematocrit level (HCT) during hospitalization did reach a significant group difference, $F(1, 98) = 5.139$, $p = .022$, where nonparticipants had a lower mean HCT.

Procedure

Guardians of participants were reimbursed for travel, lodging, and meal expenses, and child participants were compensated monetarily. Guardians were asked to accompany their children to the hospital, and informed consent was obtained in writing from one or both guardians prior to their child's participation. Guardians completed a demographic questionnaire designed for this study that included questions regarding academic performance and socioeconomic status (SES). Children completed a battery of cognitive, neurologic, behavioral, and social-emotional tests (administration lasted approximately 160–180 minutes). All assessments were conducted by licensed psychologists and psychology graduate assistants who were blind to the transfusion group of the children.

Measures

Cognitive Functioning. Cognitive functioning was assessed using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003a, 2003b). The General Ability Index (GAI) is a composite of verbal and perceptual domains that was used as an estimate of global cognitive ability. In addition, prorated index scores were obtained

for the Verbal Comprehension Index (VCI) using Similarities and Vocabulary subtests; Perceptual Reasoning Index (PRI) using Block Design and Matrix Reasoning subtests; and Processing Speed Index (PSI) using Digit Symbol-Coding and Symbol Search subtests. Internal reliability ($r = .79$ to $.90$) and test-retest reliability ($r = .76$ to $.92$) for these subtests are excellent, as are internal reliability estimates for the GAI ($r = .96$) (Raiford, Weiss, Rolfhus, & Coalson, 2005). Standard scores for GAI, VCI, PRI, and PSI were used in the analyses. The time necessary to complete these subtests is approximately 90 minutes.

Memory. Memory was assessed using the Color Span Test (Richman & Lindgren, 1978), which has established norms for ages 6 to 13 and differentiates various learning disability subtypes (Lindgren & Richman, 1984; Lindgren, Richman, & Eliason, 1986). This test assesses short-term sequential memory for information presented visually (trials 1 and 2) and verbally (trials 3 and 4). Trials 1 and 4 were used in the current study in order to detect differences in memory for visual and verbal material. In the first trial (visual-visual), information is presented visually and the participant is required to respond in a visual-motor (i.e., pointing) manner. In the fourth trial (verbal-verbal), information is presented verbally and the participant is required to respond in a verbal manner. The examiner must ensure that the child recognizes each color prior to administration. There are seven spans (increasing from two to eight colors) for each subtest. Each correct response is given 1 point, and the maximum score is 14 for each subtest. Raw scores were converted to z scores for each of the four trials. Scores for the first trial provide a measure of memory for visually presented colors and the fourth trial provides a measure of verbally presented color names. The time necessary to complete this test is approximately 20 minutes.

Associative Verbal Fluency. Associative verbal fluency was assessed using a test of Controlled Oral Word Association (COWA) (using the letters "CFL") from the Multilingual Aphasia Examination (Benton & Hamsher, 1983). Participants were asked to list as many words as possible in 1 minute for each of three common letters. The score is the total number of words provided for all three letters. Raw scores were converted to z scores, which were used in the analyses. The time necessary to complete this test is approximately 5 minutes.

Rapid Automatized Naming. Rapid naming was assessed using the Color Naming subtest of the Rapid Automatized Naming (RAN) test (Denkla & Rudel, 1976). This test requires rapid serial naming of colors that appear multiple times throughout the page. The score is the total time needed to name all colors. Raw scores were converted to z scores, which were used in the analyses. The time necessary to complete this subtest is less than 5 minutes.

Fine Motor Coordination. Fine motor coordination was assessed by the Grooved Pegboard Test (GPB). This test was developed by Kløve (1963) and is designed to assess fine-motor coordination. It requires participants to quickly place pegs into small holes using their dominant and nondominant hands. The score used in the analyses is the total completion time for the dominant hand; these times were converted to z scores for the analyses. The time necessary to complete this test is approximately 5 minutes.

Visual-Motor Integration. Visual-motor integration was assessed using the Bender Visual-Motor Gestalt Test, Second Edition (Bender-II; Grannigan & Decker, 2003). For this test, participants were asked to copy increasingly complex geometric designs from cards. Scores for each design are based on the degree of accuracy with which the figure was drawn. Raw scores were converted to z scores for the purpose of analyses. Administration time is typically under 15 minutes.

Visual-Spatial Reasoning. The Benton Judgment of Line Orientation Test (JOL; Benton, Sivan, Hamsher, Varney, & Spreen, 1994) assesses visual-spatial reasoning. Participants were asked to judge the relative orientation of lines on cards. The score is the total number correct out of 30 items. Raw scores were converted to z scores, which were used in the analyses. The test takes approximately 15 minutes to complete.

Reading Ability. The Reading subtest of the Wide Range Achievement Test, Third Edition (WRAT-3; Wilkinson, 1993) was administered to assess decoding or word recognition abilities. The raw score—or total number of correctly identified words—was converted to a standard score for each participant in order to perform the statistical analyses. The time necessary to complete this test is approximately 10 minutes.

Statistical Analysis

All analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois). Standard scores and z scores were computed for participants using population norms. For participants outside the age ranges of the available norms, z -scores were computed based upon the highest age norms available (i.e., for RAN, COWA, Color Span, JOL, and GPB). To evaluate the differences between restrictive and liberal transfusion groups, we conducted five sets of comparisons using independent samples t -tests. Analyses were performed with transfusion group as the independent variable and with no covariates. Each set comprised several comparisons, and the alpha levels were adjusted with the Bonferroni correction. The following comparisons were performed:

1. Neonatal and demographic characteristics (six variables), values below $p = .008$ are significant;
2. Cognitive ability and achievement (i.e., GAI, VCI, PRI, PSI, WRAT Reading), values below $p = .01$ are significant;
3. Language functioning (i.e., COWA, RAN), values below $p = .025$ are significant;
4. Visual-spatial/motor functioning (JOL, GPB, Bender-2), values below $p = .017$ are significant; and
5. Memory (Visual and Verbal Memory - Color Span), values below $p = .025$ are significant.

RESULTS

Demographic Characteristics

Follow-up assessments occurred when the children were between 8 and 15 years of age. Of the 100 infants enrolled in the Iowa trial, 56 participated in the follow-up assessment. Twenty-three subjects (19 males, 4 females) were from the restrictive group

Table 3 Means, Standard Deviations, and the Results of Independent Samples *t*-test Analysis on Neonatal and Demographic Characteristics of Participating Liberal and Restrictive Group.

	Liberal		Restrictive		<i>t</i>	<i>df</i>	<i>p</i> value	Effect Size
	<i>(n</i> = 33)		<i>(n</i> = 23)					
	Mean	<i>SD</i>	Mean	<i>SD</i>				
BW	936.52	210.13	956.13	183.5	0.362	54	.719	.049
GA	27.88	2.28	27.67	1.65	-0.371	54	.712	.050
IVH Grade	0.82	1.18	0.57	1.08	-0.815	54	.419	.110
HCT Mean	44.47	4.10	36.65	2.41	-8.203	54	<.001	.745
Vent	24.33	26.96	19.43	18.24	-0.758	54	.452	.103
Apnea	24.00	24.16	39.04	38.92	1.785	54	.080	.236
SNAP1	15.06	7.57	13.30	9.33	-0.771	53	.444	.105
SNAP2	10.34	6.69	10.00	6.64	-0.188	53	.851	.026
Age	11.94	1.70	12.53	1.55	1.323	54	.191	.177
SES	2.76	0.64	2.74	0.58	-0.110	54	.913	.015
Mom Ed	13.94	2.50	13.71	2.95	-0.301	52	.765	.042
Dad Ed	12.79	3.06	13.55	2.78	0.886	46	.380	.130

Note. Birth weight (BW), Gestational Age (GA), Intraventricular Hemorrhage (IVH), Vent (Days on Ventilator), Apnea (Number of Apnea episodes requiring stimulation), Score for Neonatal Acute Physiology Day of Life 0 (SNAP1), Score for Neonatal Acute Physiology Week 1 Average (SNAP2), Socioeconomic Status (SES). Mother and Father Education are reported in years or school. Effect sizes (*r*) were calculated by $r = \sqrt{t^2/(t^2+df)}$.

(median age = 12.42 years, $M = 12.53$, $SD = 1.55$). There were 33 subjects (12 males, 21 females) in the liberal group (median age = 12.42, $M = 11.94$, $SD = 1.70$). There were too few females in the restrictive group to allow gender comparisons.

Independent samples *t*-tests were conducted to compare liberal and restrictive groups with respect to neonatal and demographic characteristics (Table 3). Liberal and restrictive groups did not differ in birth weight, gestational age, grade of IVH, days on ventilator, number of apnea episodes requiring stimulation, SNAP on the day of birth, SNAP averaged over the first week of life, age at follow-up, or parental ratings of SES (based on Hollingshead scale; Hollingshead & Redlich, 1958). As expected, the mean HCT for those in the Restrictive group ($M = 36.65$, $SD = 2.41$) was significantly lower than the mean for those in the Liberal group ($M = 44.47$, $SD = 1.10$), $t(54) = -8.203$, $p < .001$. Both participating transfusion groups were predominantly Caucasian (90% in the Restrictive group and 81% in the Liberal). The Restrictive group was comprised of 1 Hispanic and 1 multiracial participant while the Liberal group was comprised of 4 African American and 2 multiracial participants.

Intelligence and Achievement

Differences between liberal and restrictive groups in cognitive and achievement measures were analyzed with independent samples *t*-tests (Table 4). Liberal group children obtained lower scores than restrictive children on all intelligence and achievement outcome variables. This reached statistical significance for reading, $t(54) = 3.300$, $p = .002$, with a large effect size of $r = .41$. No significant differences between transfusion groups were found on measures of GAI, VCI, PRI, or PSI.

Table 4 Means, Standard Deviations, and the Results of Independent Samples *t*-test Analysis on Cognitive and Achievement Scores for Liberal and Restrictive Groups.

	Liberal		Restrictive		<i>t</i>	<i>df</i>	<i>p</i> value	Effect Size
	<i>(n = 33)</i>		<i>(n = 23)</i>					
	Mean	<i>SD</i>	Mean	<i>SD</i>				
GAI	93.21	20.7	103.61	15.7	2.036	54	.047	.267
VCI	93.85	26.0	104.78	15.7	1.798	54	.078	.238
PRI	91.67	18.1	99.70	15.5	1.729	54	.089	.229
PSI	88.82	14.4	95.5	14.8	1.694	54	.096	.225
WRAT-III	93.94	15.0	105.83	10.2	3.300	54	.002	.410

Note. General Ability Index (GAI), Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Processing Speed Index (PSI), Wide Range Achievement Test, Third Edition (WRAT-III). Effect sizes (*r*) were calculated by $r = \sqrt{t^2/(t^2+df)}$.

Neuropsychological Functioning

In the same pattern seen for intelligence and achievement assessments, liberal group children scored lower than restrictive children on all neuropsychological tests. This reached statistical significance for associative verbal fluency, $t(54) = 3.072$, $p = .003$, and visual memory, $t(54) = 2.516$, $p = .015$ (Table 5), with effect sizes ranging from medium for visual memory ($r = .32$) to large for verbal fluency ($r = .39$). No significant differences between liberal and restrictive groups were found for verbal memory, rapid naming, visual-spatial reasoning, fine motor dexterity, or visual-motor integration.

DISCUSSION

The primary purpose of the current study was to examine the long-term neurocognitive impact of different transfusion strategies for preterm infants. We examined

Table 5 Means, Standard Deviations, and the Results of Independent Samples *t*-Test Analysis on Language, Visual-Spatial/Motor, and Memory Scores for Liberal and Restrictive Groups.

	Liberal		Restrictive		<i>t</i>	<i>df</i>	<i>p</i> value	Effect Size
	<i>(n = 33)</i>		<i>(n = 23)</i>					
	Mean	<i>SD</i>	Mean	<i>SD</i>				
COWA	-1.30	1.24	-0.31	1.10	3.072	54	.003	.386
RAN	0.08	1.70	0.59	1.02	1.400	53	.167	.189
JOL	-1.06	1.54	-0.81	1.23	0.540	35	.593	.091
GPB	-0.75	2.00	-0.24	0.97	1.130	54	.264	.152
Bender-II	0.12	1.19	0.75	0.90	2.138	54	.037	.279
Vis Mem	-3.05	1.75	-1.95	1.38	2.516	54	.015	.324
Ver Mem	-1.41	1.42	-0.92	0.96	1.435	54	.157	.192

Note. Controlled Oral Word Association (COWA), Rapid Automatized Naming (RAN), Judgment of Line (JOL), Grooved Pegboard (GPB), Visual Memory (Vis Mem), Verbal Memory (Ver Mem). Levene's Test of Inequality of Variances was significant for the RAN ($F = 6.610$, $p = .013$); *t*-test for unequal variances is used. Only 37 participants (20 Liberal and 17 Restrictive) were administered the JOL. Effect sizes (*r*) were calculated by $r = \sqrt{t^2/(t^2+df)}$.

neurocognitive outcomes of preterm children randomly assigned to either a liberal or a restrictive transfusion protocol. This analysis is important because of evidence from the neonatal period and later infancy suggesting that liberal transfusion may confer neuroprotection (Bell et al., 2005; Whyte et al., 2009).

On the contrary, the findings of the present study indicate that liberally transfused preterm subjects perform as poorly as or worse than restrictive subjects on measures of neurocognitive and academic functioning. Although liberal group mean scores were consistently lower than restrictive scores on all measures (see Figures 1 and 2), the differences between transfusion groups were significant only for associative verbal fluency, visual memory, and reading. These results provide evidence that liberal blood transfusion practices can have a significant negative impact on neurocognitive functioning and academic achievement above and beyond the impact that is associated with preterm status alone.

The current findings did not support the results of the initial comparison conducted in the Bell et al. (2005) trial and the PINT study (Whyte et al., 2009); both of which suggested more favorable outcomes for the liberal group — at least at younger ages. Our findings indicating better outcomes for the restrictive group are particularly noteworthy given the significantly higher proportion of males — who are typically at greater risk than females for developmental learning disabilities — in the restrictive group compared to the liberal group. Post hoc comparisons were run on neonatal characteristics (i.e., birthweight [BW], gestational age [GA] SNAP1, and SNAP2) to ensure that the children in the liberal group who participated were not sicker than those who did not participate and that those in the restricted group who did not participate were not sicker than those who did. Multivariate analysis of BW, GA, SNAP1, and SNAP2 with independent variables of transfusion group

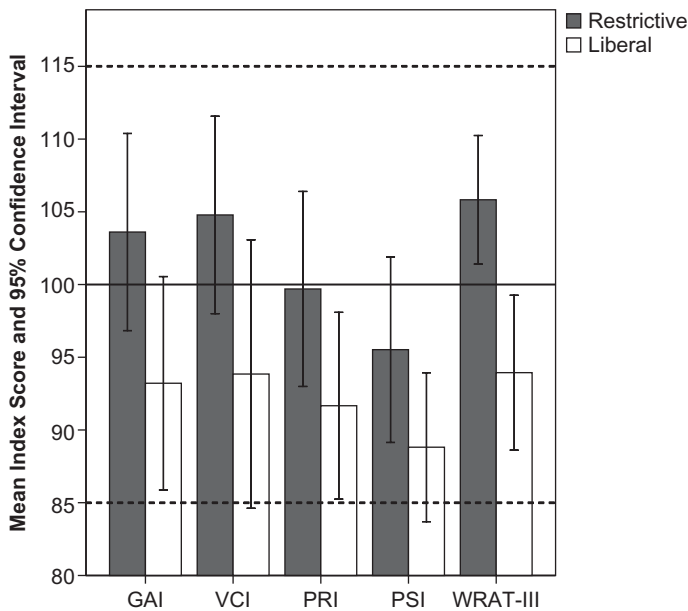


Figure 1 Mean intelligence and reading achievement scores and confidence intervals for each transfusion group. GAI = General Ability Index; VCI = Verbal Comprehension Index; PRI = Preceptual Reasoning Index; PSI = Processing Speed Index; WRAT-III = Wide Range Achievement Test, Third Edition.

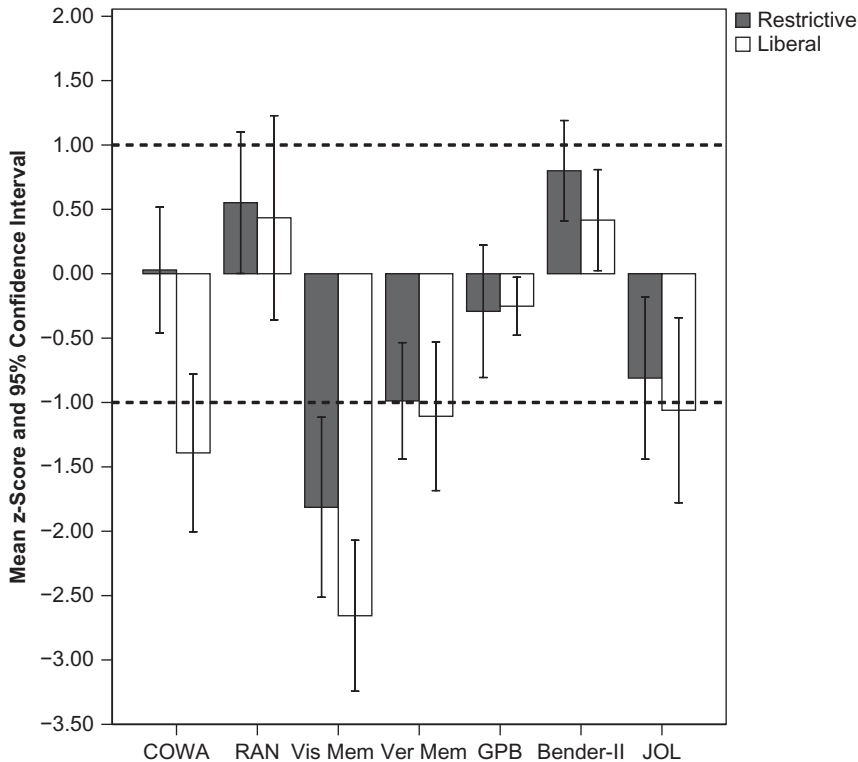


Figure 2 Mean z Scores and confidence intervals on neurocognitive tests for each transfusion group. COWA = Controlled Oral Word Association; RAN = Rapid Automatized Naming; Vis Mem = Visual Memory; Ver Mem = Verbal Memory; GPB = Grooved Pegboard; Bender-II = Bender Visual-Motor Gestalt Test, Second Edition; JOL = Judgment of Line.

and participation status did not yield any significant interaction effect, $F(4, 92) = 0.402$, $p = .807$, or main effects for transfusion group, $F(4, 92) = 0.189$, $p = .943$, or participation status, $F(4, 92) = 0.181$, $p = .948$. This ensures that it was not the sickest from the liberal group and the healthiest from the restricted group being tested.

The Possible Role of EPO Suppression

Although the mechanisms by which liberal transfusion criteria might lead to worse outcomes in the preterm infant are unknown, recent studies using animal models point to the phenomenon of erythropoietin suppression as a possible explanation. Erythropoietin (EPO) is a central nervous system protein that has been shown to play a significant role in protecting the brain against short- and long-term damage from inadequate blood supply and/or oxygen deprivation (Sirén et al., 2001). Both endogenous EPO production and treatment with recombinant erythropoietin (rEPO; an exogenous form of the hormone) may protect the brain by reducing inflammation secondary to reduced blood flow effects (Agnello et al., 2002; Jun et al., 2009; Liu et al., 2006; Sirén et al., 2001). Findings from a retrospective cohort study of 82 preterm infants evaluated at 12-months-corrected age indicated a dose-response relationship between total rEPO dose within the first 6 weeks of

life and Bayley Mental Developmental Index (MDI) scores. This finding lends further support to the possible protective effect of cumulative rEPO on developmental outcome (M. S. Brown, Eichorst, LaLa-Black, & Gonzalez, 2009). Thus, the phenomenon of EPO suppression provides a possible mechanism for the poorer neurocognitive outcomes of the liberal transfusion group in the current study. Of note, the plasma EPO levels were significantly higher in the restrictive group in the Iowa trial (Bell et al., 2005).

Studies have also shown that RBC transfusion may temporarily inhibit or delay the body's EPO response, resulting in decreased protection against infection and inflammation (Frey, 2002; Keyes, Donohue, Spivak, Jones, & Oski, 1989). In other words, RBC transfusion may reduce the body's ability to effectively respond to the threat of brain injury in a protective fashion. The protective action of EPO may have the most pronounced impact on brain areas such as the hippocampus that are known to be especially vulnerable to cell death and cerebral damage (Jun et al., 2009).

Neurocognitive Outcomes: Verbal Fluency, Visual Memory, and Reading

The liberal transfusion group performed significantly more poorly on a test of associative verbal fluency than the restrictive group. Impairments in verbal fluency, even in the absence of global cognitive impairment or structural MRI abnormalities, have been found in other preterm groups (Rushe et al., 2001; Stewart et al., 1999). Wolke and Meyer (1999) also found evidence of impairment in language and prereading skills (speech, articulation, and number naming) in a group of German preschoolers who were born preterm.

Deficits in verbal fluency, in conjunction with impaired performances on tests of memory for visual material and reading, are consistent with neurocognitive profiles frequently seen in children with developmental language and reading disability (Lindgren & Richman, 1984; Lindgren et al., 1986). Children who do not automatically apply verbal labels to visual information in order to facilitate recall also frequently demonstrate difficulty rapidly generating verbal information and calling to mind the names of well-rehearsed information (i.e., the names of colors) (Kail & Leonard, 1986; Korhonen, 1995). The finding that there were significant differences for colors presented visually but not for colors presented verbally may indicate that the problem is more one of efficient verbal labeling of visual information (Dysnomia) rather than an overall verbal memory deficit (Dysmnnesia). Word-finding or word-retrieval difficulties, which are often exacerbated under pressure or timed conditions, have been strongly associated with developmental language disorders (Kail & Leonard, 1986; Kail, Hale, Leonard, & Nippold, 1984; Kirchner & Klatzky, 1985). Verbal deficits of this nature are also strong predictors for later academic difficulties in reading, arithmetic, and spelling, in addition to problems associated with decoding and/or reading comprehension (i.e., developmental reading disability, dyslexia). Although the magnitude of difference in rapid-naming performance between liberal and restrictive groups was not statistically significant, the liberal group nevertheless demonstrated lower group mean raw differences in color-naming speed (liberals $M = 41.56$, $SD = 11.38$; restrictive, $M = 37.92$, $SD = 8.55$).

Potential distinctions between rapid naming and verbal fluency are of particular interest given our finding that the liberal group performed worse than the restrictive group on a test of associative verbal fluency but that scores were not as discrepant on a test of rapid naming. Studies suggest that associative verbal fluency is related to but separate from other common language functions, and that deficits in verbal fluency may be associated

primarily with damage or dysfunction in prefrontal/premotor and hippocampal regions (Boone, Pontón, Gorsuch, Gonzalez, & Miller, 1998; Stuss et al., 1998; Whitney et al., 2008). Research also suggests that associative verbal fluency is strongly associated with if not dependent upon processing speed (Boone et al., 1998) and executive functions, as it requires both “efficient and restricted search of the lexicon” (Narhi et al., 2005, p. 51).

One possible explanation for the more impaired associative verbal fluency in the liberal group is that liberal transfusion may increase the risk for selective damage or dysfunction to brain regions involved in verbal fluency. Findings from neuroimaging studies of adults with brain lesions (Damasio, Anderson, & Tranel, *in press*), patients with schizophrenia (Kircher, Whitney, Krings, Huber, & Weis, 2008; Spence et al., 2000), patients with temporal lobe epilepsy (Alessio et al., 2006; Gleissner & Elger, 2001), and normal healthy controls (Whitney et al., 2008) indicate significant involvement of both prefrontal and hippocampal regions in tasks of verbal fluency (although differences in brain region involvement may present as a function of whether the verbal fluency task is phonological or semantic in nature).

Though of potential interest, the current findings are preliminary and should be interpreted with caution given the current study’s limitations. It is our objective to use the current information regarding relative neurocognitive strengths and weaknesses in liberal and restrictive transfusion groups to generate a targeted follow-up evaluation that will further contribute to our understanding of the highly specific aspects of language, working memory, processing speed, inhibitory control, attention, and executive functioning potentially affected by preterm status and RBC transfusion. Evaluation of specific and subtle neuropsychological functions will likely also be fruitful in more clearly identifying vulnerable brain regions and elucidating specific patterns of neurocognitive weakness in older elementary and adolescent individuals who as neonates received differential treatment for critical illness associated with preterm status. Caution in interpreting these preliminary findings is warranted given the fact that the liberal group performed more poorly than the restrictive group on all measures; though these differences were significant only for a subset of functions assessed. It will be important to corroborate the current findings with larger samples and to investigate neurocognitive outcomes by gender.

Limitations and Future Directions

The results of this study would be strengthened if corroborated by neuroimaging data. Neuroimaging documenting abnormalities associated with the right parietal, hippocampal, prefrontal, and cerebellar regions would broaden our understanding of the impact of transfusion and preterm status on specific brain areas as well as further validate the present findings. The absence of such corroboration should be interpreted with caution, however, given research indicating that structural abnormalities are inconsistent predictors of functional impairment (Stewart et al., 1999; Vicari, Caravale, Carlesimo, Casadei, & Allemand, 2004).

Secondly, despite rigorous attempts to locate all of the original subjects for follow-up examination, a disproportionate number of females were in the restrictive transfusion group. As a result, analysis of the outcomes by sex was not conducted, limiting our understanding of potential interactions between sex and transfusion group. Given established sex differences in brain development, it will be crucial to further explore the way in which sex may alter or moderate the effects of transfusion on the brain and associated neurocognitive functions. Furthermore, we concur with Vicari et al. (2004) and Espy et al. (2009) that

cross-sectional evaluation of preterm groups is insufficient and that longitudinal follow-up of preterm cohorts will be crucial in identifying the extent to which specific neurocognitive deficits identified early in development persist, resolve or worsen over the course of adolescence and adulthood. Additional limitations of the current study include the poor retention rate (56%), small sample and power limitations, and wide age range of the participants at follow-up. It is crucial to recognize the potential impact of age, gender, and environmental factors (e.g., SES, geographic location) on preterm outcomes. These potential contributing factors will need to be better addressed in future research with larger samples.

Conclusion

The results of the current study suggest the possibility of long-term neurodevelopmental risks associated with maintaining the hematocrit at higher levels by liberally transfusing preterm neonates. The results also highlight the importance of interpreting early outcomes with caution. Research in the area of EPO suppression provides a plausible explanation for the findings of the present study. Further research with animal models and critically ill human subjects may help to elucidate whether EPO suppression is a valid and comprehensive explanation for the poorer outcomes observed in the liberal transfusion group. Future studies might also provide insight into other brain regions likely to be affected by EPO suppression as well as the exact neural mechanisms implicated in endogenous EPO reactions. It is clear that further exploration into the role of the hippocampus and related subcortical structures and neural pathways is also warranted.

The reduction in serious brain abnormalities seen on ultrasound with liberal transfusion in the Iowa trial (Bell et al., 2005) and the positive 18-month neurocognitive outcomes in the liberally transfused group from the PINT trial (Whyte et al., 2009) suggested that there might be neuroprotective effects from maintaining higher hemoglobin and hematocrit levels through more liberal transfusion. However, the findings of the current study appear to contradict this possible neuroprotective effect and suggest instead that maintaining higher hemoglobin and hematocrit levels may have long-term adverse effects on brain function. More information is needed before definitive recommendations can be made regarding the target hemoglobin or hematocrit levels that are optimal for preterm infants.

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