Adjunctive Therapies to Neonatal Ventilation

Sunil Sinha

Professor of Paediatrics and Neonatal Medicine

The James Cook University Hospital

University of Durham

United Kingdom

Neonatal Lung Diseases and Adjunctive Therapeutic Agents Used

R.D.S.
- Surfactant
- Oxygen
- Methylxanthines
- Loop Diuretics

B.P.D.
- Oxygen
- Methylxanthines
- Corticosteroids (Early)
- Vitamin A and E
- iNO
- Diuretics
- Superoxide Dismutase
- Inositol
- Bronchodilators & Cromolyn
- Erythromycin

P.P.H.N.
- Oxygen
- iNO
- Inotropic agents

Meconium Aspiration Syndrome
- Oxygen
- Surfactant
- Corticosteroids (Late)

Transient Tachypnea of Newborn
- Oxygen
- Diuretics

Outline

Adjunctive therapies to mitigate the course of neonatal lung disease

- Surfactant
- Methylxanthines (Caffeine)
- Corticosteroids
- Inhaled Nitric Oxide
- Vitamin A
- Diuretics
- Inositol

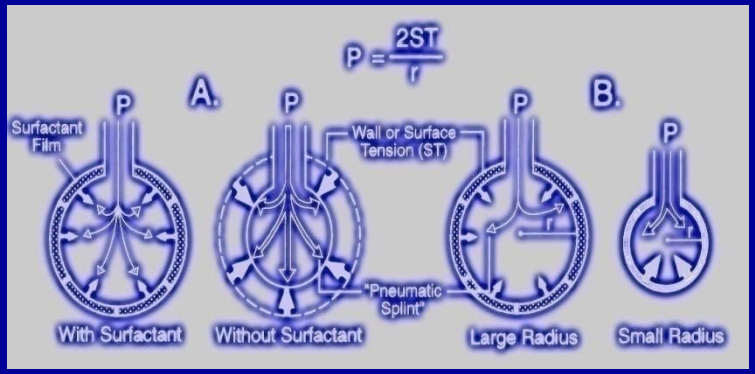
Other Adjunctive therapies

- Pain control
- Sedation
- Fluid bolus

Surfactant Therapy

- One of the most well-studied therapies in neonatology

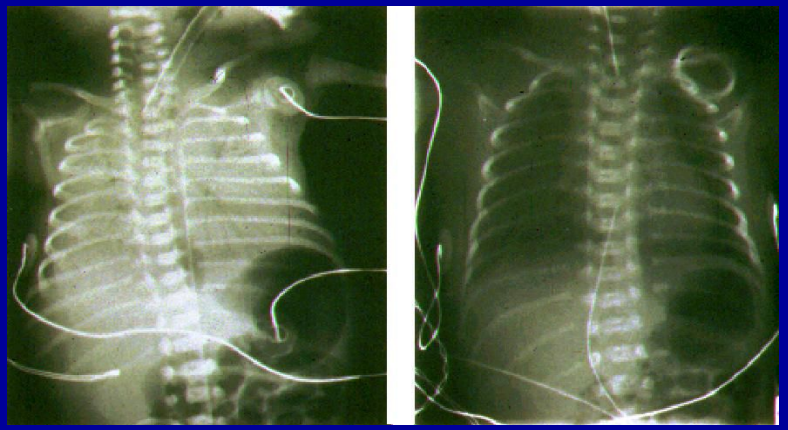
- Good understanding of mechanisms of action



Limitations:

- Wide variations in
  - phospholipid concentrations
  - phospholipid per dose

- Difference practice/population
  - Early use of PEEP/CPAP
  - antenatal steroid use



Surfactant Therapy for RDS

Treatment

- Synthetic surfactants v Control (6 trials)
- Natural surfactants v Control (13 trials)

Prophylactic

- Synthetic surfactants v Control (7 trials)
- Natural surfactants v Control (8 trials)

SIGNIFICANTLY REDUCES THE RISK OF:

- Pneumothorax
- Death
- Death or BPD (28 d)

Cochrane Database of Systematic Reviews 2009

Strategies of Surfactant Therapy

Prophylactic v Selective Use (8 trials)

Outcome	Studies (n)	Participants (n)	RR (95% CI)
Pneumothorax	6	2515	**0.62 (0.42, 0.89)**
Neonatal Mortality	7	2613	**0.61 (0.48, 0.77)**
Mortality prior d/c	5	1207	**0.75 (0.59, 0.96)**
BPD (28 d)	8	2816	0.96 (0.82, 1.12)
Death or BPD	8	2816	**0.84 (0.76, 0.95)**

Cochrane Database of Systematic Reviews 2009

Strategies of Surfactant Therapy

Early surfactant and extubation v Selective (rescue) surfactant and ventilation (6 trials)

Outcomes	Studies (n)	Participants (n)	RR (95% CI)
Need for ventilation	6	664	**0.67 (0.57, 0.79)**
BPD (28 d) **-FiO2 ≤ 0.45 at entry** -FiO2 > 0.45 at entry	4 3 1	262 194 68	**0.51 (0.26, 0.99)** **0.43 (0.20, 0.92)** 0.94 (0.20, 4.35)
Air leak syndromes	6	664	**0.52 (0.28, 0.96)**
Neonatal Mortality	6	396	0.52 (0.17, 1.56)

Cochrane Database of Systematic Reviews 2009

Strategies of Surfactant Therapy

Multiple v Single dose surfactant for severe RDS

Outcome	Studies (n)	Participants (n)	RR (95% CI)
Pneumothorax	3	1220	**0.70 (0.52, 0.94)**
BPD	3	1220	1.13 (0.83, 1.54)
Mortality	3	1220	**0.59 (0.44, 0.78)**
Death or BPD	2	1170	0.83 (0.68, 1.01)

Cochrane Database of Systematic Reviews 2009

Natural and Synthetic Surfactants

Natural v Synthetic Surfactants for RDS

Outcome	Study (n)	Participants (n)	RR (95% CI)
Pneumothorax	9	4550	**0.63 (0.53, 0.75)**
Mortality	10	4588	**0.86 (0.76, 0.98)**
BPD (36 weeks)	5	3179	1.01 (0.90, 1.12)
Death or BPD	4	2565	0.98 (0.90, 1.06)

Protein containing synthetic surfactants v natural

Outcome	Study (n)	Participants (n)	RR (95% CI)
Mortality	2	1028	0.79 (0.61, 1.02)
BPD (36 weeks)	2	1028	0.99 (0.84, 1.18)
Death or BPD	2	1028	0.96 (0.82, 1.12)

Cochrane Database of Systematic Reviews 2009

Surfactant Therapy in Neonatal Ventilation

- **Surfactant administration (prophylactic as well as rescue) improves important clinical outcomes**

- **Prophylactic surfactant (for "high risk" infants) or Early replacement therapy (for infants with features of RDS) improves clinical outcomes (??)**

RCTs comparing CPAP with mechanical ventilation in preterm infants

Trial	GA (wks)	N	Comparison	Death or BPD at 36 wks
Vermont Oxford 2011	26-29	648	Surfactant & MV vs Insure vs early CPAP with intubation & surfactant	No difference
CURPAP 2010	25-28	208	Prophylactic Surfactant & CPAP vs nCPAP & Selective Surfactant	No difference No difference (Need for MV in first 5 days)
SUPPORT 2010	24-28	1316	nCPAP vs surfactant & MV	No difference
COIN 2008	25-29	610	nCPAP vs surfactant & MV	No difference

Surfactant Therapy in Neonatal Ventilation

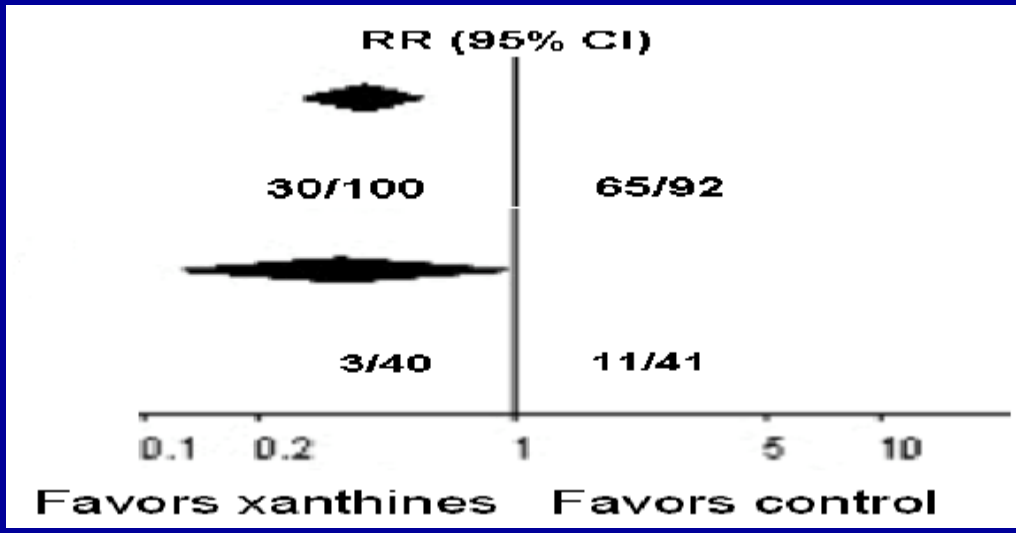
- Surfactant administration (prophylactic as well as rescue) improves important clinical outcomes
- Prophylactic surfactant (for "high risk" infants) or Early replacement therapy (for infants with features of RDS) improves clinical outcomes (??)
- Multiple doses, compared to single dose surfactant reduces the risk of pneumothorax and mortality in infants with severe RDS
- Natural surfactants are more desirable choices compared to currently available synthetic surfactants
- Two recent trials of Protein containing synthetic surfactants showed similar efficacy compared to natural surfactants

Methylxanthines: FACTS

Methylxanthines reduce

Apnea of prematurity

Mechanical ventilation



- **Safety of xanthine therapy is uncertain**

Henderson-Smart DJ et al. In: The Cochrane Library, Issue 3, 2001. Oxford: Update Software

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 8, 2007 VOL. 357 NO. 19

Long-Term Effects of Caffeine Therapy for Apnea of Prematurity

Barbara Schmidt, M.D., Robin S. Roberts, M.Sc., Peter Davis, M.D., Lex W. Doyle, M.D., Keith J. Barrington, M.D., Arne Ohlsson, M.D., Alfonso Solimano, M.D., and Win Tin, M.D., for the Caffeine for Apnea of Prematurity Trial Group*

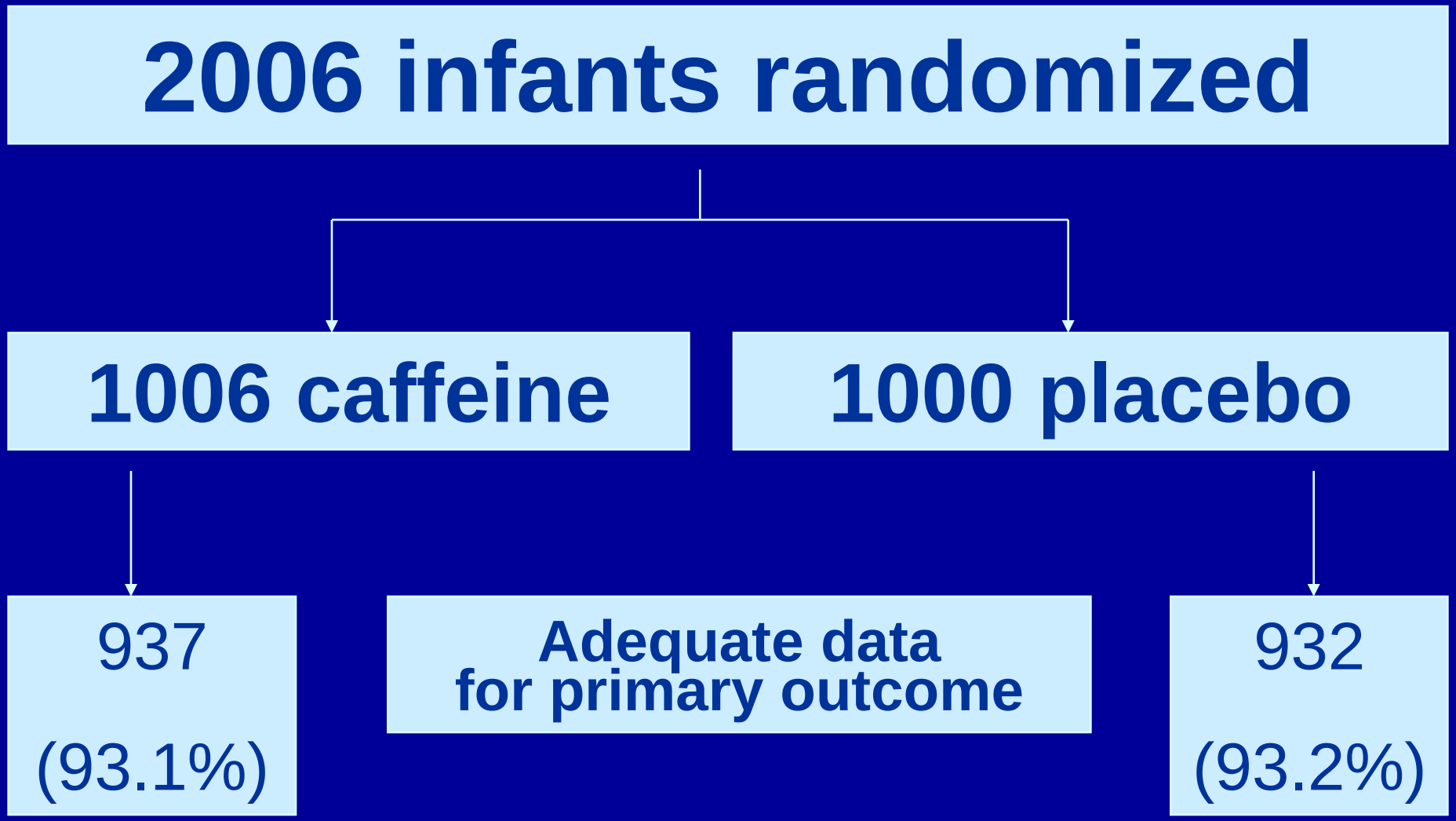
P Among very-low-birth-weight infants who are at risk of apnea of prematurity,

I does the use of caffeine

C compared with placebo

O increase the risk of death or neurosensory disability

T at a corrected age of 18 months


2006 infants randomized
1006 caffeine
1000 placebo
937
(93.1%)
Adequate data
for primary outcome
932
(93.2%)

The CAP Trial
Outcomes at Neonatal Discharge

	Caffeine	Placebo	OR (95% CI)
B.P.D	36%	47%	0.6 (0.5-0.8)
P.D.A.	30%	40%	0.6 (0.5-0.8)
P.D.A. Ligation	5%	12%	0.3 (0.2-0.5)
Death	5.2%	5.5%	0.9 (0.6-1.4)
N.E.C.	6.2%	6.7%	0.9 (0.6-1.3)
Brain Injuries	13%	14%	0.9 (0.7-1.2)

Schmidt et al NEJM 2006

The CAP Trial: Primary Outcome

Caffeine	Placebo
377 of 937 40%	431 of 932 46%

OR = 0.77 95% CI 0.64-0.93 p = 0.008*

Schmidt et al NEJM 2007

CAP Trial: Benefits may vary in subgroups

RESULTS:

- **Size and direction of Caffeine Effect differed depending on PPV at randomisation (P=0.03)**

- ETT support: OR (95% CL); 0.73 (0.57 – 0.94)
- Non-invasive support: OR (95% CL); 0.73 (0.52 – 1.03)
- No resp support : OR (95% CL); 1.32 (0.81 – 2.14)

- **PMA at time of discontinuing PPV was shorter with early treatment (started ≤ 3 days)**

Davis et al, J Pediatr 2010

Postnatal Corticosteroids: Early Use≤7d

Short Term

28 RCTs, n=3740

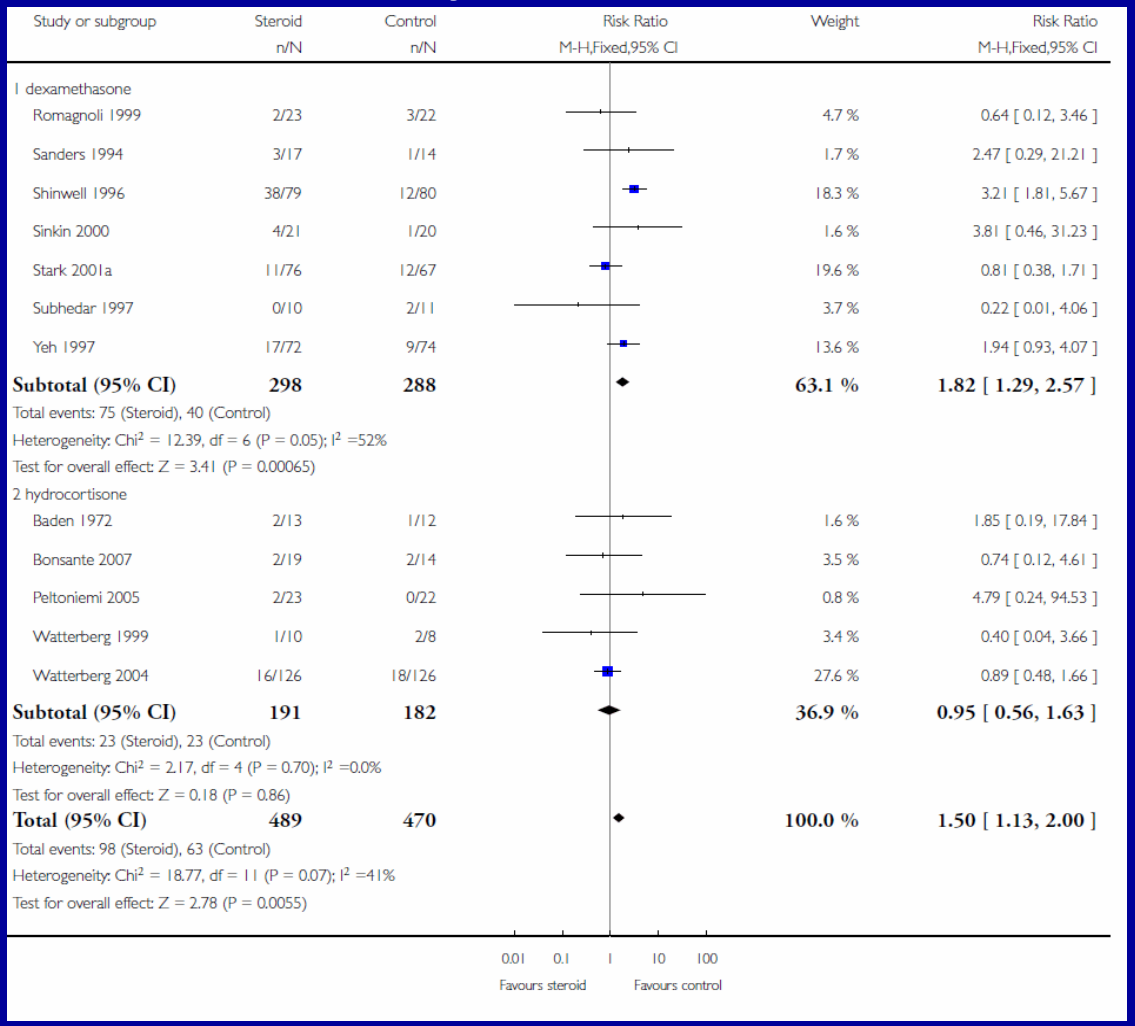
- Earlier extubation
- Decreased risk of
  - CLD, PDA
- Increased risk of
  - GI bleeding, perforation
  - Hypertension
  - Hyperglycaemia
  - Growth Failure

Long Term

12 RCTs

- Increased risk of adverse neurodevelopmental outcome

Outcome: Cerebral Palsy in Survivors assessed



Halliday et al. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD001146

Postnatal Corticosteroids: Late Use >7d

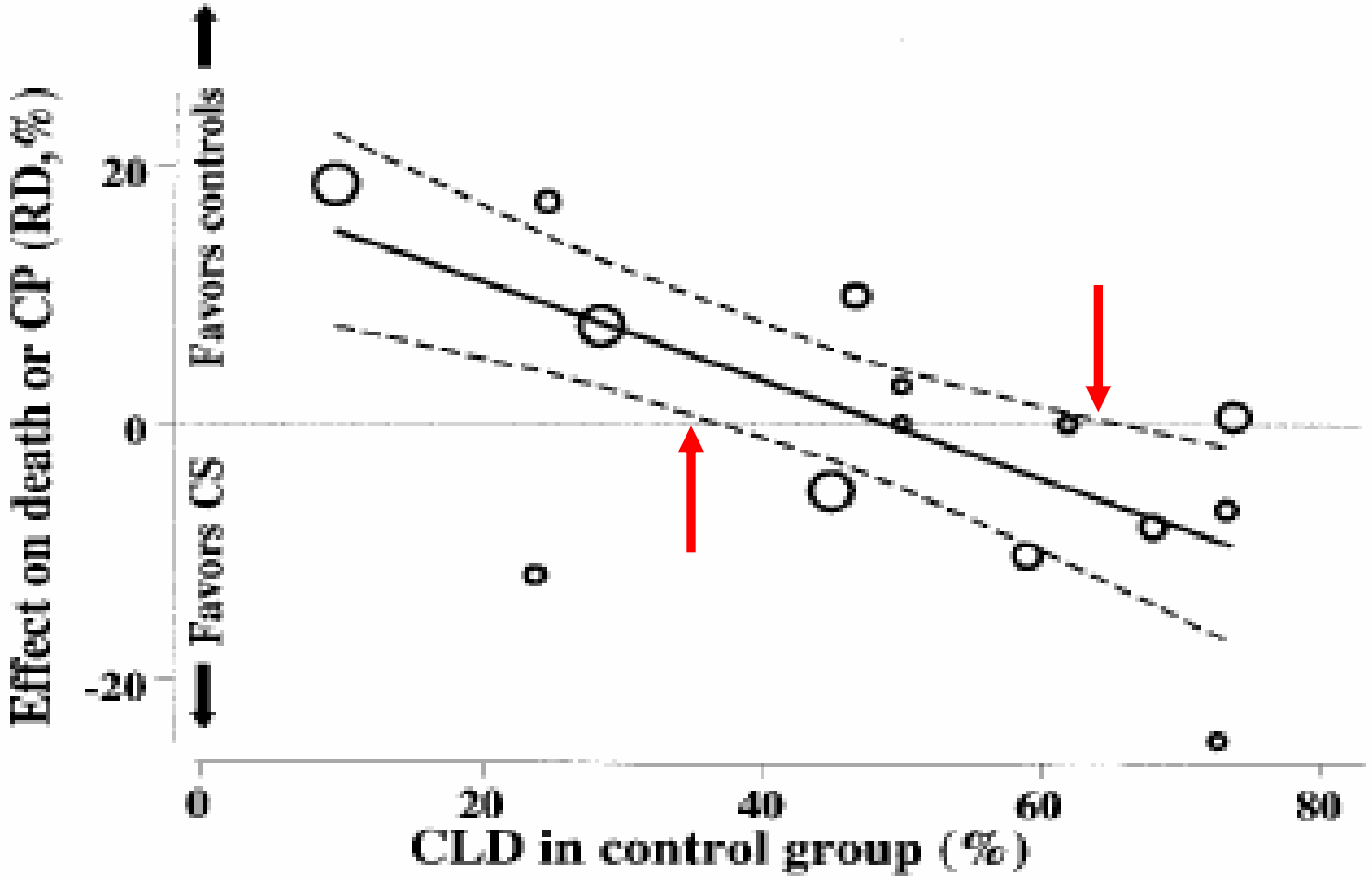
- **19 RCTs, n= 1345**
- **No effect on mortality**
- **Decreased risk of CLD**
- **Increased risk of hypertension, hyperglycaemia, GI bleeding**
- **No increase in neurodisability (limited follow up data)**

Authors conclusion:

- Given the evidence of both benefits and harms of treatment, and the limitations of the evidence at present, it appears prudent to reserve the use of late corticosteroids to infants who cannot be weaned from mechanical ventilation and to minimise the dose and duration of any course of treatment.

Halliday et al. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001145

Effect Modification by Risk for CLD



Doyle et al. Pediatrics 2007

Inhaled Steroid in preventing BPD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 15, 2015 VOL. 373 NO. 16

Early Inhaled Budesonide for the Prevention of Bronchopulmonary Dysplasia

Dirk Bassler, M.D., Richard Plavka, M.D., Ph.D., Eric S. Shinwell, M.D., Mikko Hallman, M.D., Ph.D., Pierre-Henri Jarreau, M.D., Ph.D., Virgilio Carnielli, M.D., Johannes N. Van den Anker, M.D., Ph.D., Christoph Meisner, Ph.D., Corinna Engel, Ph.D., Matthias Schwab, M.D., Henry L. Halliday, M.D., and Christian F. Poets, M.D., for the NEUROSIS Trial Group*

- N=863, Gest: 23 – 27 weeks
- Randomised within 24 h
- Inhaled Budesonide or Placebo
- Till no oxygen and positive pressure needed or till 32 weeks

Table 3. Primary Outcome.*

Outcome	Budesonide Group	Placebo Group	Unstratified Relative Risk (95% CI)	Stratified Relative Risk (95% CI)†	P Value	Odds Ratio (95% CI)‡
	no./total no. (%)					
Composite primary outcome	175/437 (40.0)	194/419 (46.3)	0.86 (0.74–1.00)	0.86 (0.75–1.00)	0.05	0.71 (0.53–0.97)
Components of primary outcome						
Death	74/437 (16.9)	57/419 (13.6)	1.24 (0.90–1.71)	1.24 (0.91–1.69)	0.17	1.39 (0.89–2.18)
Survival with bronchopulmonary dysplasia§	101/363 (27.8)	138/363 (38.0)	0.73 (0.59–0.90)	0.74 (0.60–0.91)	0.004	0.61 (0.44–0.85)

Inhaled Nitric Oxide

iNO for Pulmonary hypertension

- Potent vasodilator, with a very short half life (2-4 s)
- Selective pulmonary vasodilation without lowering systemic blood pressure

iNO for Preventing BPD (animal studies)

- Reduces lung inflammation
- Improves surfactant production
- Promotes lung growth

iNO in preterm infants: Death or BPD

Early "rescue" treatment:

- 8 RCTs, n=958
- RR 0.94 (95% CI 0.87, 1.01)

"Routine" use of iNO in infants with pulmonary disease:

- 3 RCTs, n=1800
- RR 0.93 (95%CI 0.86, 1.01)

Later treatment with iNO based on the risk of BPD:

- 2 RCTs, n=624
- RR 0.9 (95%CI 0.80, 1.02)

The Cochrane Library 2009, Issue 1

NIH Consensus Development Conference Statement: Inhaled Nitric Oxide Therapy for Premature Infants

CONCLUSIONS: (Three out of five conclusion points)

- **Available evidence does NOT support use of iNO in early-routine, early-rescue, or late-rescue in preterm <34 weeks' gestation**

- **There are rare clinical situations (pulmonary hypertension, pulmonary hypoplasia (inadequately studied) in which iNO may have benefit in infants <34 weeks' gestation**

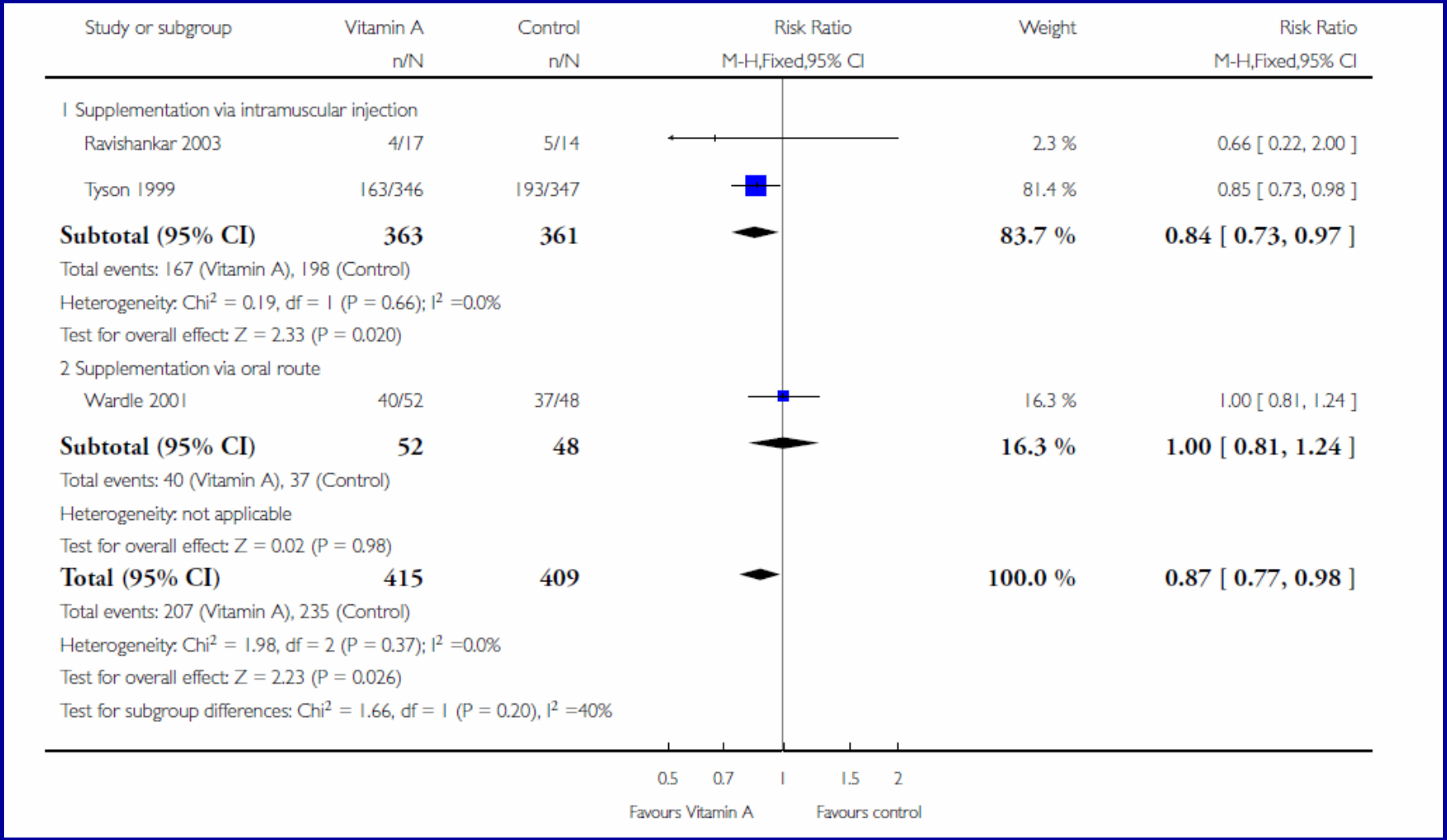
- **On the basis of assessment of currently available data, hospitals, clinicians, and the pharmaceutical industry should avoid marketing iNO for premature infants of <34 weeks' gestation**

Pediatrics 2011; 127: 363-369

Vitamin A

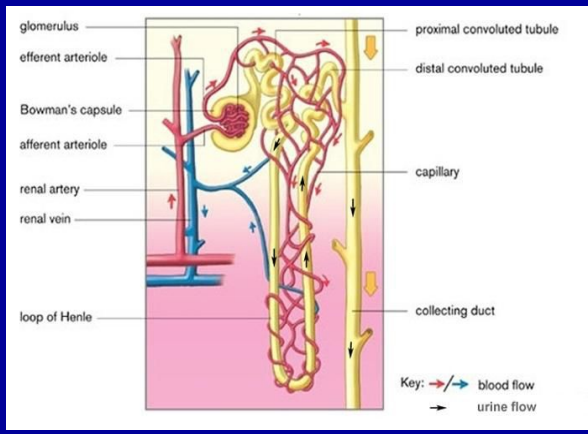
- Involves in cell growth and multiplication
- Maintains integrity of epithelial cells of respiratory tract
- Anti oxidant property in dietary precursors of vitamin A
- Relatively deficient in preterm infants
- Deficiency was shown to be associated with BPD

Vitamin A and BPD (Oxygen use at 36 weeks PMA)



Cochrane Database of Systematic Reviews 2011

Diuretic Therapy



Diuretics in R.D.S.

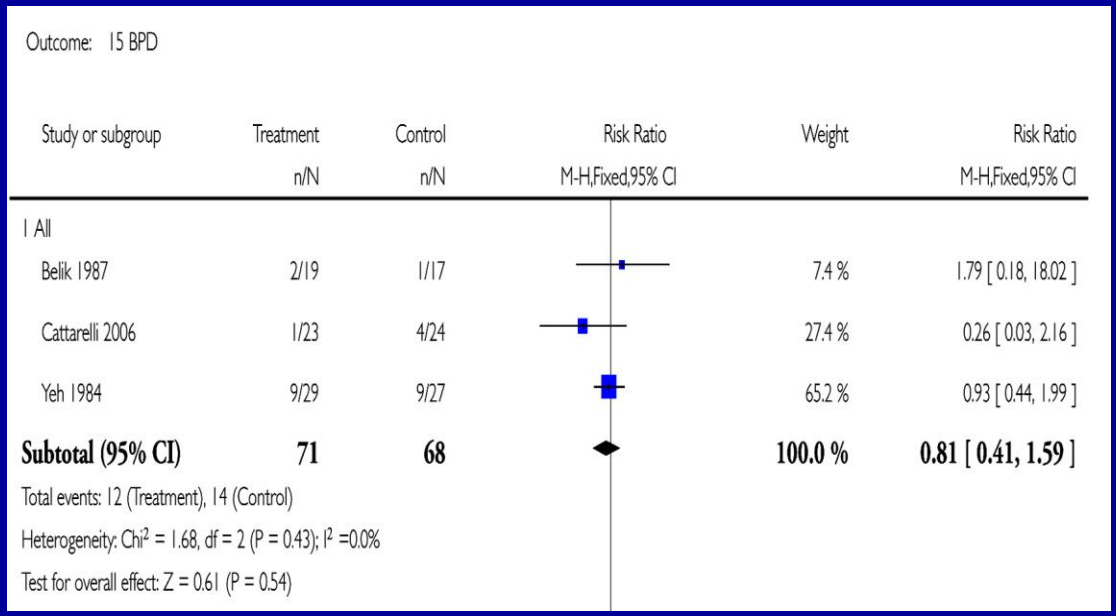
- Commonly used
  - Loop diuretics (furosemide)
- Reasons
  - lung oedema, PDA, renal insufficiency
- Benefits
  - improvement in lung function

- Risks
  - electrolyte loss
  - PDA (early use)
  - ototoxicty
  - renal calcium deposition (prolonged use)

Diuretics in R.D.S.

Systematic Review[1]
(7 Trials)

- **No effect on :**
  mortality, CLD
  duration of ventilation
  duration of O_2 therapy
  length of hospitalisation



- **before the era of antenatal steroid and surfactant therapies**
- **no evidence to support the routine use of furosemide/other diuretics in preterm infants with RDS**

1. ***Brion LP, Soll RF. Diuretics for respiratory distress syndrome in preterm infants. Cochrane Database of Systematic Reviews 2008, Issue 1.***

Diuretics in B.P.D.

Thiazide diuretic ± spironolactone as well as Single dose aerosolized furosemide

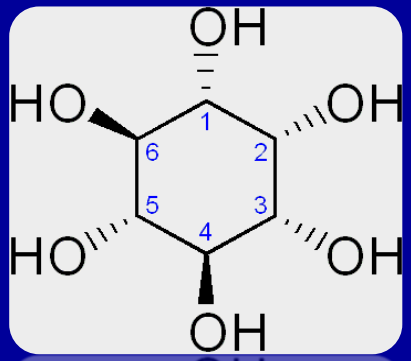
- **Transient improvement in pulmonary mechanics in preterm infants (3 weeks) with CLD**

- **No evidence of benefit on clinically important outcomes (mortality, duration of ventilation and O_2 dependency, hospitalization and long term outcomes)**

- **NO evidence to support "routine" use of diuretics**

Cochrane Database of Systematic Reviews 2008, Issue 1.

Inositol (Myo-inositol)



- Essential nutrient (six carbon sugar alcohol)
- May play a critical role in early fetal and neonatal life
- High levels potentiate glucocorticoid induces acceleration of surfactant production
- Serum levels rise after birth in breast fed infants but fall in infants who receive TPN
- Prophylactic nutritional supplementation can be used by intravenous or oral route to reduce:

  - severity of RDS

  - severity of ROP

Inositol

Systematic Review (3 RCTs)

Outcome	Study (n)	Participants (n)	RR (95% CI)
Mortality	2	295	**0.48 (0.28, 0.80)**
BPD	3	336	0.68 (0.45, 1.02)
Death or BPD	2	295	**0.56 (0.42, 0.77)**
Severe ROP	2	262	**0.09 (0.01, 0.67)**
IVH (grades 3/4)	2	307	**0.55 (0.32, 0.95)**

- **No data on long term outcomes**

Conclusions:

- **Inositol supplementation results in significant reductions in clinically important neonatal outcomes**

- **Multi-centre RCT of appropriate size is justified to confirm these findings**

Other Adjunctive Therapies to Neonatal Ventilation

- Opioids
- Sedatives
- Fluid Bolus

Opioids in Neonatal Ventilation

- **Widespread use because of the perceived notion that infants feel pain during mechanical ventilation and this may affect clinical and neurodevelopmental outcomes**

- **Use of drugs that reduce pain might be important in improving survival and neurodevelopmental outcomes**

- **Morphine sulphate (most common), Fentanyl**

  - continuous IV infusion or bolus IV

Opioids v Placebo or No treatment:

Pain Scores

Outcome & Subgroups	Studies (n)	Participants (n)	Mean Diff. (95% CI)
PIPP			
All studies	4	1113	**-1.71 (-3.18, -0.24)**
High quality studies	3	1093	-1.51(-3.17, 0.14)
Very preterm studies	2	943	-2.68 (-6.62, 1.27)
NFCS			
All studies	1	22	0.19 (-1.15, 1.53)
High quality studies	0	0	Not estimable
Very preterm studies	1	22	0.19 (-1.15, 1.53)
NIPS			
All studies	1	150	-0.19 (-0.72, 0.34)
High quality studies	1	150	-0.19 (-0.72, 0.34)
Very preterm studies	0	0	Not estimable
Other scales			
All studies	6	310	**-0.89 (-1.46, -0.31)**
High quality studies	3	215	**-0.73 (-1.40, -0.06)**
Very preterm studies	2	67	**-0.66 (-1.15, -0.16)**

Opioids v Placebo or No treatment:
Clinical Outcomes (all studies)

Outcome	Studies (n)	Participants (n)	RR (95% CI)
Mortality prior d/c	4	178	0.99 (0.52, 1.88)
BPD (36 w)	3	833	0.95 (0.73, 1.22)
NEC	2	203	0.93 (0.36, 2.37)
Severe IVH (grade 3/4)	5	1166	0.98 (0.70, 1.38)
PVL	5	1166	0.79 (0.51, 1.22)
Disability at 5-6 yrs	1	95	1.46 (0.51, 4.24)

Cochrane Database of Systematic Reviews 2008, Issue 4

- **No beneficial effects on important clinical outcomes**
- **Very limited information regarding long term safety**

Opioids in Neonatal Ventilation

Summary

- Infants who received opioids showed reduced "Pain Scores" compared to the controls (CAUTION!)
- Very preterm infants who received morphine took significantly longer to reach full enteral feeding
- Insufficient evidence to recommend "routine use" of opioids
- Systematic review recommends "selective use" of opioids in mechanically ventilated newborns

Sedatives in Neonatal Ventilation

- **Use of Midazolam Infusion is not uncommon in mechanically ventilated newborn infants**

<u>Systematic Review</u>

- **3 RCTs, each showed significantly high sedative scales in treatment groups**

  - Sedative scales – NOT validated in preterms

- **Concerns on safety**

  - Higher risk of death/ severe IVH/PVL in one study

  - meta-analysis of results of 2RCTs- longer NICU stay

Cochrane Database of Systematic Reviews 2010

Pump up the volume? The routine early use of colloid in very preterm infants

Arch Dis Child Fetal Neonatal Ed 1998;78:F163-F165

- Rarely does a very low birth weight infant escape at least 10 ml/kg of colloid in the first few hours of life. Most units do not give volume routinely on admission, in the same way that most units don't prescribe routine antibiotics, yet almost every very preterm baby gets both, as routinely as vitamin K or a photograph for the mother.

- In the case of antibiotics there is usually some feature of the history or examination that can be invoked to suggest a risk of infection...

- In the case of colloid there is always a slight metabolic acidosis, or a lowish temperature on arrival from labour ward, or a casual tweak of the big toe..... , provides conclusive proof of hypovolaemia.

Peter Hope

The Volume Expansion Trial (NNNI Trial Group)

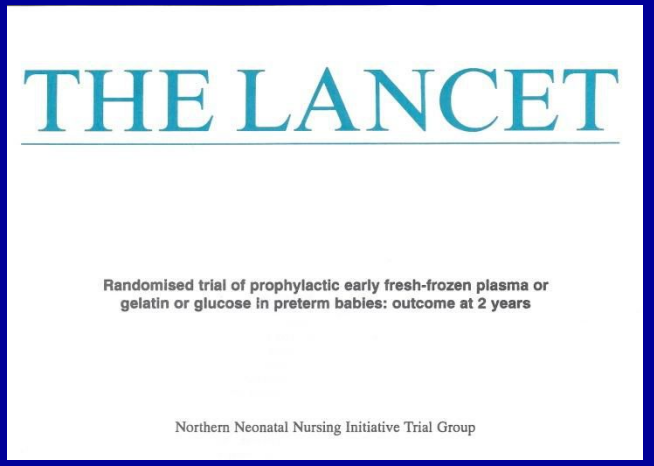
< 32 weeks
N = 776

- FFP (N=257)
- 20 ml/kg, then 10 ml/kg 24 h later

- Gelatin (N=261)
- 20 ml/kg, then 10 ml/kg 24 h later

- Control (N=258)
- Glucose infusion as routine

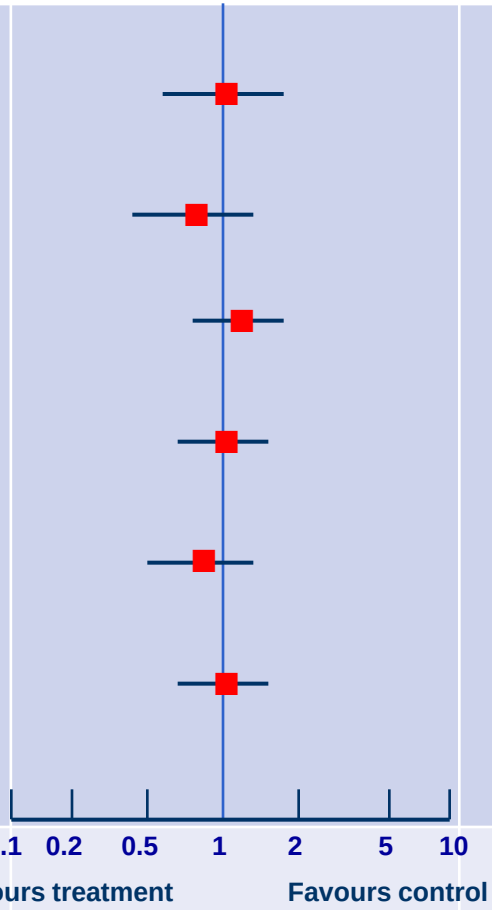
- Assessment at two years of age (N=604)
  - Medical history & Clinical Examination
  - Griffiths Mental Developmental Scales
  - Vision & Hearing
  - Anthropometry



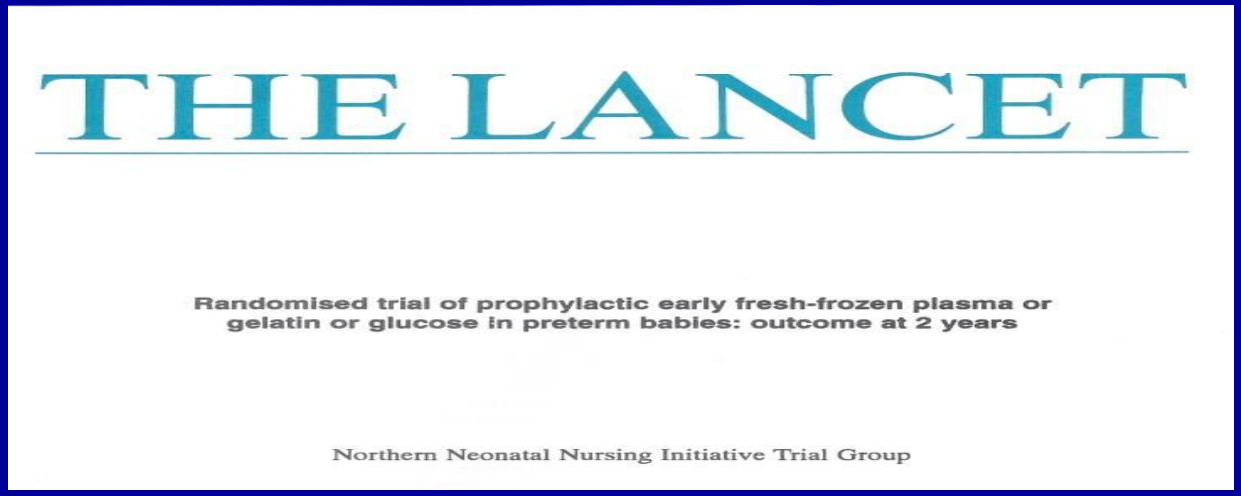
- Minimisation before 2 h of age
- 84% of eligible infants enrolled
- **Primary outcome:** Survival without major disability
- Follow up rate: 100%
- All eligible (but not enrolled) children also had same assessments

RCT of prophylactic early FFP or gelatin or glucose in preterm babies

Outcome	Volume n/N	Control n/N	Risk Ratio (95% CI)
Severe P/IVH	26/266	14/147	1.03 (0.55, 1.90)
NEC	18/518	14/258	0.64 (0.32, 1.27)
Sepsis	93/518	36/258	1.29 (0.90, 1.83)
Death (before 2 yrs)	107/518	47/258	1.13 (0.83, 1.54)
Severe Disability	45/399	29/205	0.80 (0.52, 1.23)
Death/ severe disability	164/518	82/258	1.00 (0.80, 1.24)



Tin et al Lancet 1996



THE LANCET

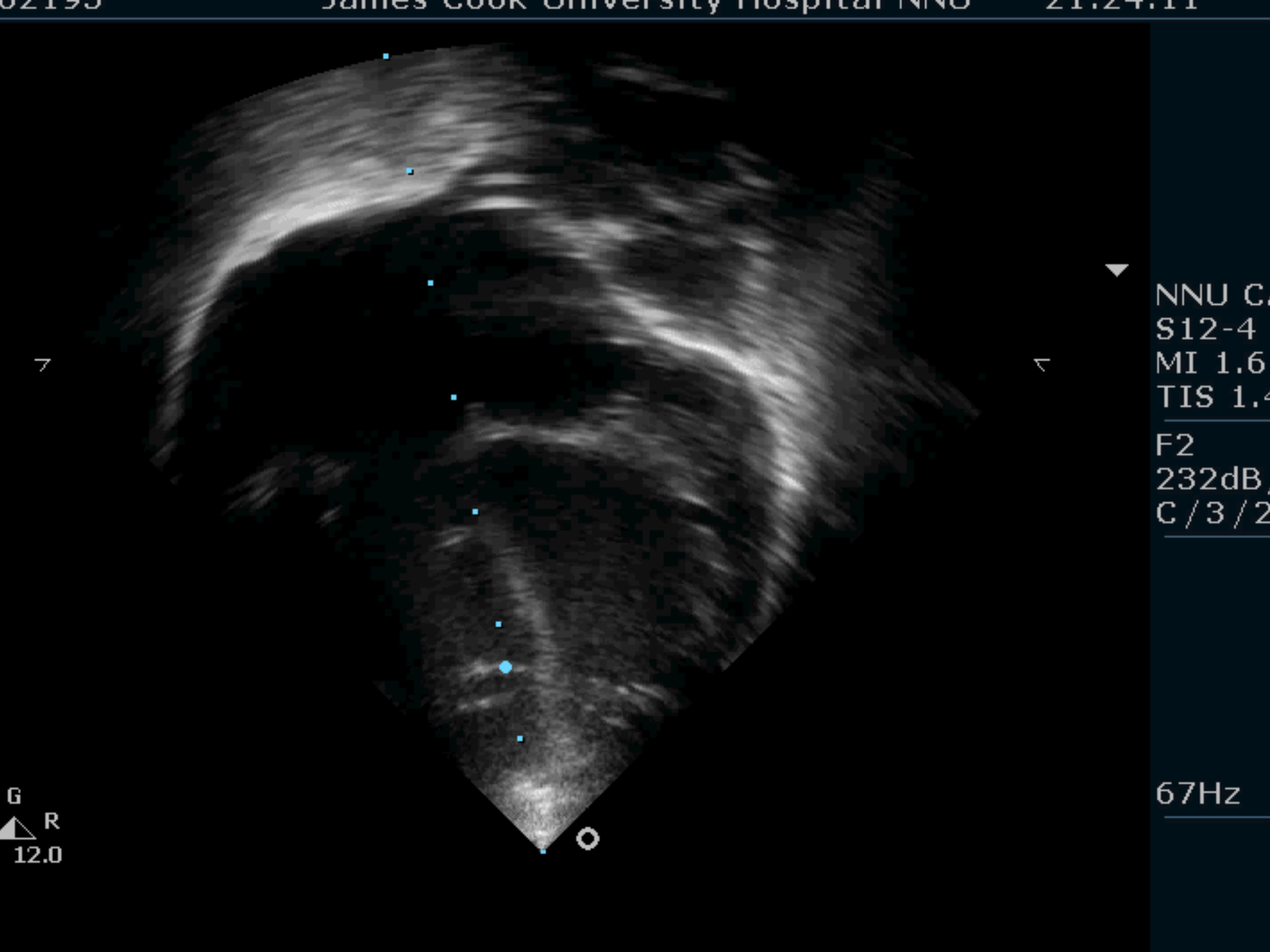
Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years

Northern Neonatal Nursing Initiative Trial Group

Conclusion:

- **This trial provides no evidence that the routine use of FFP, or some other form of intravascular volume expansion, affects the risk of death or disability in babies born more than 8 weeks before term.**

Tin et al Lancet 1996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Key messages

- Adjunctive therapies are commonly used alongside neonatal ventilation
- Many therapies have made their way into practice without being assessed “adequately”
- Little or no evidence to support the use of several therapies
- “Rationalised” approach to use unproven therapies (in specific clinical situations) may be justifiable
- “Routine use” of unproven therapies must be avoided
- Clinicians MUST collaborate to search for evidence

THANK YOU!!