THE PREMATURE INFANTS IN NEED OF TRANSFUSION (PINT) STUDY: A RANDOMIZED, CONTROLLED TRIAL OF A RESTRICTIVE (LOW) VERSUS LIBERAL (HIGH) TRANSFUSION THRESHOLD FOR EXTREMELY LOW BIRTH WEIGHT INFANTS

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Objective To determine whether extremely low birth weight infants (ELBW) transfused at lower hemoglobin thresholds versus higher thresholds have different rates of survival or morbidity at discharge.

Study design Infants weighing <1000 g birth weight were randomly assigned within 48 hours of birth to a transfusion algorithm of either low or high hemoglobin transfusion thresholds. The composite primary outcome was death before home discharge or survival with any of either severe retinopathy, bronchopulmonary dysplasia, or brain injury on cranial ultrasound. Morbidity outcomes were assessed, blinded to allocation.

Results Four hundred fifty-one infants were randomly assigned to low (n = 223) or high (n = 228) hemoglobin thresholds. Groups were similar, with mean birth weight of 770 g and gestational age of 26 weeks. Fewer infants received one or more transfusions in the low threshold group (89% low versus 95% high, $P = .037$). Rates of the primary outcome were 74.0% in the low threshold group and 69.7% in the high ($P = .25$; risk difference, 2.7%; 95% CI –3.7% to 9.2%). There were no statistically significant differences between groups in any secondary outcome.

Conclusions In extremely low birth weight infants, maintaining a higher hemoglobin level results in more infants receiving transfusions but confers little evidence of benefit. *(J Pediatr 2006;149:301-7)*

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Extremely low birth weight infants (ELBW < 1000 g) accounted for 0.4% of all Canadian births in 1996 to 1997 and 9% of all neonatal intensive care unit admissions.[1] These newborn infants rapidly become anemic from a combination of frequent laboratory blood sampling and an immature hematopoietic system,[2-4] leading to the transfusion of allogeneic red blood cells (RBCs) in at least 94%.[5] RBC transfusion guidelines available at the start of this trial[6,7] recommended the maintenance of the hemoglobin of ELBW infants at "physiologic" levels, but the justification for such an intervention is poorly supported. The risks and benefits of RBC transfusions to ELBW infants are unclear: Limiting RBC transfusions may reduce transfusion-associated infection and iron overload, but the resulting low hemoglobin levels may result in the morbidities associated with chronic anemic hypoxemia. A study in adult patients in critical care[8] reported no benefit in survival from liberally transfusing allogeneic RBCs to maintain a hemoglobin concentration between 100 and 120 g/L. A restrictive RBC

BPD	Bronchopulmonary dysplasia	RBC	Red blood cell
ELBW	Extremely low birth weight	ROP	Retinopathy of prematurity
PINT	Premature infants in need of transfusion		

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Table I. Hemoglobin threshold levels (g/L) triggering RBC transfusion

Age in days	Blood sampling	Low threshold		High threshold	
		Respiratory support	No respiratory support	Respiratory support	No respiratory support
1-7	Capillary	≤115	≤100	≤135	≤120
	Central	≤104	≤90	≤122	≤109
8-14	Capillary	≤100	≤85	≤120	≤100
	Central	≤90	≤77	≤109	≤90
≥15	Capillary	≤85	≤75	≤100	≤85
	Central	≤77	≤68	≤90	≤77

transfusion strategy (maintaining the hemoglobin concentration between 70 and 90 g/L) was at least as good as, and, for some subgroups, better than the liberal strategy.

In this randomized, controlled trial, we randomly assigned ELBW newborn infants to RBC transfusion algorithms, incorporating restrictive or liberal (low or high) hemoglobin "thresholds." The primary outcome was a composite of either death before home discharge or survival with severe morbidity, where severe morbidity was defined as one or more of (1) retinopathy of prematurity (ROP), (2) bronchopulmonary dysplasia (BPD), or (3) brain injury on cranial ultrasound. This composite outcome captured the competing outcomes of death, or survival with severe morbidity, in one measure. The purpose of this trial was to determine whether maintaining ELBW infants at a restrictive hemoglobin level, by adopting a restrictive (lower) RBC transfusion threshold, led to a difference in clinical outcome compared with a liberal RBC transfusion threshold, in the first weeks of post-natal life.

METHODS

Study Population

Newborn infants were enrolled from 10 neonatal intensive care units in Canada, the United States, and Australia (Appendix; available at www.jpeds.com). Eligible babies were required to be of birth weight <1000 g, gestational age <31 weeks, and to be <48 hours old at the time of enrollment. Infants deemed non-viable by the attending physician were excluded, as were those with cyanotic heart disease, congenital anemia, acute shock, transfusion after 6 hours of age, or known parental opposition to transfusions, a family history of anemia and hemolytic disease, or where the attending physician anticipated using erythropoietin. Informed consent was requested from the parents or guardians. After consent, infants were individually randomly assigned to either the restrictive or the liberal threshold for RBC transfusion. Treatment allocation was by telephone to an interactive voice system at the coordinating center. The concealed computer-generated randomization sequence was stratified by center and birth weight (≤750 g, 751 to 999 g) and incorporated random block sizes. The study was approved by each local research ethics board.

Intervention

Infants were allocated to a transfusion algorithm of low or high hemoglobin thresholds for transfusion (Table I). The algorithm was developed by consensus among participating sites, against the background of then current guidelines.[6,7] The appropriate hemoglobin threshold was adjusted for capillary or arterial/venous blood sampling according to prior work.[9] The thresholds developed were based on whether or not the infant was receiving respiratory support (assisted ventilation, continuous positive airway pressure, or supplemental oxygen) and on post-natal age. The protocol did not dictate how or how often the hemoglobin value was to be determined, but all hemoglobin values were recorded. Phlebotomy losses were not recorded. Transfusion was indicated whenever the hemoglobin equaled or fell below the threshold value. In addition, attending neonatologists were allowed to give non-algorithm dictated RBC transfusions in the event of shock, severe sepsis, coagulation defects, surgery, or for unanticipated emergencies. RBC transfusions were given within 6 hours of the hemoglobin determination, but as soon as possible after the attainment of a threshold value. All transfusions consisted of washed, packed RBCs (homologous or directed donation) given at 15 mL/kg at rates determined by local policy. No attempt was made to blind caregivers with respect to treatment group, as the concealment of hemoglobin values was considered both unethical and impractical. The transfusion algorithm was distributed widely and placed prominently at the site of care of each study patient. The allocated transfusion algorithm was maintained after discharge from tertiary care to the level 2 nursery, but data collection was limited to transfusions, hemoglobin levels prompting transfusion, and hemoglobin at discharge. All centers used iron supplementation according to local guidelines.

Data Collection

All data, including Score for Acute Physiology (SNAP) scores, were collected from entry to discharge by using specifically designed case report forms. Routine care of ELBW infants at all participating institutions included first-week and pre-discharge cranial ultrasounds and pre-discharge retinal examination. Donor exposure to RBCs, platelets, and fresh

frozen plasma was ascertained retrospectively from blood bank records at each institution.

Primary Outcome

The primary outcome included the main clinically relevant morbidities experienced before first neonatal discharge home and was a composite of either death or survival with one or more of

(i) ROP: Grades 3 through 5[10];
(ii) BPD: Supplemental oxygen requirement at a postconceptual age of 36 weeks or later[11];
(iii) Brain injury: Presence of cystic periventricular leukomalacia, intra-parenchymal echodensity, porencephalic cyst, or ventriculomegaly on the "worst" cranial ultrasound available before discharge.[12]

In all infants, these assessments were performed in the first week of life and before discharge from the tertiary care hospital. The presence of severe ROP was based on a locally interpreted retinal assessment conducted by an ophthalmologist unaware of treatment group. The need for oxygen at 36 weeks was determined by the attending physician. Cranial ultrasounds were interpreted independently by a blinded, two-person committee (JM and PG) who reviewed all images; where one reviewer disagreed with the local report, the committee adjudicated the final results.

Secondary Outcomes

Pre-specified secondary outcomes included hemoglobin level, numbers of RBC transfusions, numbers of donor exposures, rate of growth (as weekly weights and head circumferences), and serum ferritin change from early to discharge values. Other recorded outcomes included numbers of infants with necrotizing enterocolitis or with apnea requiring treatment and the use of xanthines or doxapram, culture proven infections, or requiring post-natal steroids. We also recorded time in oxygen, time to extubation, and time to discharge.

Sample Size and Statistical Analysis

The planned sample size of 424 neonates was based on detecting, with 90% power, an absolute risk reduction of 15% in either direction (a two-sided α of 0.05) for the primary outcome. Analyses of outcomes were adjusted for birth weight stratum and center, using a logistic regression model. Cumulative mortality was estimated with the Kaplan-Meier method.[13] The analysis was conducted on an intention-to-treat basis. Data were reviewed by an external safety and monitoring committee. One formal interim analysis of efficacy was conducted at the mid-point, which required a value of $P <$ .001 to stop the trial.

RESULTS

Study Population

A total of 795 infants were screened for entry into the study from January 2000 to February 2003 inclusive, of whom 694 were eligible and 451 were subsequently randomly assigned (Figure 1; available at www.jpeds.com). Consent was not obtained for 136 infants, and the parents of 107 were not approached to participate because parents were not available or not accessible for consent within 48 hours of birth. Two hundred twenty-three infants were allocated to the restrictive (low threshold) group and 228 to the liberal (high threshold) group. Both groups were similar with respect to initial maternal and infant variables, including those reflecting severity of illness (Table II; available at www.jpeds.com). Birth weight was not significantly different between those enrolled and those eligible but not enrolled ($P = .28$). Numbers recruited ranged in the 10 centers from 6 to 94 (median 42).

Hematologic and Transfusion Outcomes

From initially similar levels, hemoglobin declined with time in both treatment groups but with a weekly mean consistently higher in the high threshold group (Table III). The separation in the mean hemoglobin levels was statistically significant within the first week and stabilized at about 10g/L by week 4. The mean hemoglobin separation slowly declined during the remainder of the neonatal hospitalization, remaining statistically significantly different up to 12 weeks, becoming no longer significantly different by discharge (Figure 2). As a result of maintaining a reduced hemoglobin level, the low threshold group received fewer RBC transfusions (mean, 4.9 units) than the high threshold group (mean, 5.7 units) but this difference did not reach statistical significance ($P = .070$). However, the mean number of transfusions triggered by a hemoglobin threshold was significantly lower in the low threshold group, but this difference was offset by a small but statistically significant difference in the opposite direction in transfusions given for "clinical reasons," many of which were for bleeding or surgery (Table IV; available at www.jpeds.com). However, the total number of these transfusions was low (7.4% low group versus 3.1% high group). The median day of first transfusion was 4 days in both groups. By discharge from the hospital, 89% of infants in the low threshold group had received a transfusion either by algorithm or clinical decision, compared with 95% in the high threshold group ($P = .037$). The mean number of blood product donors to which infants were exposed was slightly lower in the low threshold group, both for all blood products and for RBCs specifically, but the differences were only statistically significant for RBC donors ($P = .035$).

Primary Outcome

The primary outcome was the combination of either death or survival with bronchopulmonary dysplasia, severe retinopathy of prematurity, or brain injury. The outcome status of all infants was known (ie, there was no loss of infant data). During the neonatal period, 74.0% of the low threshold group had this outcome, compared with 69.7% of infants allocated to the high threshold cohort (Table V). The birth weight–adjusted and center strata–adjusted difference of 2.7%

Table III. Treatment effects on hemoglobin and transfusions

Variable	Low threshold	High threshold	Difference mean (95% CI)	*P* value
Hemoglobin (g/L)*				
Initial	164 (25)† (n = 223)	165 (23) (n = 227)	−0.5 (−5.0, 4.0)	.83
Week 1	143 (19) (n = 223)	149 (17) (n = 227)	−6.4 (−9.7, −3.1)	<.001
Week 2	119 (15) (n = 204)	131 (13) (n = 207)	−12.5 (−15.2, −9.8)	<.001
Week 3	109 (15) (n = 187)	120 (13) (n = 194)	−10.9 (−13.8, −8.0)	<.001
Week 4	101 (12) (n = 174)	112 (13) (n = 185)	−10.3 (−12.8, −7.7)	<.001
Discharge	106 (18) (n = 177)	108 (16) (n = 190)	−2.6 (−6.1, 0.9)	.14
Transfusions				
No. of transfusions	4.9 (4.2)	5.7 (5.0)	−0.83 (−1.68, 0.02)	.070
Triggered by hemoglobin	4.1 (3.3)	5.3 (4.4)	−1.23 (1.95, −0.50)	.0044
Clinical decision	0.8 (2.0)	0.4 (1.3)	0.39 (0.08, 0.72)	.0069
Ever transfused	89%	95%	−5.5% (−10.5%, −0.5%)	.037
No. of donors	3.7 (5.1)	4.2 (7.2)	−0.52 (−1.67, 0.64)	.38
RBC donors	2.1 (2.0)	2.6 (2.7)	−0.48 (−0.92, −0.03)	.035

*Capillary equivalent.
†Mean (standard deviation).

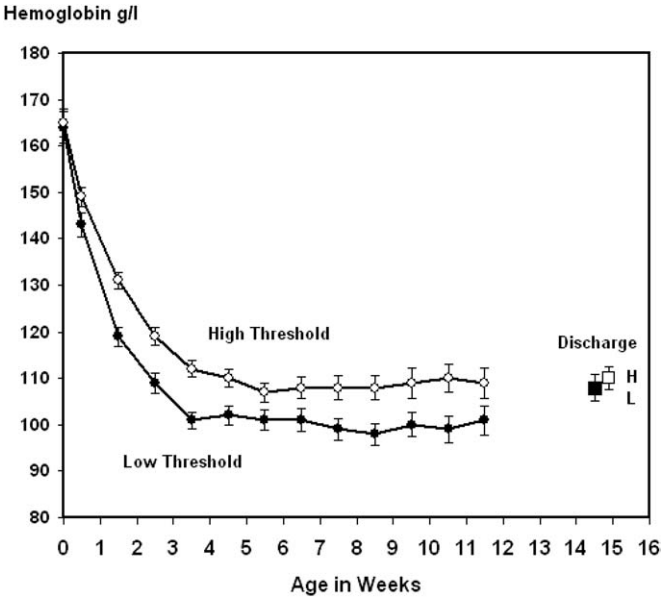

Figure 2. Hemoglobin levels by post-natal age according to cohort assignment up to 12 weeks' post-natal age.

was not statistically significant ($P = .25$; 95% CI, −3.7% to 9.2%). With the exception of brain injury, the individual components of the composite primary outcome each slightly favored the high threshold group, but all differences were statistically nonsignificant. Table VI (available at www.jpeds.com) details the frequency of the head ultrasound findings by group and by survival status. The frequency of the primary outcome between centres was not significantly different ($P = .75$). The Kaplan-Meier plot (Figure 3; available at www.jpeds.com) shows no significant differences in cumulative mortality rates at any time after random assignment. At the median follow-up of 12 weeks, the cumulative mortality rate approximates the overall mortality rate, as seen in Table V. There was no evidence that the treatment effect varied by birth weight strata.

Secondary Outcomes

The treatment effects on protocol-designated secondary outcomes and other outcomes assessed during hospitalization are shown in Table VII. Data for growth were analyzed at 32 weeks' corrected age because of varying times of discharge. There were no significant differences demonstrated in any secondary outcomes. In particular, there were no statistically significant differences in duration of ventilatory support, growth, or length of hospital stay. Similarly, the observed differences in the other outcomes were all quite consistent with chance variation, given the number of comparisons being made.

DISCUSSION

In this randomized, controlled trial, we allocated acutely ill, ELBW infants during their first 2 days of life to an algorithm of either a low or a high hemoglobin transfusion threshold, which was maintained until discharge. As a result, the high threshold group had a mean hemoglobin concentration about 10 g/L higher than the low threshold group during the first 4 weeks of life. This difference in hemoglobin level slowly dissipated over the neonatal hospitalization period as

Table V. Primary outcome

Outcome cluster	Low threshold	High threshold	Treatment effect* (95% CI)	*P* value
Composite primary				
Death, severe ROP, BPD, or head ultrasound brain injury	165/223 (74.0%)	159/228 (69.7%)	OR: 1.30 (0.83, 2.02) RD: 2.7% (−3.7%, 9.2%)	.25
Individual components				
Death	48/223 (21.5%)	40/228 (17.5%)	OR: 1.38 (0.84, 2.27) RD: 2.6% (−3.5%, 8.8%)	.21
Survived with severe ROP	33/175 (18.9%)	33/188 (17.6%)	OR: 1.27 (0.71, 2.26) RD: 1.1% (−4.6%, 6.8%)	.42
Survived with BPD	101/175 (57.7%)	103/188 (54.8%)	OR: 1.18 (0.76, 1.85) RD: 3.9% (−4.6%, 12.4%)	.46
Survived with head ultrasound brain injury	22/175 (12.6%)	30/188 (16.0%)	OR: 0.86 (0.53, 1.39) RD: −3.3% (−9.9%, 3.4%)	.53

*Point estimate and 95% confidence intervals for odds ratio (OR) and risk difference (RD) adjusted for birth weight stratum and center.

blood sampling declined and the infant matured. This was associated with a lower likelihood of receiving at least one transfusion in the low threshold group despite a slightly higher use of "clinically" driven RBC transfusions. Presumably, the hemoglobin thresholds in the low threshold group resulted in later RBC transfusions as well as a reduction in algorithmic determined RBC transfusions when compared with the high threshold group.

No statistically or clinically important between-group difference was observed in the primary composite outcome of death or neonatal morbidity. The primary composite outcome captured the competing risks of death or survival with serious morbidity, by combining the most frequent and serious complications in the ELBW survivors with death. These complications (ultrasound brain injury, ROP, BPD) independently adversely affect neurodevelopmental outcome at 18 months' corrected age.[14] These conditions are thought to result from hypoxic ischemia, oxygen radical toxicity, or iron overload mediated oxygen toxicity.[15-19] Our study was of sufficient size to detect a 15% absolute difference in this clinically relevant primary outcome with 90% power. Despite this, the 95% confidence interval for the true risk difference ranged from −3.7% (favoring low) to 9.2% (favoring high). Therefore, as a worse-case scenario, the prescribing clinician must weigh whether adopting a low hemoglobin threshold with a potential 9% increase in poor neonatal outcome is offset by the need for fewer RBC blood transfusions. Nonetheless, the adjusted difference of 2.7% (only slightly favoring the high threshold) is most likely the true effect size in the confidence interval range.

Two studies exist of similar strategies to limit early transfusions.[20,21] One trial, using adjunctive therapy with erythropoietin, found no significant clinical differences.[20] Our thresholds were similar to prior recommendations.[20-22] In a trial of late RBC transfusion, restriction had no effect on the incidence or severity of ROP.[23] We found no important differences in either the composite outcome or the individual outcomes over the initial neonatal hospitalization.

A similar but smaller trial (n = 100) by Bell et al[21] was powered for the primary outcome of number of transfusions. They achieved a larger hemoglobin separation and correspondingly bigger effect on the mean number of transfusions, and reported a significant difference (in favor of the liberal, high threshold group) for the combined outcome of intraventricular hemorrhage (IVH) grade 4 or periventricular leukomalacia (PVL). This latter combination was not a prespecified outcome. In addition, Bell et al enrolled infants later and may have received up to two prior transfusions; furthermore, late head ultrasound findings were reported in only half of the infants enrolled. The PINT secondary outcome of "brain injury" includes a somewhat different mix of ultrasound findings but shows little evidence of a treatment difference, and, if anything, favors the low threshold group. These discrepant findings may be attributable to the play of chance, differences in protocols of enrollment, and outcome measurement.

Before the current generation of trials,[20-23] two small, randomized trials were performed in larger, more stable infants.[24,25] No differences in short-term outcomes were described. Prior recommendations for allogeneic RBC transfusion were derived from small, non-randomized studies, advocating allogeneic RBC transfusions to prevent apnea, to foster weight gain and growth,[26] or to increase oxygenation in ventilated infants.[27] Others have challenged the notion of impaired oxygenation from lower hemoglobin values,[28] although other observational studies caution against lower hemoglobins.[29] None of the secondary outcomes in our study indicate the presence of harm from adopting a lower transfusion threshold regimen. The lack of statistically significant, important differences in numbers of infants with apnea are consistent with studies of apnea frequency measured objectively with pneumocardiography, where there was no documented increase in number or severity of apneas by hemoglobin range.[30] Volume infusion alone, whether as RBCs or as albumin, was associated with similar reductions in apnea rate. This is consistent with observations of Bell et al of a decrease in the rate of apnea associated with transfusion, which did not translate into a significant reduction in the numbers of infants with apnea.[21]

Prior attempts to minimize allogeneic RBC transfu-

Table VII. Secondary outcomes

Outcome	Low threshold	High threshold	Difference (95% CI)	*P* value
Protocol-specified secondary outcomes				
Growth (32 weeks corrected age)*				
Weight gain (g)	448 (223)†	466 (325)	−18.4 (−77.8, 41.1)	.54
Head circumference (cm)	27.2 (1.30)	27.1 (1.40)	0.12 (−0.20, 0.43)	.47
Age at final extubation (d)*	37 (33)	36 (35)	1.5 (−5.6, 8.5)	.69
Length of hospitalization (d)*	104 (38)	101 (38)	3.0 (−4.9, 11.0)	.45
Other outcomes				
Any supplemental oxygen (all infants)	96%	96%	−0.5% (−4.1%, 3.2%)	.81
Age at last supplemental oxygen (days)*	80 (48)	79 (49)	1.6 (−8.5, 11.6)	.76
Any positive-pressure ventilation	95%	99%	−3.6% (−5.7%, −0.02%)	.031
Age at last positive-pressure ventilation*	55 (34)	54 (34)	0.9 (−6.1, 8.0)	.79
Apnea requiring treatment	55%	60%	−4.9% (−14.4%, 4.6%)	.30
Confirmed necrotizing enterocolitis	8.5%	5.3%	3.3% (−1.8%, 7.8%)	.20
Bowel perforation	10.8%	6.1%	4.6% (−0.9%, 9.5%)	.090
Serum ferritin (μg/L) (change discharge-baseline)	4.8 (286)	16.5 (259)	−10.7 (−71.0, 49.6)	.73
Blood culture–proven sepsis	43%	41%	1.8% (−7.7%, 11.3%)	.70

*In infants alive at neonatal discharge.
†Mean (standard deviation).

sions have focused largely on one of three main strategies: minimizing sampling loss, using erythropoietin, or using simple transfusion guidelines.[31] Enthusiasm for early intervention with erythropoietin[32] has been tempered both by safety concerns[33] and disappointing results from clinical trials.[34]

Many RBC transfusion guidelines have suggested downward revisions, but the safety or potential benefits of either the upper or lower hemoglobin limits recommended have not been adequately tested. Our study incorporated transfusion thresholds that fall within then-current clinical practice boundaries and guidelines.[6] Controversy arose from the ARDS NET trial, from suggestions that the chosen interventions were beyond the boundary of clinical practice.[35,36] In this trial, we incorporated a comparison of algorithms, which, while within clinical practice boundaries, were expected to create a separation in mean hemoglobin between groups. We decided to allow additional "clinically driven" RBC transfusions in specific situations. We recognized that this clinical judgment might be differentially applied; in fact, these "clinical" transfusions were more frequent in the lower hemoglobin arm. However, there was no way to achieve a pragmatic trial without, for example, enabling surgeons and anesthetists to transfuse for "clinical reasons." Although the contrast between high and low groups was slightly less than that achieved in adults in the TRICC trial (107 versus 85)[8] or in Bell's study,[21] this present study achieved a likely physiologically important difference in hemoglobin between groups throughout much of the hospital stay. This difference was especially evident in the first 2 weeks of life. This trial could not be powered to detect differences in rates of RBC transfusion-related infections. However, transfusion frequency was taken as a proxy for this outcome, and this was marginally reduced in the low threshold group. Rates of all bacterial culture–proven infections were similar in the two groups (Table VII).

The present findings provide evidence that transfusion thresholds in ELBW infants can be moved downward by at least 10 g/L, without incurring a clinically important increase in the risk of death or major neonatal morbidity. Further studies will be required to clarify residual concerns about secondary outcomes.

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APPENDIX

List of the PINT Investigators

Albany Medical Center, USA: Angel Rios, P. Graziano, Susan Boynton.

Brooklyn Hospital Center, USA: Meena LaCorte, Patrick Leblanc, A. Braithwaite.

Edmonton Royal Alexandra, Canada: Abraham Peliowski, M. Athaide, D. Morstad.

Kingston General Hospital, Canada: Robert Connelly.

Halifax IWK Health Centre, Canada: Robin Whyte, Sharon Stone.

McMaster University, Hamilton, Canada: Haresh Kirpalani, Morris A. Blajchman, Nancy M. Heddle, Janice Cairnie.

Melbourne Mercy for Women, Victoria, Australia: Chad Andersen, Anna Burdett.

Melbourne Royal Women's Hospital, Victoria, Australia: Colin Morley, Chad Andersen, Elisabeth Crowe.

Royal Victoria Montreal, Canada: Keith Barrington, Tom Kokkotis.

Sunnybrook and Women's College Health Sciences Centre, Toronto, Canada: Elisabeth Asztalos, Lisa Golec.

Coordinating and Methods Center: Robin Roberts, Carole Chambers, Lorrie Costantini, Kevin Thorpe.

Ultra-Sound Adjudication Committee: John Mernagh, MD, McMaster University; Phyllis Glanc, MD, Sunnybrook and Women's College Health Sciences Centre.

External Safety and Efficacy Monitoring Committee: Michael Gent (Chair); Edmund Hey, MD; Heather Hume, MD; Max Perlman, MD; Kevin Thorpe.

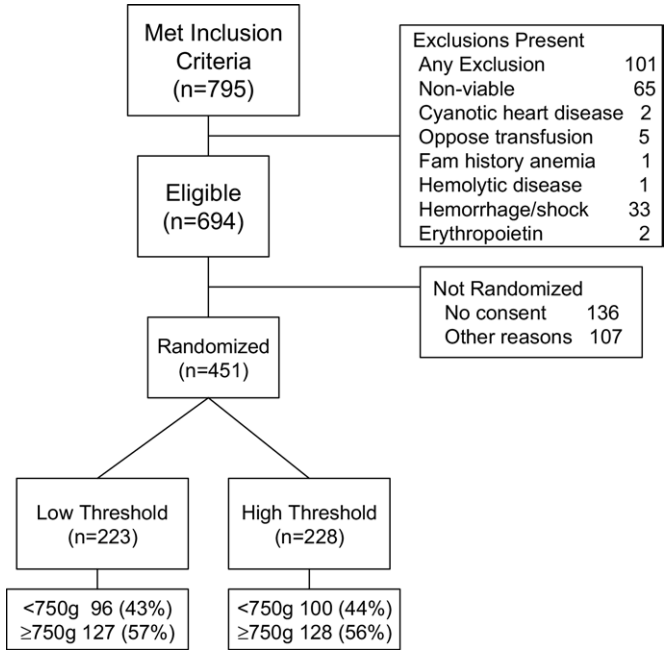

Figure 1. Screening process and random assignment. Patient flow-through from eligibility to stratification. The proportion of infants weighing below and above 750 g is seen to be equivalent in both arms.

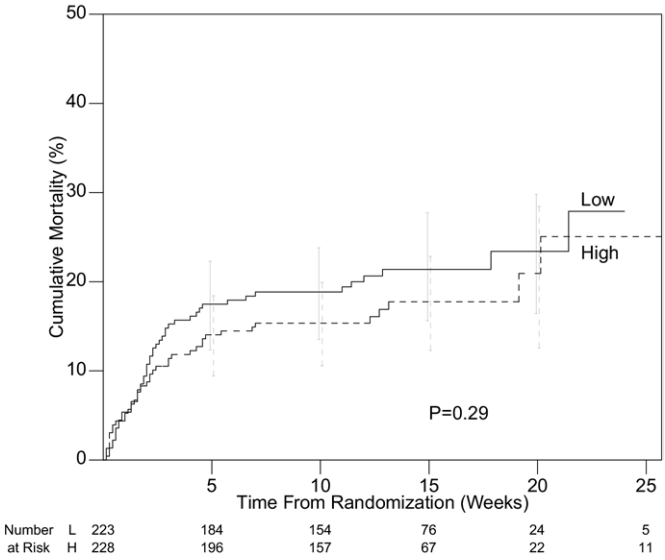

Figure 3. Cumulative mortality rates with 95% confidence intervals. Kaplan-Meier curve is plotted from time from random assignment by group. *Dotted line* depicts the low threshold group; *solid line* depicts high threshold group. At time intervals of 5, 10, 15, and 20 weeks after randomization, 95% confidence intervals are depicted. Overall $P = .29$. Below *x*-axis are the "number at risk" in both the low and high groups. These are the infants still alive at that time and not yet discharged home from the neonatal intensive care unit, that is, all infants who have not yet reached one of the primary end points.

Table II. Baseline data: Mother and infant

Characteristic	Low threshold (n = 223)	High threshold (n = 228)
Mother		
Age (y)		
Mean (SD)	29.5 (5.9)	29.3 (5.7)
Antenatal steroids		
Any	85%	86%
≥One completed course	61%	64%
Placental abruption	19%	16%
Caesarian section	59%	63%
Clinical chorioamnionitis	28%	26%
Infant		
Sex: male	49%	48%
Birth weight (g)		
Mean (SD)	771 (138)	769 (144)
Gestational age (wk)		
Mean (SD)	26.1 (1.9)	26.1 (1.8)
Inborn	90%	86%
Intubated at random assignment	84%	81%
SNAP score		
Median (interquartile range)	14 (7-25)	14 (9-25)

Table IV. Justification for transfusion (as reported by center)

Justification	Low threshold	High threshold
Hemoglobin trigger	918 (84.1%)	1218 (93.3%)
Clinical reasons (total)	173 (15.9%)	87 (6.7%)
Bleeding	35 (3.2%)	22 (1.7%)
Surgery	34 (3.1%)	12 (0.9%)
Sepsis/shock	21 (1.9%)	10 (0.8%)
<6 hr old	2 (0.2%)	2 (0.2%)
Other	81 (7.4%)	41 (3.1%)
Total transfusions	1091	1305

Table VI. Head ultrasound: Individual findings

Head ultrasound finding	Low threshold	High threshold	*P* value
All patients			
Any brain injury	40/216 (18.5%)	46/218 (21.1%)	.50
intra-parenchymal Echo-dense lesion	22 (10.2%)	20 (9.2%)	
Cystic PVL	5 (2.3%)	8 (3.7%)	
Porencephalic Cyst	3 (1.4%)	4 (1.8%)	
Ventriculomegaly	26 (12.0%)	31 (14.3%)	
Survivors to discharge home			
Any brain injury	22/175 (12.6%)	30/188 (16.0%)	.53
intra-parenchymal Echo-dense lesion	8 (4.6%)	7 (3.7%)	
Cystic PVL	3 (1.7%)	5 (2.7%)	
Porencephalic Cyst	2 (1.1%)	4 (2.1%)	
Ventriculomegaly	14 (8.0%)	20 (10.7%)	