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of South Australia

Children, Youth and
Women's Health Service

Women's
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Hospital

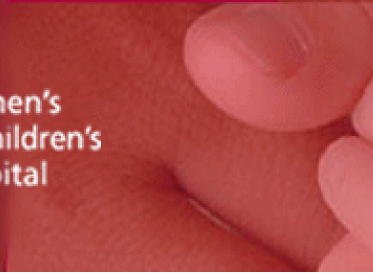
When should we transfuse very premature newborns?

Chad Andersen

Adelaide

Contents

- Very premature newborn: < 28 weeks gestation
- Short historical perspective
- Brief rationale of transfusion
- Two trials
    - PINT / PINTOS
    - Bell
- Summary
- Why might the newborn be different?
- Brain injury, oxygen delivery / consumption
- Conclusion

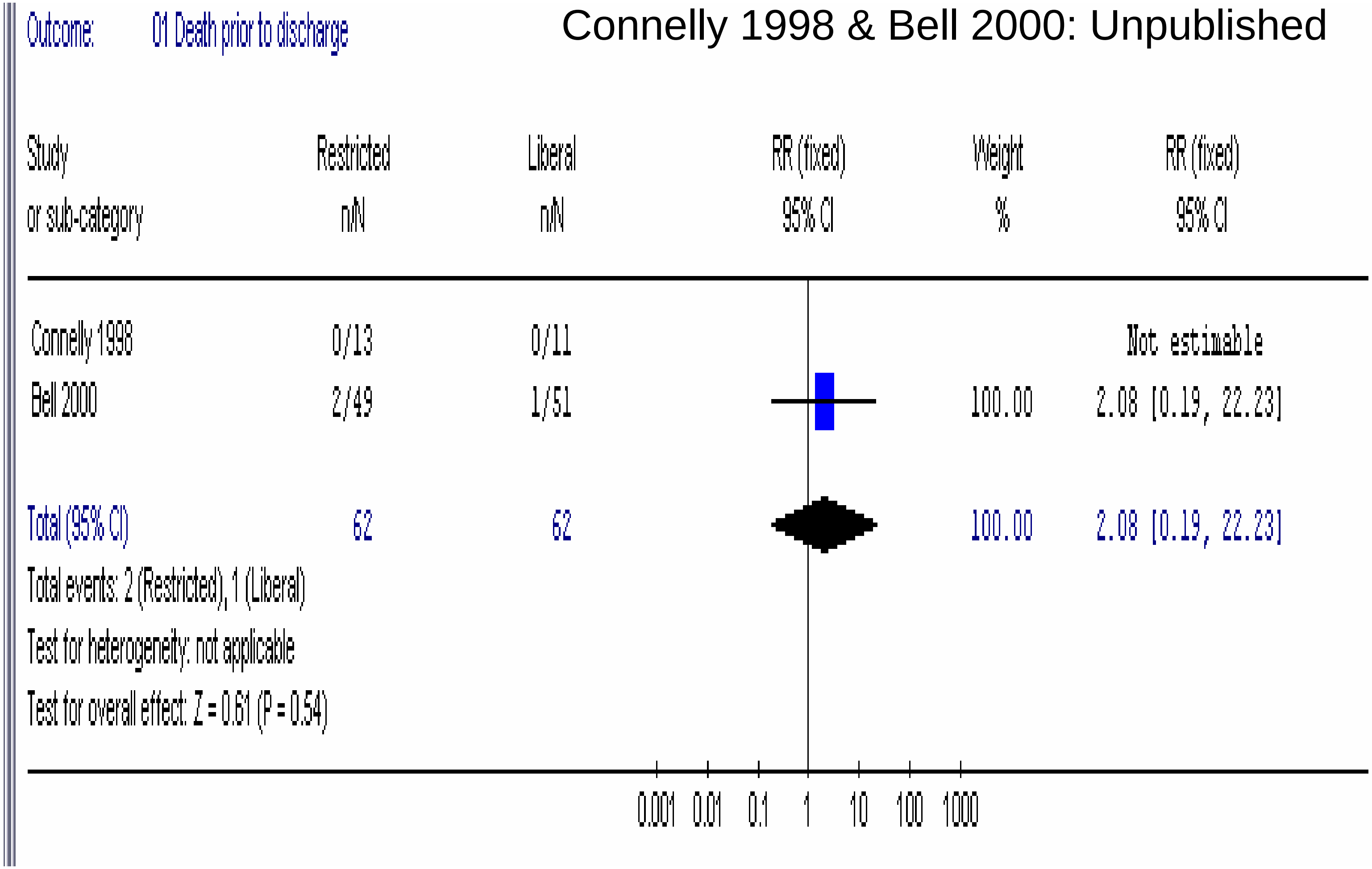


Historical perspective

- Richard Lower credited with the first transfusion in 1665 in canines and soon after in a human subject suffering “harmless insanity”.
- Few randomised trials in premature newborns – notably Connelly (1998) and Bell (2000).
- Historically progressive restriction in transfusion rate with no change in longer term outcome.

Overview: Lower or Higher Hb Threshold for Transfusion in VLBW

Connelly 1998 & Bell 2000: Unpublished



Outcome: 01 Death prior to discharge

Study or sub-category	Restricted n/N	Liberal n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Connelly 1998	0/13	0/11			Not estimable
Bell 2000	2/49	1/51		100.00	2.08 [0.19, 22.23]
Total (95% CI)	62	62		100.00	2.08 [0.19, 22.23]

Total events: 2 (Restricted), 1 (Liberal)

Test for heterogeneity: not applicable

Test for overall effect: Z = 0.61 (P = 0.54)

Favours lower threshold Favours higher threshold

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Rationale

- What are the reasons for transfusion?
  - – Optimise tissue oxygen delivery and thereby
  - – Minimise end organ hypoxia and subsequent injury – avoidance of the anaemic critical threshold.
- Hb is a continuous variable – why do we think the answer is a single number?

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Randomised transfusion trials

- PINT / PINTOS – Multicentre Randomized Clinical Trial of Blood Transfusion Thresholds in premature newborns less than 1000 grams birth weight (ELBW). 451 ELBW infants (2001-2003). *Kirpalani H, Whyte RK, AndersenC, Asztalos EV, Heddle N, Blajchman MA, Peliowski A, Rios A, LaCorte M, Connelly R, Barrington K, Roberts RS. 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. J Pediatr. 2006 Sep;149(3):301-307.*
- Bell – Multicentre Randomised Clinical Trial of Transfusion Thresholds in premature newborns between 500 and 1300 grams. 100 newborns (1992-1997) *Bell EF, Strauss RG, Widness JA, Mahoney LT, Mock DM, Seward VJ, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusions in preterm infants. Pediatrics 2005;*

  115:1685-1691.

PINT

- Inclusion
    - Less than 1000 g birth weight
    - Less than 31 wk gestational age
    - Less than 48 hours of age
- Exclusion
    - Non-viable condition
    - Cyanotic congenital heart disease
    - Congenital anemia
    - Acute shock, septic DIC
    - Transfused after 6 hours of life
    - Anticipated erythropoietin

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PINT
Intervention

- Central computer-based automatic randomization (Trials centre).
- Stratified by centre and birth weight:
  - ≤ 750 g
  - 751-999 g
- Allocation and outcome measurements blind to intervention – but allocated group not blinded.
- Random allocation within 48 hours of birth to either a high Hb transfusion algorithm or a low Hb transfusion algorithm.
- Algorithms based on variation of clinical practice – from questionnaires.
- Remained in allocated group up to the time of discharge home.
- Additional transfusions permitted in the context of shock, severe sepsis, coagulopathy, surgery or at consultants request.
- Transfusion volume fixed at 15 ml/kg packed red cells

PINT

Transfusion Algorithms

Algorithms based on chronologic age, Hb threshold and the need for respiratory support.

	Low Threshold		High Threshold	
	Respiratory Support		Respiratory Support	
Age	Yes	No	Yes	No
1 Week	115	100	135	120
2 Weeks	100	85	120	100
≥ 3 Weeks	85	75	100	85

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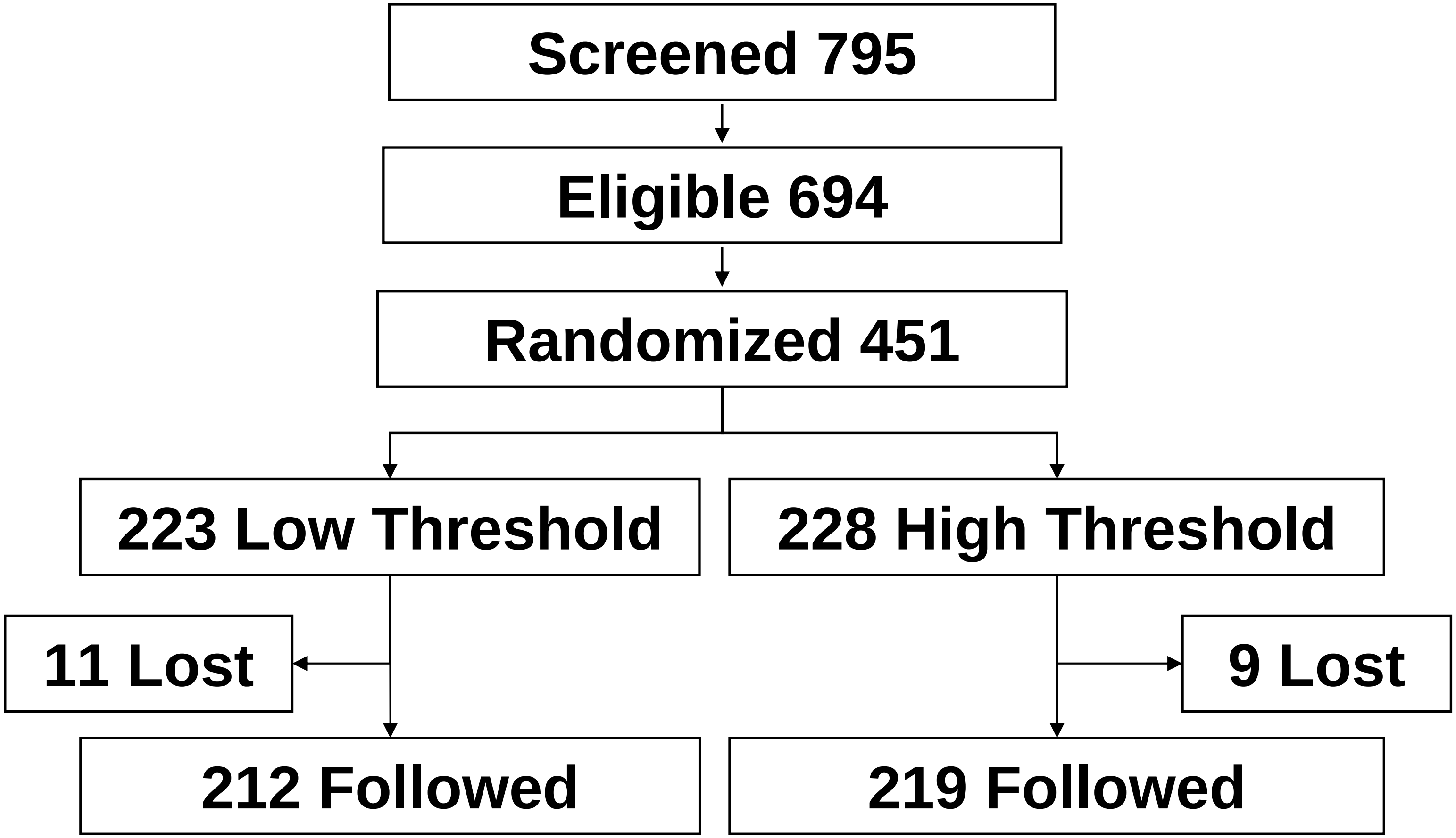
PINT

Outcome and sample size

- Primary Outcome
    - Death or significant morbidities; defined as
        - » BPD (supplemental oxygen at 36 weeks CGA)
        - » ROP (stage 3 or greater)
        - » Brain injury - >GII IVH, VE, PVL
- Secondary Outcome
    - » Growth, ferritin, NEC (surgery), steroids, time to extubation and time to discharge.
- Sample Size
    - Risk reduction in composite primary outcome from 72 to 57%
    - Power 90%, 2 tailed alpha = 0.05.
    - N = 424 infants

PINT
Patient Flow



Screened 795

Eligible 694

Randomized 451

223 Low Threshold

228 High Threshold

11 Lost

9 Lost

212 Followed

219 Followed

96% followed

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PINT
Baseline Characteristics

	Low (n=223)	High (n=228)
Birth weight g*	771 (137)	769 (144)
Gestational age wk*	26 (2)	26 (2)
Antenatal steroids	190 (85%)	197 (86%)
Placental abruption	42 (19%)	36 (16%)
Caesarean section	131 (59%)	144 (63%)
SNAP II score*	17 (14)	17 (13)

*Mean (sd) ** n (%)

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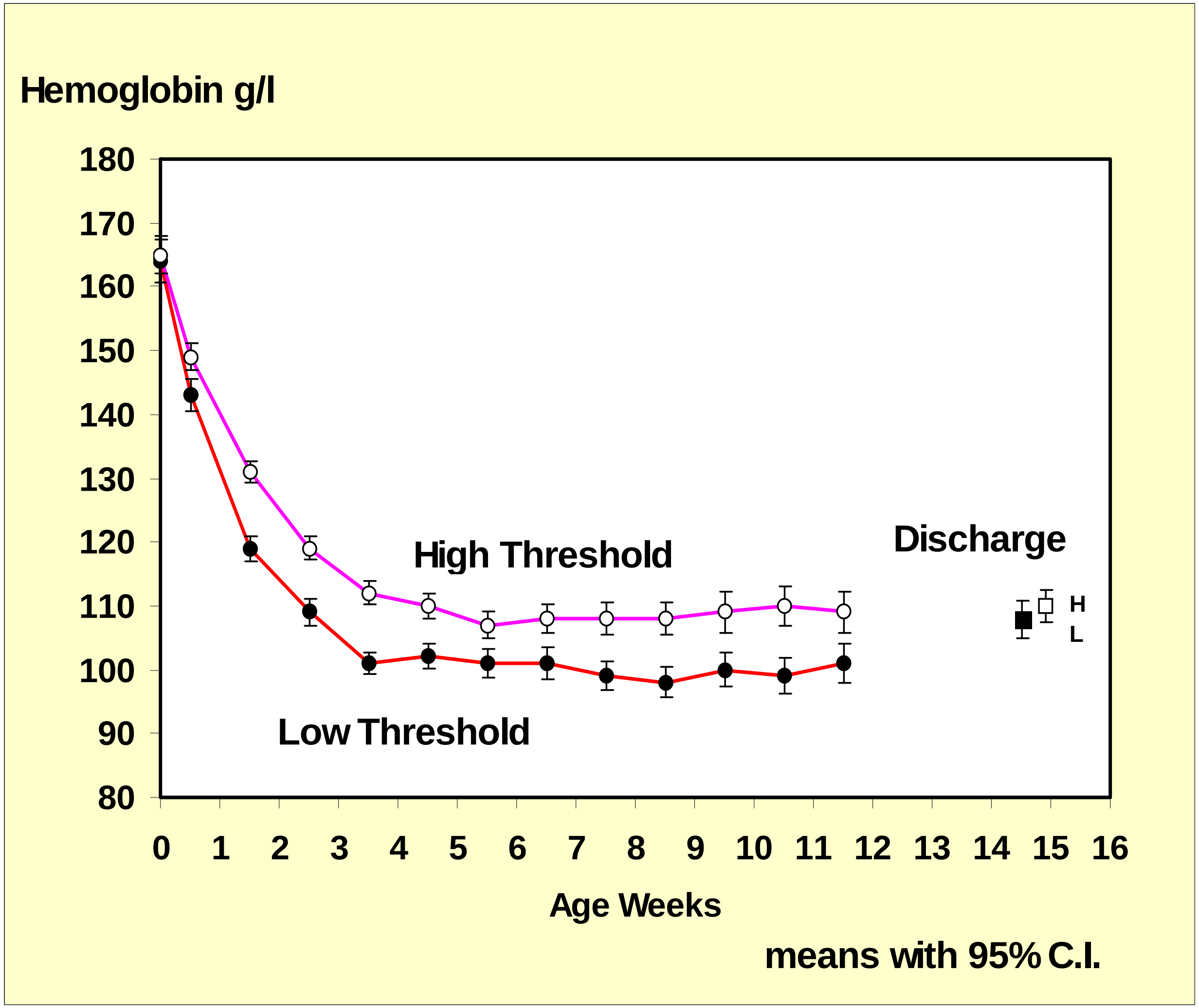
PINT
Haemoglobin by Age



Statistically significant difference of between 10 and 12 g/L was maintained in the first weeks of life however there was no difference at the time of discharge home

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PINT
Primary Outcome

	Threshold		
	Low	High	OR (95% C.I.)
Death before discharge	22%	18%	1.4 (0.8, 2.3)
Death or Major Morbidity*	74%	70%	1.3 (0.7, 2.0)

p = 0.25; risk difference, 2.7%; 95% CI -3.7% to 9.2%

* Severe Retinopathy or Bronchopulmonary Dysplasia or Brain Injury on Ultrasound

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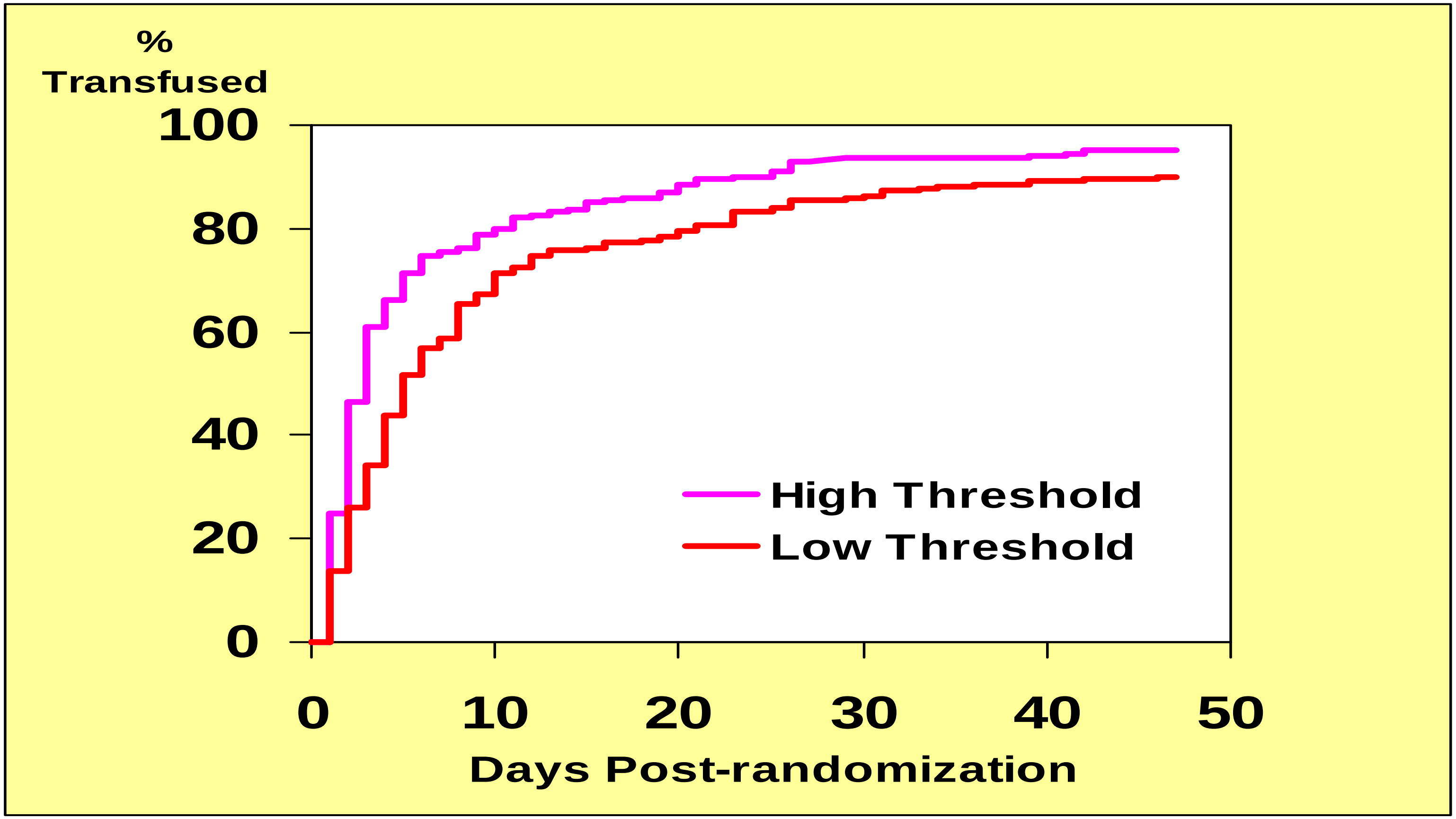
PINT
Transfusions



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PINT

Transfusion data

	Threshold		
	Low	High	
Determined by Transfusion Algorithm [mean (SD)]	4.0 (3.3)	5.1 (4.3)	p = 0.008
Clinical Decision [mean (SD)]	0.8 (2.0)	0.4 (1.2)	p = 0.013
Total [mean (SD)]	4.8 (5.2)	5.5 (4.8)	p = 0.096

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PINT
Transfusion data

	Threshold		
	Low	High	
Never transfused	11%	5%	p= 0.037
Nº of Donors [mean (SD)]	3.7 (5.1)	4.2 (7.2)	p=0.38
Nº of RBC Donors [mean (SD)]	2.1 (2.0)	2.6 (2.7)	p=0.035

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PINT
Outcome Study (PINTOS)

- Predetermined follow-up of the PINT study
- Outcomes: composite of death or severe disability.
- Survivors assessed at 18 months corrected age with psychomotor tests (Baileys), parent questionnaires, growth and haematologic parameters.
- Developmental Follow-up Programmes in Canada, Australia and USA

PINTOS
Outcome

- Composite outcome:
  - Death or
  - Cerebral palsy – validated assessment tool - determined by clinician on physical and neurological examination
  - Cognitive delay - defined as a BSID-II MDI below 70 (i.e.>2 SDs below age norm)
  - Visual impairment - defined as the best corrected vision in the better eye of visual acuity of less than 20/200 (legally blind).
  - Hearing impairment - defined as a hearing loss requiring amplification or the insertion of a cochlear implant

PINTOS

Primary Composite Outcome

	Hemoglobin Threshold		
	Low	**High**	
	n = 208	**n = 213**	
Primary Composite	**94**	**82**	$p_{\alpha} = 0.091$
	45.2%	**38.5%**	

Treatment Effect		**95% confidence limits**
Odds Ratio (High/Low)	**0.69**	**0.45 , 1.06**
Risk Difference (Low-High)	**3.5 %**	**- 3.9% , 10.9 %**

PINTOS

Components: Death

	Hemoglobin Threshold		
	Low	High	
	n = 212	n = 219	
Death	48	45	$p_\alpha = 0.052$
	22.6%	20.6%	

Treatment Effect		**95% confidence limits**
Odds Ratio (High/Low)	0.85	0.45 , 1.06
Risk Difference (Low-High)	1.2%	-3.9% , 10.9%

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PINTOS

Components: Cerebral Palsy

	Hemoglobin Threshold		
	Low	**High**	
	n = 163	**n = 172**	
Cerebral Palsy	**11**	**9**	$p_\alpha = 0.055$
	6.7%	**5.2%**	

Treatment Effect		**95% confidence limits**
Odds Ratio (High/Low)	**0.76**	**0.31 , 1.89**
Risk Difference (Low-High)	**0.5%**	**- 4.4% , 5.4%**

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PINTOS

Components: Cognitive Delay

	Hemoglobin Threshold		
	Low	**High**	
	n = 156	**n = 165**	
Cognitive Delay	**38**	**29**	$p_{\alpha} = 0.060$
	24.4%	**17.6%**	

Treatment Effect		**95% confidence limits**
Odds Ratio (High/Low)	**0.57**	**0.32 , 1.02**
Risk Difference (Low-High)	**1.2%**	**-1.0% , 16.4%**

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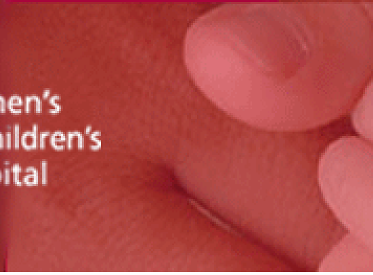

PINTOS

Size at 18 months

	Hemoglobin Threshold			
	Low	**High**	**Adj diff (95% cl)**	**p_α**
Weight kg	10.35 (1.78)	10.35 (1.87)	0.01 (-0.036 , 0.38)	0.96
Length cm	79.7 (4.0)	79.3 (4.3)	0.4 (-0.6 , 1.4)	0.46
Head Circ cm	47.2 (1.8)	46.8 (2.3)	0.4 (-0.1 , 0.8)	0.11

Means (sd)

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PINTOS

Final Hematology

Hemoglobin Threshold

	Low	High	pα
Hemoglobin g/l	124.9 (10.6)	125.7 (11.1)	0.88
Hematocrit	0.37 (0.036)	0.37 (0.031)	0.93
MCHC	321 (72)	315 (81)	0.60
MCV	88.6 (12.3)	89.4 (14.1)	0.61
Ferritin	27,7 (23.5)	28.0 (23.8)	0.90

PINTOS

Cognitive delay: Post hoc analysis

- Cognitive delay is continuous
- 2SD are mostly used to describe moderate – severe impairment – likely non independent survival.
- A 1SD cut-point used to dichotomize the mental developmental index led to rates of “cognitive delay” of
  - 70/156 (44.9%) in the low group and
  - 56/165 (33.9%) in the high group
  - adjusted OR=1.81, 95% confidence interval 1.12 to 2.93, p=0.016.

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Bell Trial

- Multicentre
- Inclusion
    - birth weight 500 – 1300 grams
- Exclusion
    - Alloimmune haemolytic disease
    - CHD including significant PDA
    - Imminent death
    - Major abnormality
    - Greater than 2 transfusions before enrolment
- Randomisation (fixed block), stratified by weight
    - 500 – 750
    - 751 – 1000
    - 1001 – 1300

Bell Trial

- Transfusion algorithm based on need for respiratory support
- Transfusion volume fixed (15mls/kg)
- Additional transfusion at discretion of physician, CCF, h’age, refractory apneoa, surgeon, anaesthetist.
- No EPO

Bell Trial Outcomes

- Transfusion and donor number
- Survival
- Morbidities
    - BPD
    - IVH / PVL – note only 52 of 100 had late scan
- Lab measurements at 6 weeks

Bell Trial
Demographics

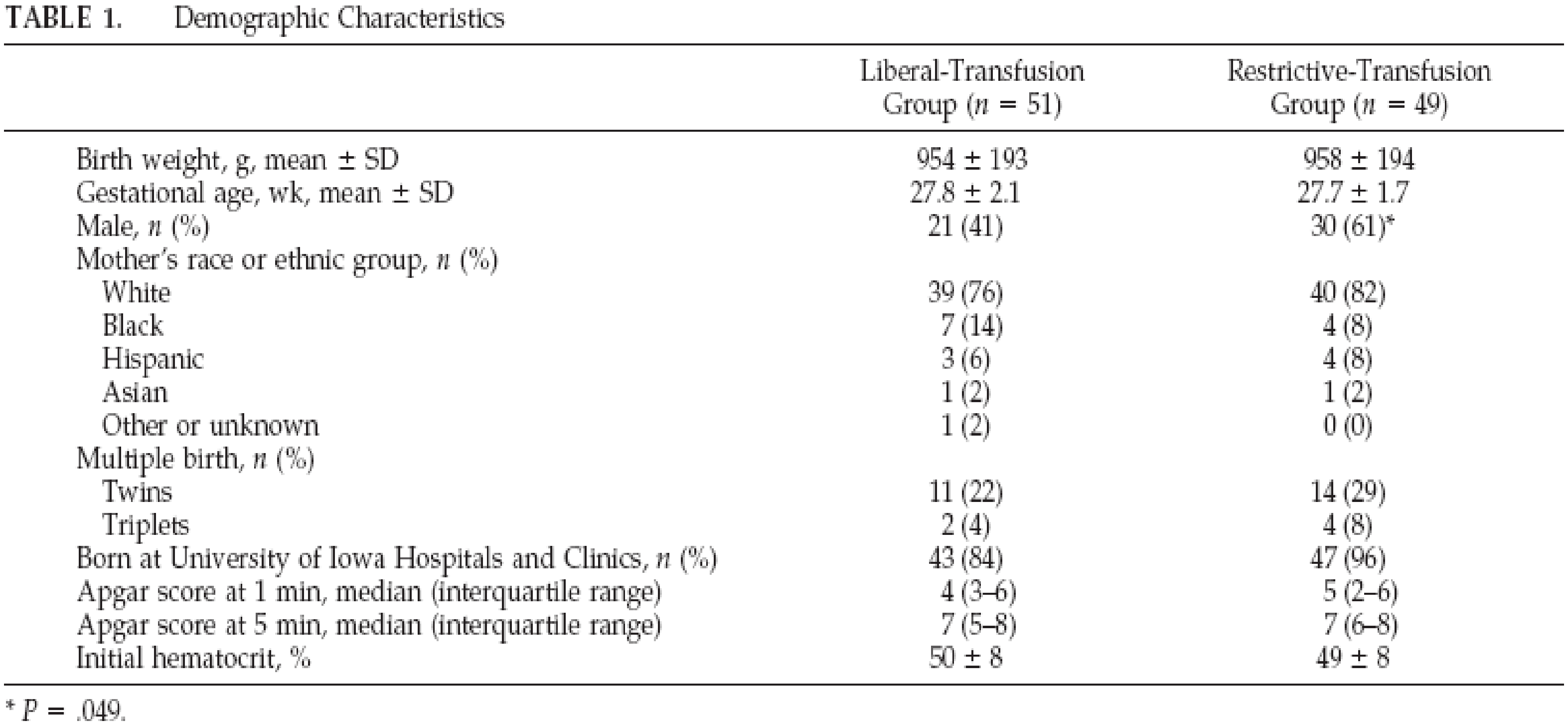

TABLE 1. Demographic Characteristics

	Liberal-Transfusion Group (*n* = 51)	Restrictive-Transfusion Group (*n* = 49)
Birth weight, g, mean ± SD	954 ± 193	958 ± 194
Gestational age, wk, mean ± SD	27.8 ± 2.1	27.7 ± 1.7
Male, *n* (%)	21 (41)	30 (61)*
Mother's race or ethnic group, *n* (%)		
White	39 (76)	40 (82)
Black	7 (14)	4 (8)
Hispanic	3 (6)	4 (8)
Asian	1 (2)	1 (2)
Other or unknown	1 (2)	0 (0)
Multiple birth, *n* (%)		
Twins	11 (22)	14 (29)
Triplets	2 (4)	4 (8)
Born at University of Iowa Hospitals and Clinics, *n* (%)	43 (84)	47 (96)
Apgar score at 1 min, median (interquartile range)	4 (3–6)	5 (2–6)
Apgar score at 5 min, median (interquartile range)	7 (5–8)	7 (6–8)
Initial hematocrit, %	50 ± 8	49 ± 8

* *P* = .049.

Bell Trial

Transfusion algorithm

	LIBERAL HCT (Hb g/L)	RESTRICTIVE HCT (Hb g/L)
ENDOTRACHEAL INTUBATION	**< 46 (150)**	**< 34 (112)**
NASAL CPAP OR SUPPLEMENTAL OXYGEN	**> 38 (125)**	**> 28 (92)**
NO SUPPORT	**> 30 (99)**	**> 22 (73)**

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Bell Trial

Outcomes

	Liberal	Restrictive
Survival (%)	98	96
Severe adverse brain event (%)	12	0

(Note, not all had late scans)

No difference in LOV, LOS or in hospital growth

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Bell Trial

Transfusions

	Liberal	Restrictive
No transfusion (%)	12	10
Nº of transfusions	4 (2-8)	2 (2-5)
Nº of donor exposures	2 (1-4)	2 (1-2)

Summary

- Both Bell and PINT trials favour a liberal transfusion strategy in very premature babies without a difference in donor exposure. Neither study provides certainty.
- Both trials have a “brain effect”.

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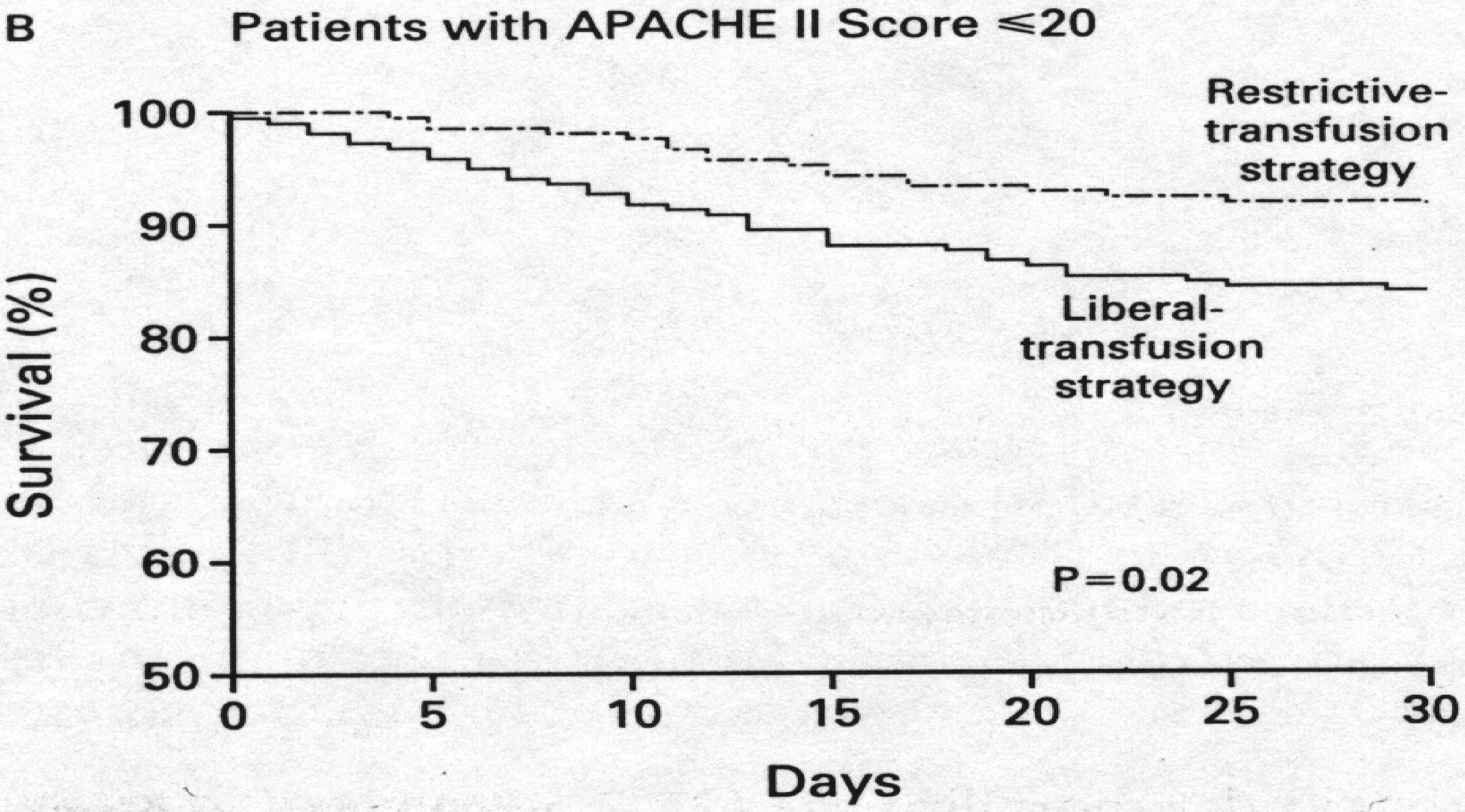
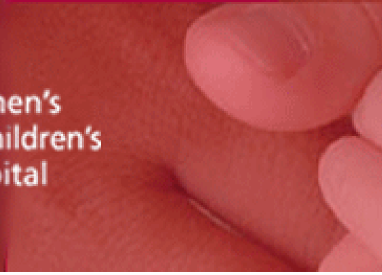
TRICC Trial: Transfusion Requirements in Critical Care

Hebert PC Et Al: NEJM; 1999



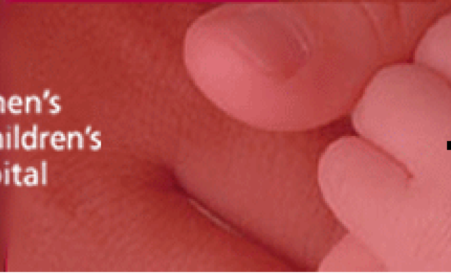
Interpretation

- What does this mean?
    - Trials in adults and children measure death however we are also interested in survival without impairment.
- How might a premature baby be different from adults and children in ICU?
- Early brain injury
- Oxygen delivery and the anaemic critical threshold
- Blood



Early Brain Injury

- Early brain injury is common, particularly in VPN infants and leads to life long impairment.
- ANZNN 2004 IVH GIII or greater ~9%
- PINT data (451 ELBW newborns) – 25% have a significant brain injury including IVH (> GII), PVL, VM at hospital discharge and at 2 years approx 40% have either died or developed one of the primary composite outcomes (cognitive delay, CP, blind, deaf).



Tissue dysoxia

- Insufficient oxygen to maintain mitochondrial respiration
- Oxygen transfer dependent on diffusion
  - oxygen gradient between the blood and cell becomes important.
  - Microcirculation
- Gradient different in different organs though likely to be shallowest in the brain (high metabolic rate).

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Early Brain Injury

- Early intraventricular haemorrhage is associated with poor cardiac output in very low birth weight infants (Kluckow 2000a).
- Poor cardiac output is associated with both death and / or significant IVH (Kluckow 2000b, Holberton 2007), however this is not universal.
- Well, ventilated VLBW newborns increase FOE in response to an alteration in paO_2 / SaO_2 target, so that oxygen delivery is no different (Schulze). FOE is the arterio-venous saturation difference expressed as a percentage.
- As cardiac output increases over the first days of life there is a simultaneous fall in cerebral fractional oxygen extraction (FOE) (Kissack 2004a).
- Infants with elevated cerebral FOE are at greatest risk of an hypoxic-ischaemic injury in the form of haemorrhagic parenchymal infarction – Grade IV IVH (Kissack 2004b).

Flow

Oxygen delivery and oxygen delivery and consumption

- Oxygen delivery is determined by
  - Cardiac output (CO = SV x HR)
  - Hb concentration
  - Hb saturation
- Final tissue oxygen extraction is dependent on the oxygen diffusion gradient, the diffusion distance and cellular uptake mechanisms.
- Driving pressure partly determined by Hb affinity. Increasing p50 will cause a leftward shift in critical (anaerobic) threshold and potentially alter oxygen extraction.

Supply dependence:

A pathologic state defined by supply limited / restricted oxygen consumption.

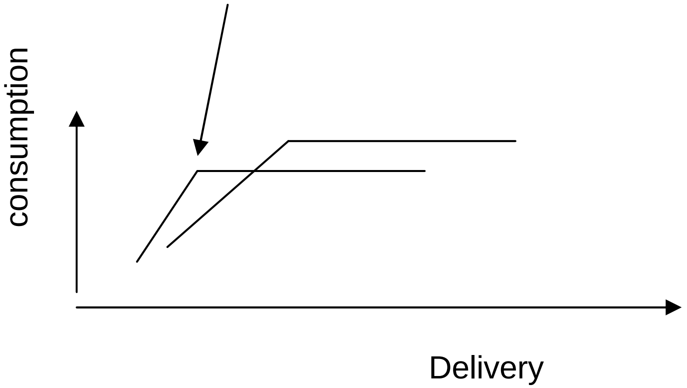
Predicts poor outcome in adults with ARDS

Recognised from;

(i) the slope of the VO2/DO2 curve (>10%)

(ii) activation of the anaerobic pathway with resultant lactic acidosis.

Critical threshold



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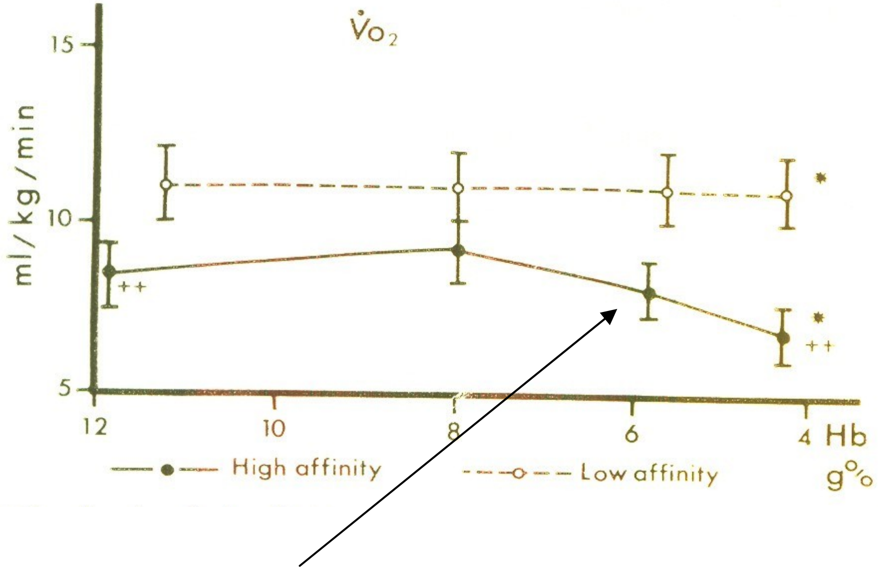
Gradient
Hb Affinity

Lamb model of exchange transfusion.
Oxygen consumption of newborn lambs with high versus low affinity red cells in relation to progressive anaemia.

Random allocation to control or isovolaemic exchange with maternal PRBC (low affinity).
During severe anaemia, blood with low affinity is more capable of adequately oxygenating tissues.
Van Ameringen etal *Pediatr Res* 1981



Supply limited

Gradient Hb Affinity

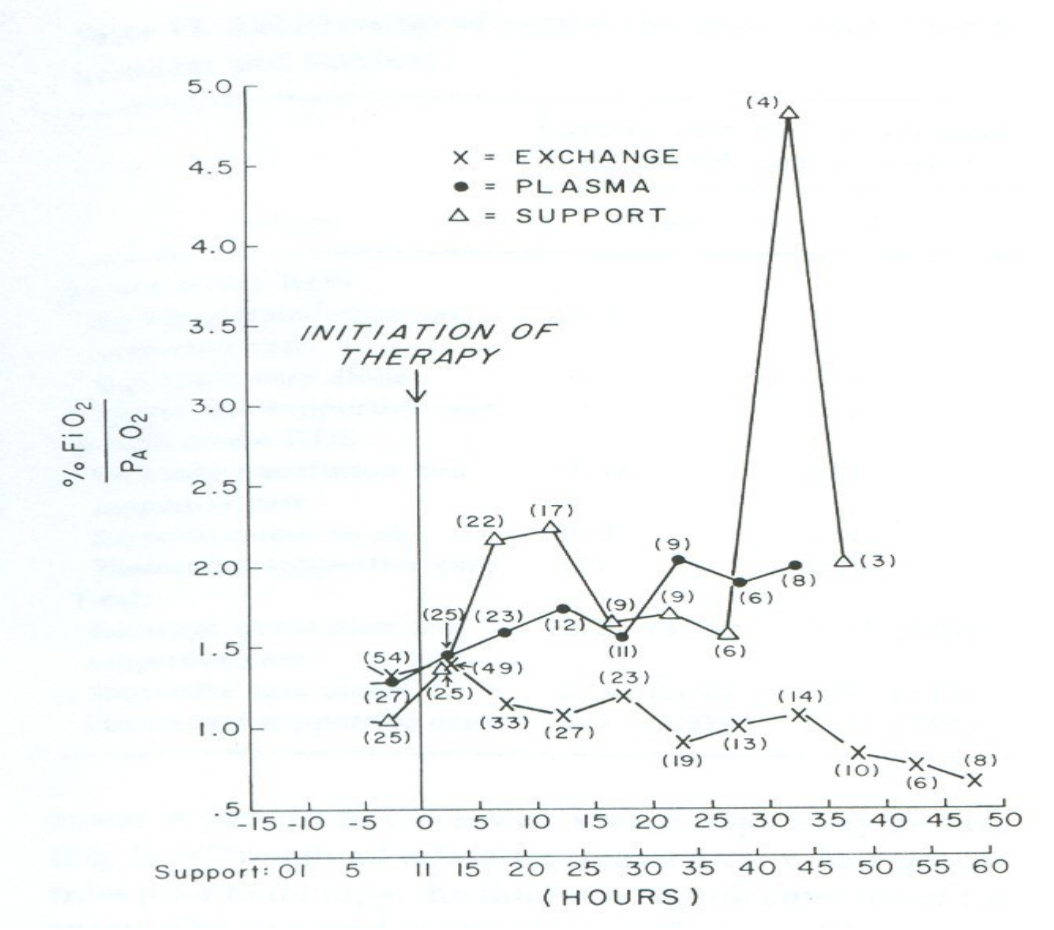
- In rats, allosteric modification of Hb that results in a reduction in Hb affinity increases fractional oxygen extraction and reduces lactate production (Eichelbronner 2002).
- Despite improved conditions, oxygen delivery was inadequate to allow complete compensation – no change in the anaemic critical threshold however in further experiments this alteration resulted in a reduction in neuronal injury from incomplete global ischaemia in rats.
- Is this similar to newborns?

Gradient Transfusion in LBW infants

The relationship of therapy to changes in the ratio of FiO_2/ PaO_2.

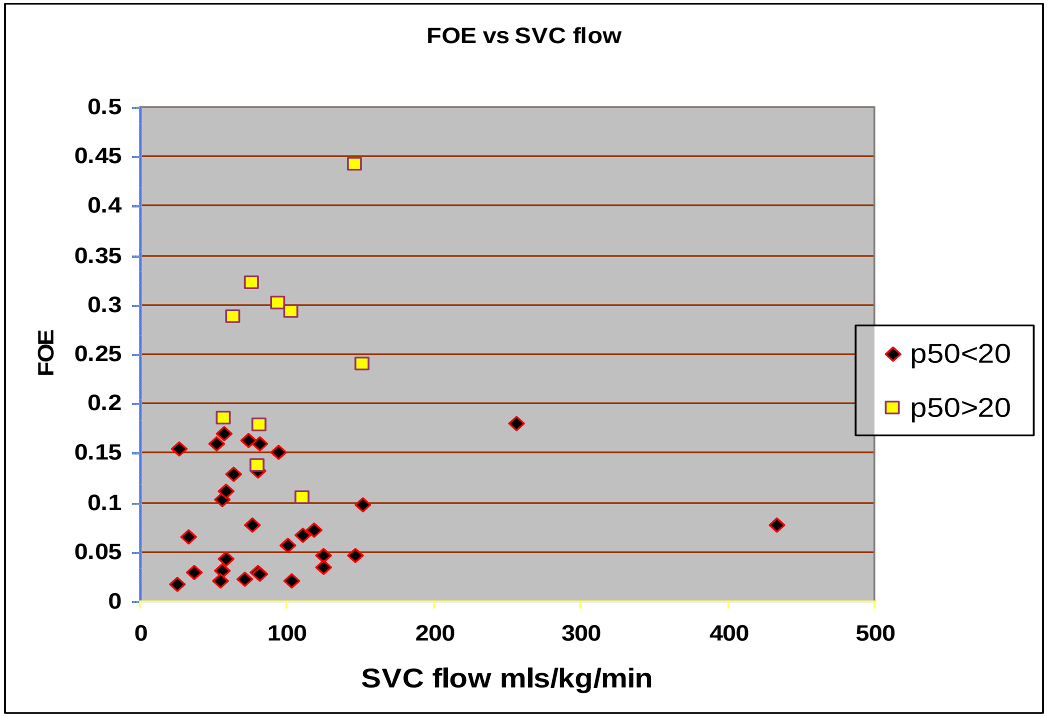
Ratio is significantly lower in exchange transfusion group infants by 5 hours

Gottuso etal *J Pediatr* 1976



Gradient Oxygen Extraction vs Cardiac Output separated by Hb affinity

Lower body FOE (arterial – IVC saturation) versus cardiac output (SVC flow) for infants in the SCENT I study (Hart etal 2004). Remember that blood in the IVC has higher saturation as it receive blood from lower extraction organs.



Regardless of SVC flow, infants with high HOA (low p50) had on average lower FOE (p=0.004, CI 2.6, 12.9). However low SVC flow was not confined to infants with high HOA *Hart 2004.*

Bring this together

- Poor CO in the first hours of life is associated with death and / or brain injury though this is not universal (Kluckow, Holberton).
- Poor CO is associated with high cerebral FOE (Kissack).
- Imbalance of oxygen delivery and consumption (supply dependence) is predictive of in hospital mortality in adults with ARDS.
- Does the same mechanism apply in ELBW newborns?

- Transfusion with adult PRBC will
  - possibly increase CO (preload) without increasing oxygen consumption.
  - Increase oxygen carrying capacity
  - Increase the oxygen pressure gradient by altering HBOA
- Given that the brain has a high metabolic rate and shallow gradient the anaemic critical threshold may be high.
- By altering flow and gradient, transfusion may favourably alter anaemic critical threshold.

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Conclusion

- No good evidence to support transfusion for weight gain, apnoea requiring ventilation or dependency on supplemental oxygen.
- Precise timing unclear.
- Newborn developing brain may be different (anaemic critical threshold).
- Microcirculation and viscosity.

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Frame shift in thinking

- Away from the concept that all blood transfusion is harmful and restrictive transfusion strategies should seek to not worsen important outcomes.
- Towards the concept that targeted blood transfusion is an important positive intervention that may potentially improve early outcome through its effect on imbalance between oxygen delivery and consumption that may contribute to early brain injury in very premature newborns.

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Conclusion

- Consider early packed red cell transfusion in the setting of poor circulation (define) to improve oxygen delivery and potentially reduce the risk of early brain injury in very premature newborns.

- Use liberal PINT transfusion algorithm / Bell transfusion thresholds to direct transfusion of well growing newborns with consideration of efficient use of satellite packs.

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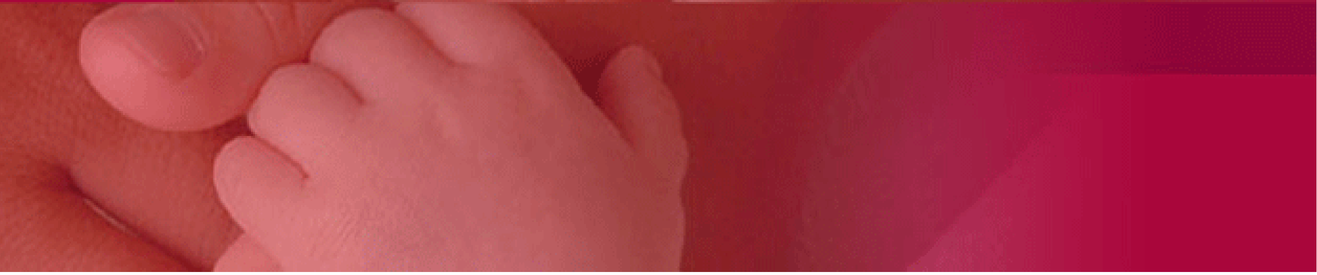

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