Nebulised surfactant – where are we now?

Dr David Sweet
Consultant Neonatologist,
Royal Maternity Hospital,
Belfast, Northern Ireland

Declaration

- In the past received speakers fees
  - Chiesi,
  - Abbvie,
  - Armstrong Medical

- PI for Curoneb Trial in Belfast
- Local PI for planned Aerofact Study

  (Confidentiality Clause!)

Surfactant Nebulisation

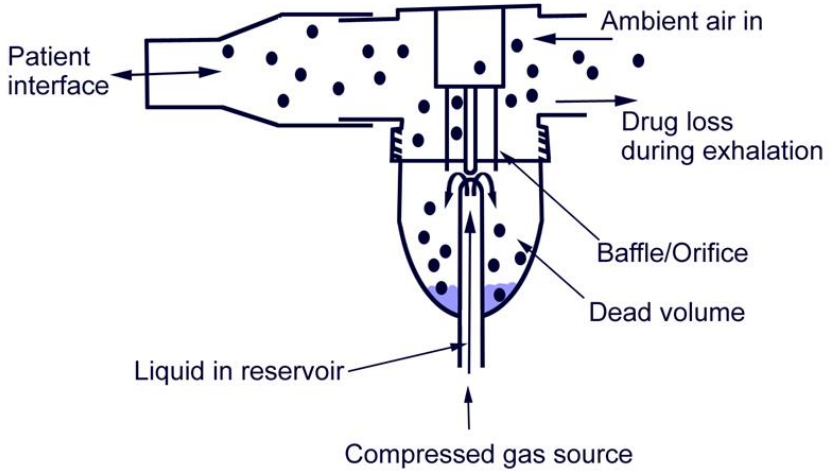
- 1st attempt 1964
  - Case series 11 babies. 8 survived

Microaerosol Administration of Synthetic β-γ-Dipalmitoyl-L-α-Lecithin in the Respiratory Distress Syndrome: A Preliminary Report

E. ROBILLARD, M.D., Y. ALARIE, Ph.D.,* P. DAGENAIS-PERUSSE, M.D., E. BARIL, M.D. and A. GUILBEAULT, M.D., *Montreal, Que.*

Canad. Med. Ass. J. Jan. 11, 1964, vol. 90

- 1990s Animal studies- continuous jet nebulisation via E-T tube
  - Small amounts of surfactant reach target
  - Some improvement in lung mechanics
  - Most drug in tubing and filters

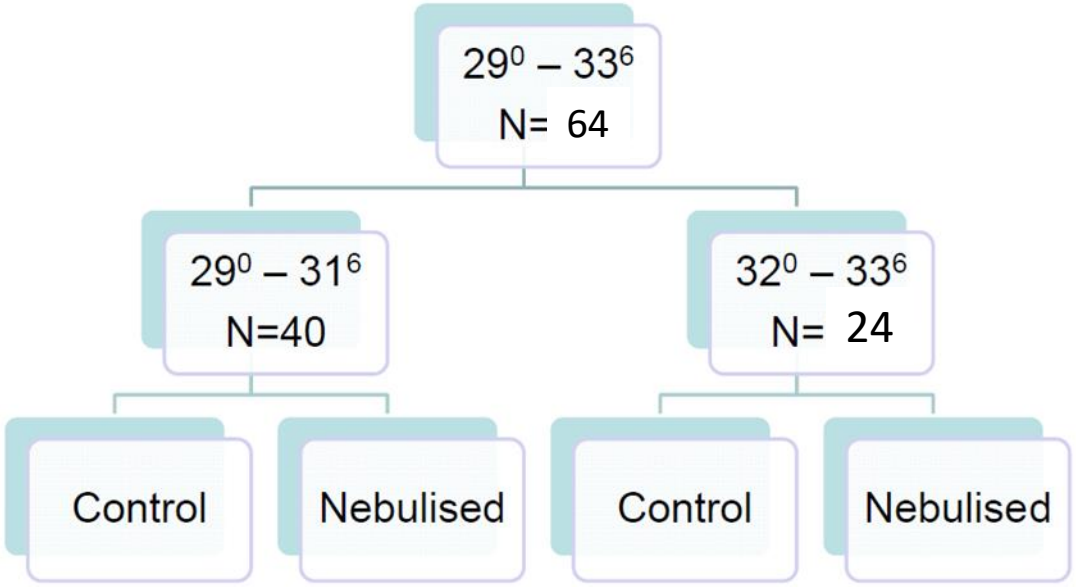


Clinical Trials in Preterm Infants

	SURFACTANT	METHOD	POPULATION	OUTCOME
Jorch G 1997 (letter)	Alveofact	Jet nebuliser	28-35 weeks (n = 20)	A-aO2 gradient, pCO_2 and Silverman score improved
Arroe M 1998	Exosurf	Side stream nebuliser	23-36 weeks (n = 22)	No significant benefit
Berggen E 2000	Curosurf	Jet nebuliser Infant flow + CPAP	27-34 weeks (n = 34)	No significant benefit
Finer N 2010 (Pilot)	Aerosolised KL4	Aeroneb (mesh) + CPAP	28-32 weeks (n = 17)	Safe
Pillow J 2019 CureNeb study	Curosurf	Pari eFlow (mesh) + CPAP via nasal mask	29-33 weeks (n= 70)	Reduction in CPAP failure in 31-32 weekers

CureNeb Study

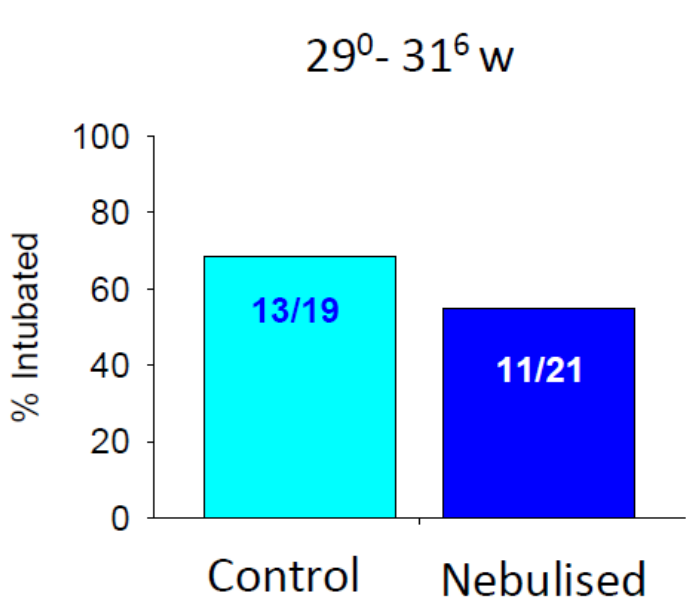
- Single centre, blinded RCT
- Infants 29-33^{+6} weeks <4h old with evolving RDS (FiO_2 0.22-0.3)
- Randomised to receive 200mg/kg poractant alfa or sham nebuliser
- Pre-defined failure criteria
  - FiO_2 > 0.3 > 30 mins or >0.45 anytime
  - 2 apnoea's requiring B&M
  - Two pHs < 7.2 and CO_2 > 65 mmHg
  - Clinician decision intubation necessary
- Primary outcome need for intubation first 72 hours



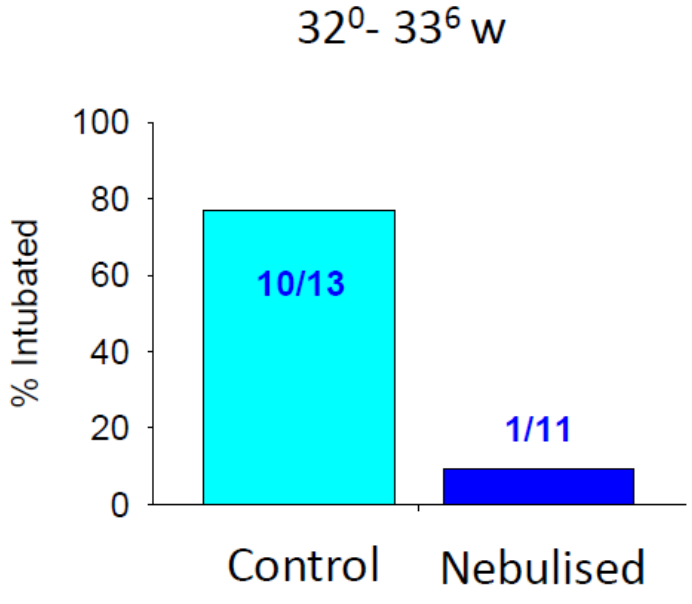
Minocchieri et al ADCFN 2019

CureNeb Study

- Surfactant nebulisation reduced risk of intubation RR 0.52(0.29-0.95)



RR: 0.860 (0.399 to 1.854)
p=0.984



RR: 0.118 (0.178 to 0.784)
p=0.004

Minocchieri et al ADCFN 2019

2020….

Aerosolized Calfactant for Newborns With Respiratory Distress: A Randomized Trial

James J. Cummings, MD, MS,[a] Erick Gerday, MD,[b] Stephen Minton, MD,[b] Anup Katheria, MD,[c] George Albert, MD,[d] Jaime Flores-Torres, MD,[e] Mobolaji Famuyide, MD,[f] Andrea Lampland, MD,[g] Scott Guthrie, MD,[h] Devon Kuehn, MD,[i] Jörn-Hendrik Weitkamp, MD,[j] Prem Fort, MD,[k] Elie G. Abu Jawdeh, MD, PhD,[l] Rita M. Ryan, MD,[m] Gregory C. Martin, MD,[n] Jonathan R. Swanson, MD,[o] Neil Mulrooney, MD,[p] Fabien Eyal, MD,[q] Dale Gerstmann, MD,[r] Praveen Kumar, MD,[s] Greg E. Wilding, PhD,[t] Edmund A. Egan, MD,[u] AERO-02 STUDY INVESTIGATORS

- Multicentre RCT in 22 NICUs in USA
  - Any infant with respiratory distress requiring CPAP
  - Randomised to receive up to three doses in 72 hours of 210mg/kg calfactant aerosolised via modified Solarys nebuliser sitting in the mouth (pacifier)
  - Vs. standard care
  - Outcome intubation for surfactant within first 4 d of age
  - NO predefined criteria for entry or when intubation should be considered

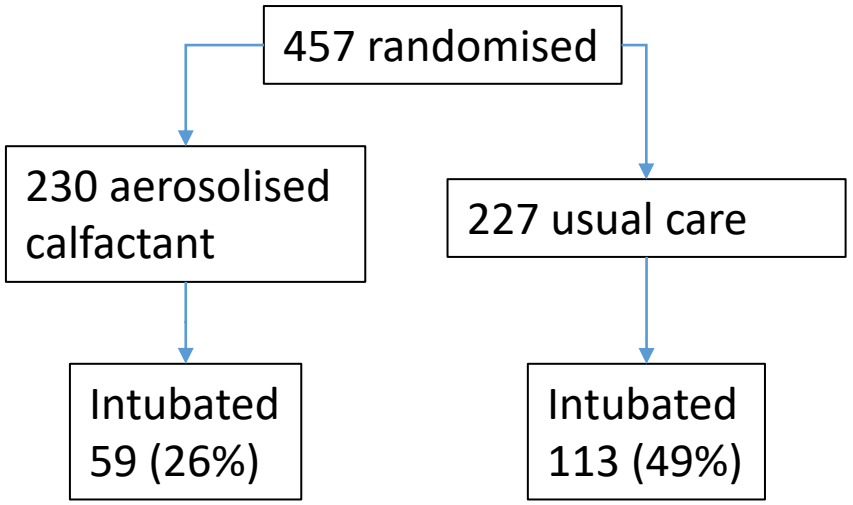
Cummings et al Paediatrics 2020

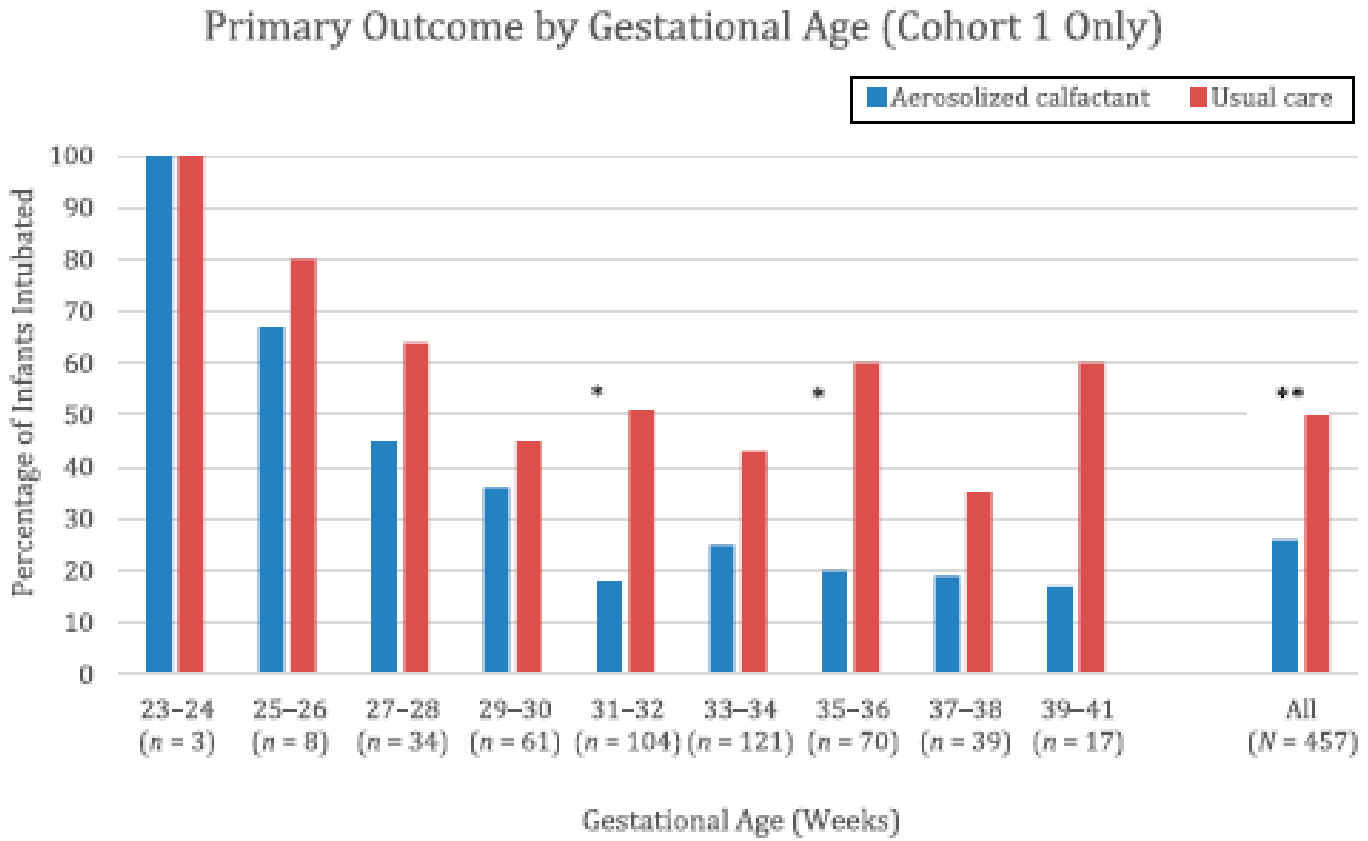
Quote (From methods)

…. The decision to intubate a newborn with RDS is both highly complex and individualised. During pre-trial discussions site investigators were unanimous that this critical decision be left up to the clinical provider… adding pragmatic strength and ethically compliant with infants best interest…..

..Therefore no set criteria for primary endpoint nor any requirement of documentation of the clinicians reasoning in making this decision

Aerosolised calfactant….



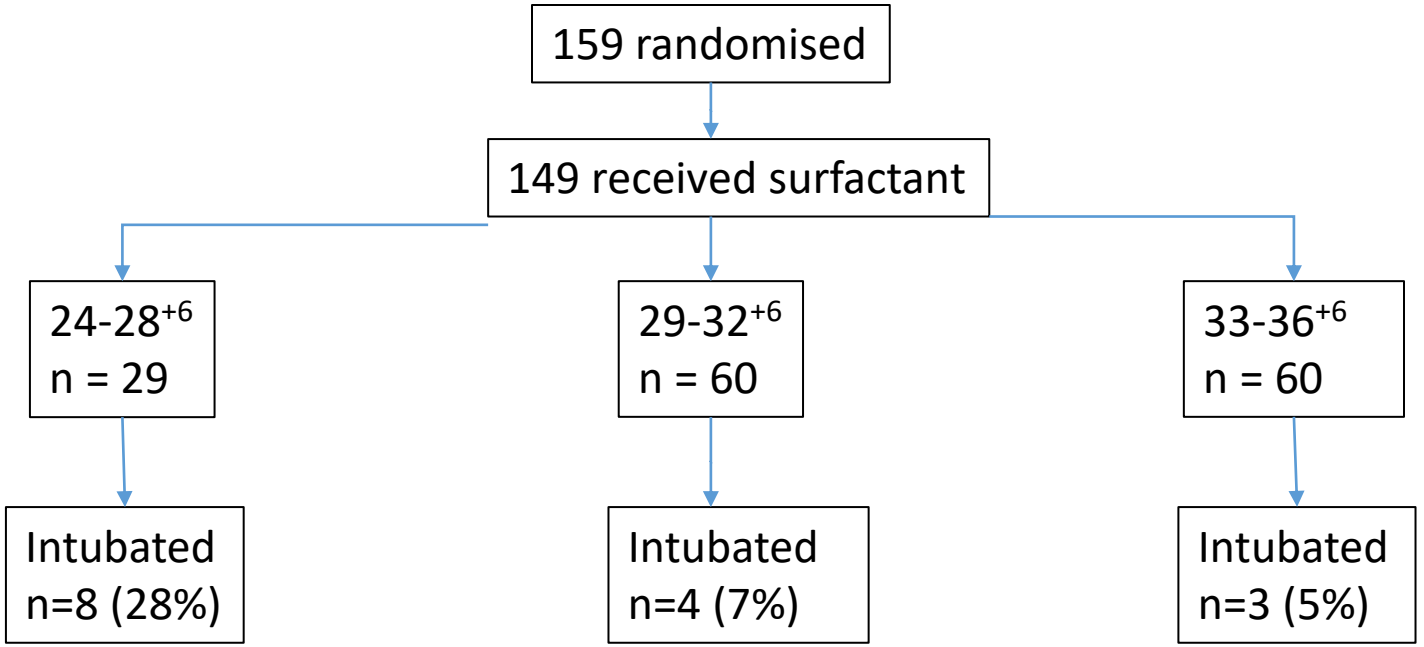


Cummings et al Paediatrics 2020

In the meantime….. Nebulised Beractant

- Aerosolized Beractant in neonatal respiratory distress syndrome: A randomized fixed-dose parallel-arm phase II trial
- Infants 24 – 36^{+6} weeks single level III NICU
  - Four doses/ dilutions of Beractant (100 or 200 mg/kg; 12.5 or 8.3 mg/mL)
  - Two different nebulisers (Miniheart jet or Aeroneb solo vibrating mesh)
  - Given Caffeine if < 32 weeks
  - Predefined failure criteria
- Designed to test safety, feasibility, impact of dosing schedules, efficacy
- Retrospective Controls

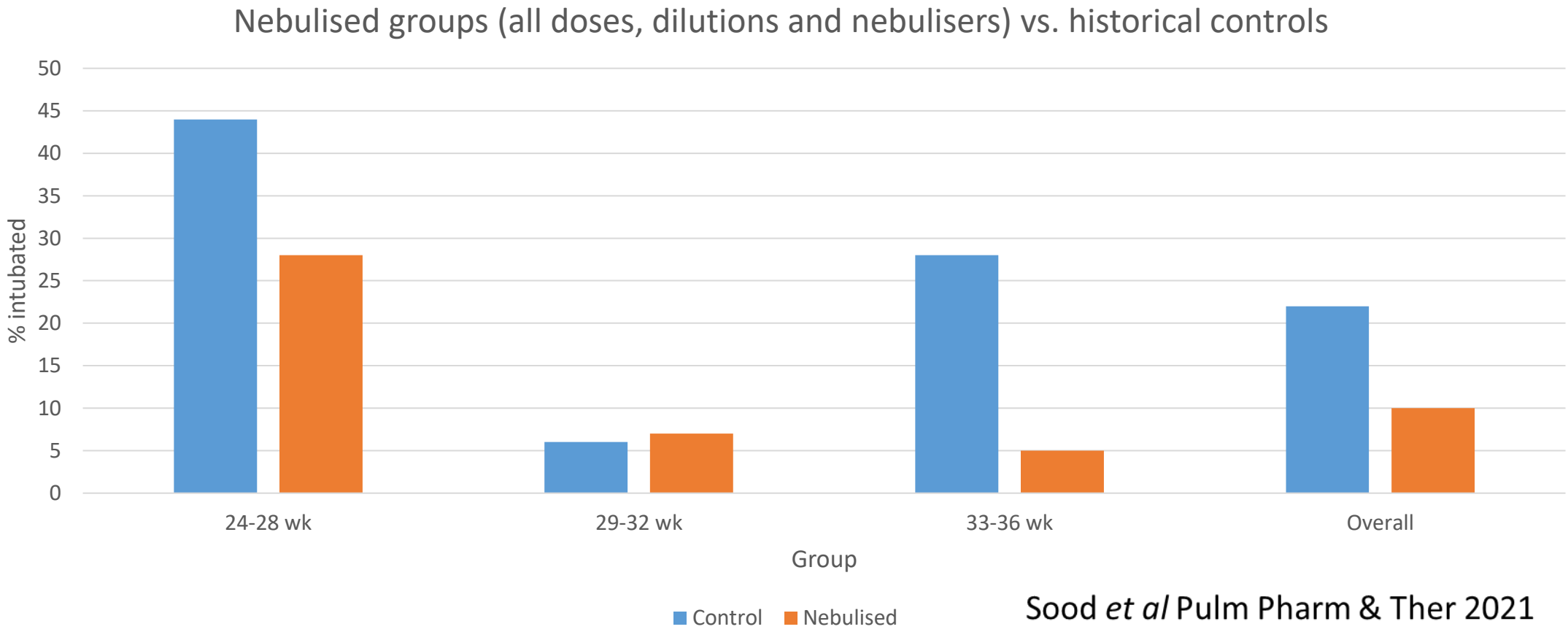
Sood *et al* Pulm Pharm & Ther 2021



Then identified 79 retrospective controls who might have been eligible for study as comparison group (But they received caffeine at a later time!)

Sood et al Pulm Pharm & Ther 2021

Outcomes



Sood *et al* Pulm Pharm & Ther 2021

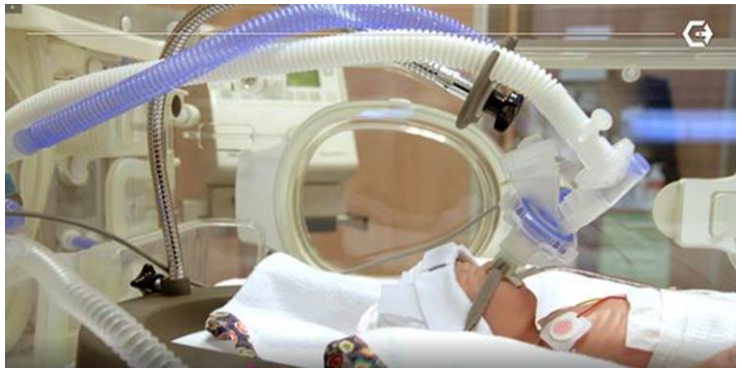
CURONEB Study

- A Study To Investigate The Safety, Tolerability And Efficacy Of Nebulised Curosurf® In Preterm Neonates with RDS
- Phase I component – dose finding study
- Phase II open RCT to test two best doses against CPAP alone
  - $28\text{-}32^{+6}$ weeks FiO_2 0.25-0.4 with radiologically confirmed RDS
  - Recruited between 60 minutes and 12 hours of age
  - Investigational membrane nebuliser (Pari-eFlow Neos) via nasal prongs

Dani J Peds 2022

A Randomized, Controlled Trial to Investigate the Efficacy of Nebulized Poractant Alfa in Premature Babies with Respiratory Distress Syndrome

Carlo Dani, MD[1], Gyula Talosi, MD[2], Annalisa Piccinno, Msc[3], Virginia Maria Ginocchio, MD[3], Gyorgy Balla, MD[4], Anna Lavizzari, MD[5], Zbynek Stranak, MD[6], Eloisa Gitto, MD[7], Stefano Martinelli, MD[8], Richard Plavka, MD[9], Barbara Krolak-Olejnik, MD[10], Gianluca Lista, MD[11], Francesca Spedicato, MSc[3], Giorgia Ciurlia, MSc[3], Debora Santoro, Msc[3], and David Sweet, MD[12], on behalf of the CURONEB Study Group*



- August 2017 to June 2018
- 34 centers in 6 countries

	Nebulized Poractant alfa 200 mg/kg (n=9)	Nebulized Poractant alfa 400 mg/kg (n=9)	Nebulized Poractant alfa 600 mg/kg (n=9)	Control nCPAP (n=9)
Duration of nebs (min), mean (range)	12 (9;15)	29 (17;45)	39.5 (20;55)	
Respiratory failure 72 h, n (%)	4 (44)	6 (67)	5 (56)	6 (67)

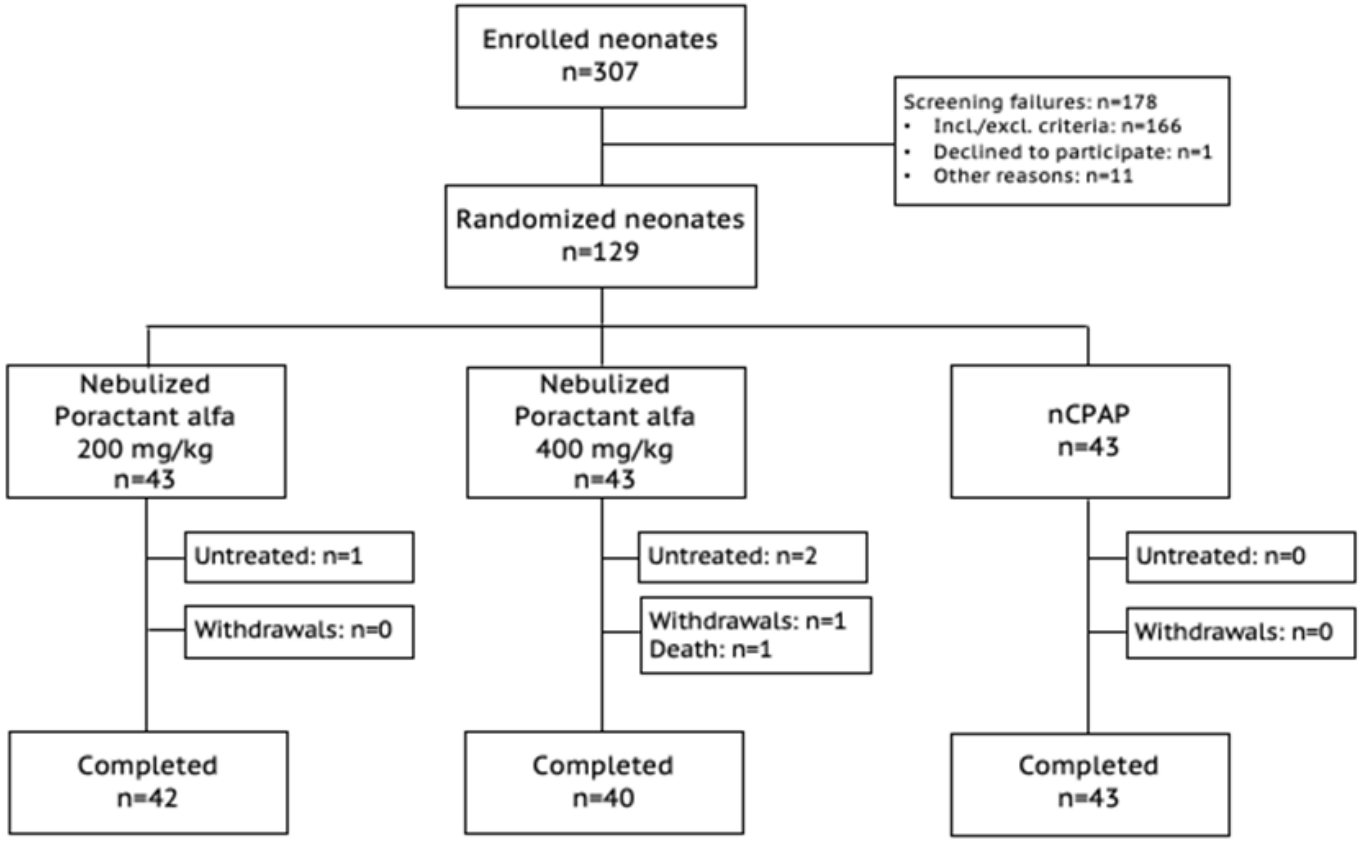
Dani J Peds 2022

Curoneb trial Phase II

- Infants 28^{+0} to 32^{+6} confirmed RDS requiring CPAP FiO_2 0.25-0.4 between 1 and 12 hours of age
- Administered 200 or 400mg/kg poractant via Pari-eflow neos nebuliser, with option for repeat dosing
- Vs. CPAP continuing without nebulisation
- Primary Outcome respiratory failure before 72 hours defined as
  - FiO_2 > 0.4 > 30mins
  - 4 apnoeas/hr or 2 requiring bagging
  - Respiratory acidosis pH<7.2 CO_2 > 65mmHg
- 84 per group required for 80% power to show reduction in respiratory failure from 40% to 20% at two-sided significance of 5%

Dani J Peds 2022

Study stopped… change in the benefit-risk balance driven by a negligible efficacy profile



Baseline

	200mg/kg nebuliser n=42	400mg/kg nebuliser n=41	CPAP only n=43
Gestation (wk)	30.4 (1.4)	30.9 (1.2)	30.6 (1.4)
Weight (g)	1330 (422)	1469 (328)	1450 (346)
Male, n (%)	22 (52)	28 (68)	20 (46)
Antenatal steroids, n (%)	38 (90)	38 (93)	40 (93)
C-section, n (%)	35 (83)	36 (88)	32 (74)
FiO_2 (%)	32.5 (6.6)	32.1 (5.3)	30.0 (4.6)

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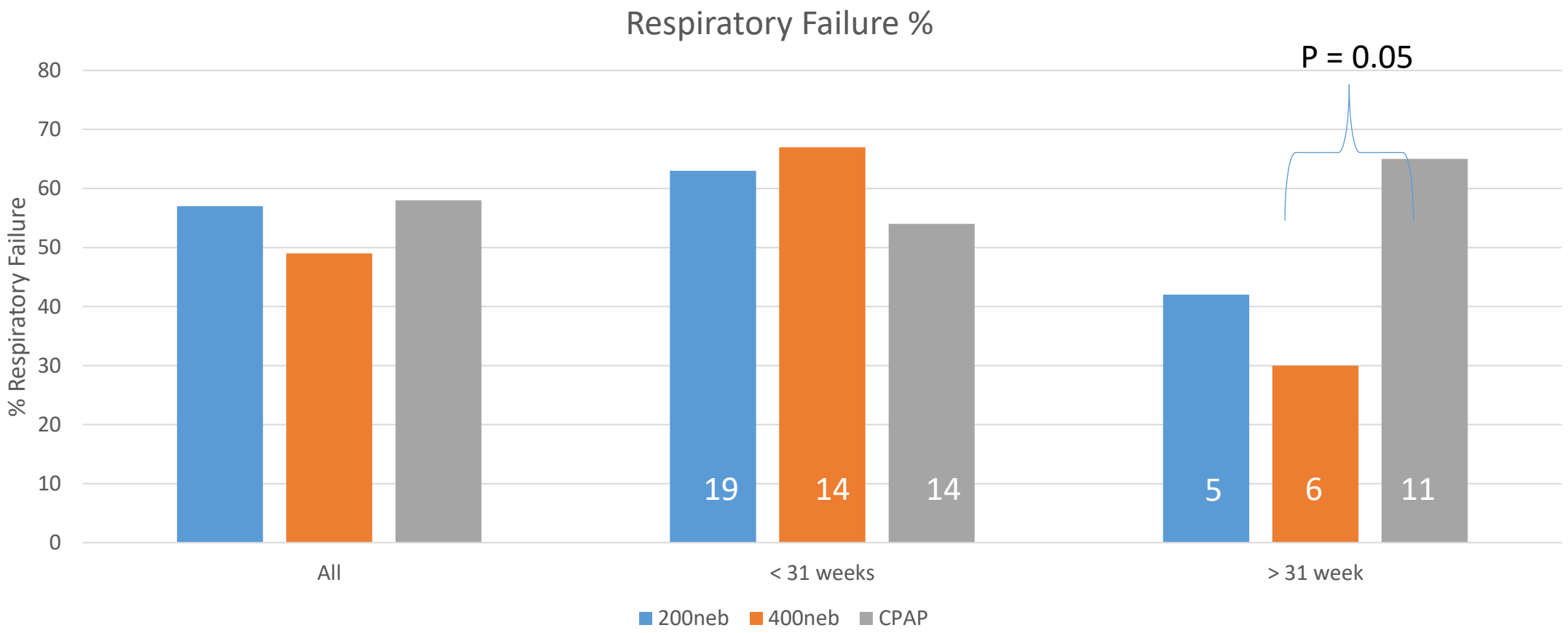
Primary outcome



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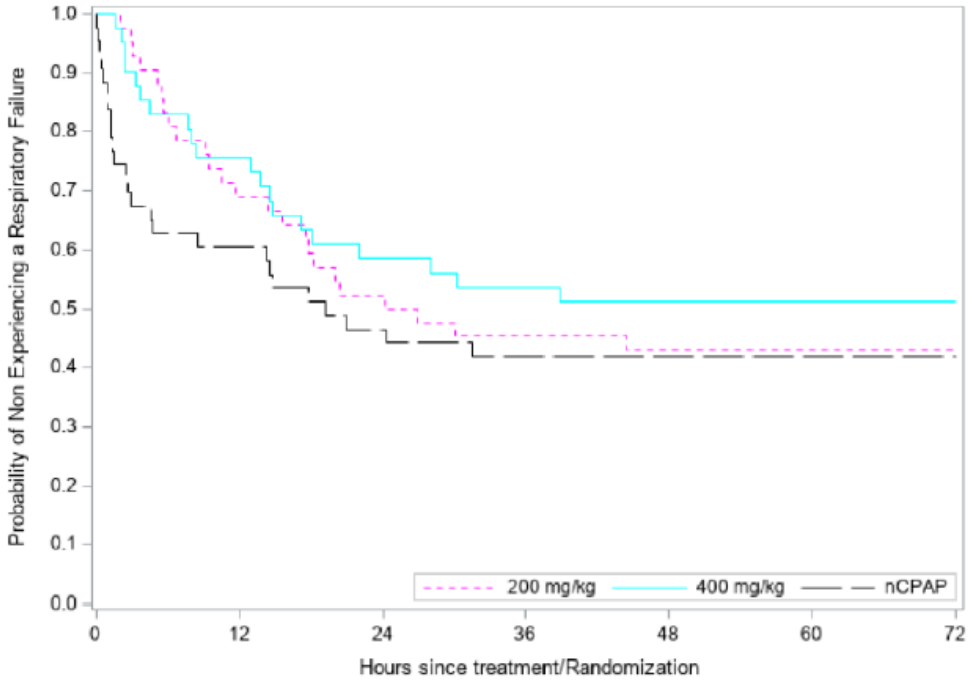
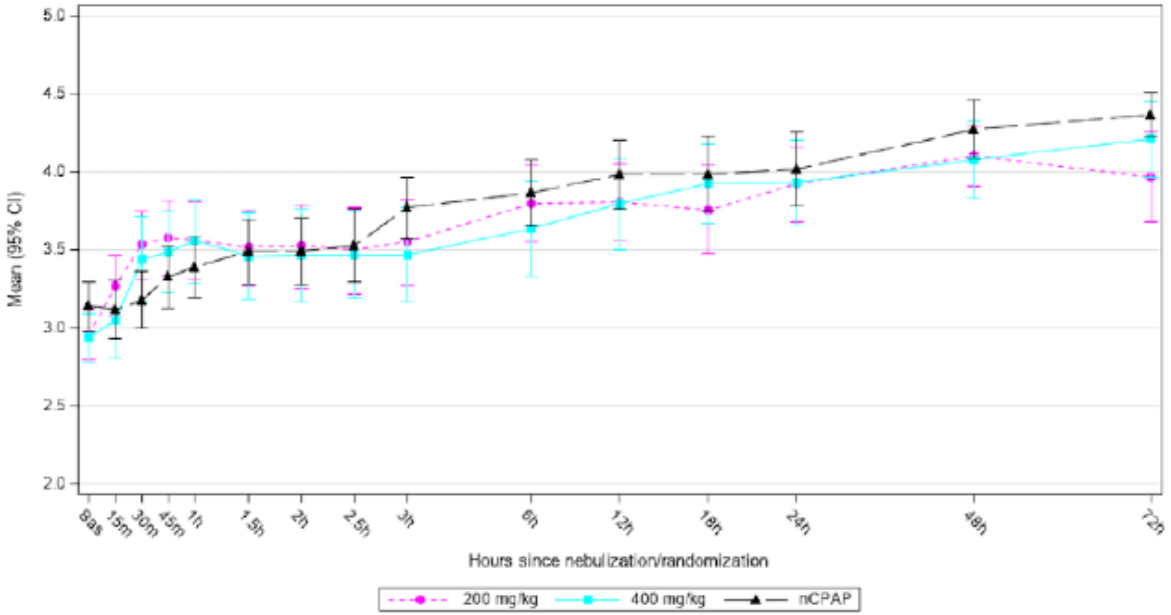
Secondary outcomes

- No difference in any secondary outcomes
- No safety concerns

A Time to respiratory failure



SPO_2/FiO_2 ratio



Dani J Peds 2022

Conclusion

- No clear indication that nebulisation of surfactant would make any difference to any important outcomes
- Any apparent benefit is in relatively more mature babies
- Nebulisation takes time and could potentially delay early liquid surfactant treatment using other methods for babies with genuine surfactant deficiency

Dani J Peds 2022

Surfactant Nebulization to Prevent Intubation in Preterm Infants: A Systematic Review and Meta-analysis

Vincent D. Gaertner, MD, BSc, Janine Thomann, MD, Dirk Bassler, MD, MSc, Christoph M. Rüegger, MD

B

Study or Subgroup	Nebulized surfactant Events	Total	Control Events	Total	Weight	RR M–H, Fixed, 95% CI	Year
NCT02074059 2017	18	39	21	40	10.1%	0.88 (0.56-1.38)	2017
Minocchieri 2019	13	32	23	32	11.2%	0.57 (0.35-0.91)	2019
NCT02528318 2019	17	24	16	24	7.8%	1.06 (0.73-1.56)	2019
Cummings 2020	54	202	102	199	50.2%	0.52 (0.40-0.68)	2020
EUCTR-004547-36 2021	59	110	31	52	20.6%	0.90 (0.68-1.19)	2021
Total (95% CI)		**407**		**347**	**100.0%**	**0.68 [0.58, 0.80]**	
Total events	161		193				

Heterogeneity: $X^2 = 14.58$, df = 4 ($P = .006$); $I^2 = 73\%$
Test for overall effect: Z = 4.78 ($P < .00001$)

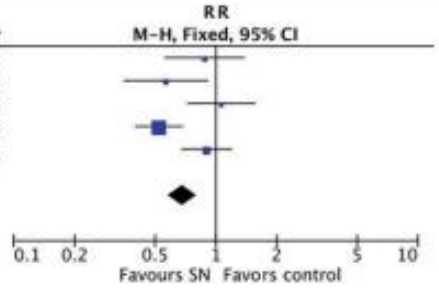


FIGURE 2
Fixed-effects meta-analysis of the primary outcome, intubation rate at 72 hours after birth. A, Including all studies; B, including only studies with identical outcome definitions. [a]Study excluded in sensitivity analysis (B): Guo et al[44] (no time frame for intubation) and NCT02636868[49] (intubation or worsening respiratory status) (see Supplemental Table 3). M–H, Mantel-Haenszel method.

Reduced intubation rates

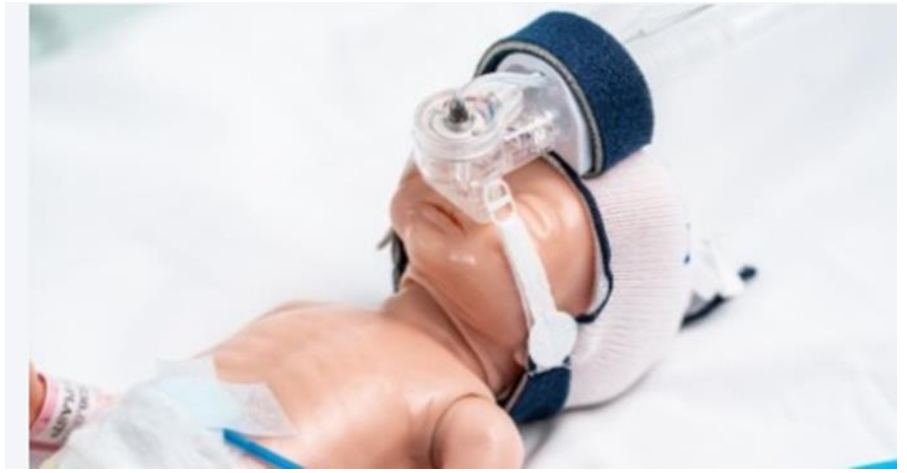
No difference in important outcomes

- Greatest benefit in bigger babies
- Significant risk of bias in trials

Gaetner Pediatrics 2021

TABLE 2 Fixed-Effects Meta-Analysis of RR of Key Secondary Outcomes

	Overall					Sensitivity Analysis					
Outcome	*N* Studies	*N* Infants	Combined Effect RR (95% CI)	*P*	I^2, %	*N* studies	*N* infants	Combined Effect RR (95% CI)	*P*	I^2, %	Excluded Studies
Death	7	1000	0.89 (0.30 to 2.65)	.83	0	7	1000	0.89 (0.30 to 2.65)	.83	0	—
BPD (oxygen need at 36 wk PMA)	7	998	0.99 (0.74 to 1.32)	.96	33	5	435	0.72 (0.39 to 1.35)	.31	45	Cummings et al[a]; EUCTR-004547-36[b]
Severe IVH (grade ≥3)[34]	7	994	0.65 (0.29 to 1.44)	.29	0	2	465	0.20 (0.02 to 4.08)	.29	N/A	Berggren et al[c]; NCT02074059[c]; NCT02528318[c]; NCT02636868[c]; EUCTR-004547-36[d]
Air leak	7	1000	1.03 (0.69 to 1.52)	.90	0	7	1000	1.03 (0.69 to 1.52)	.90	0	—
Pulmonary hemorrhage	5	904	0.48 (0.14 to 1.68)	.25	0	5	904	0.48 (0.14 to 1.68)	.25	0	—
Sepsis	5	904	0.90 (0.58 to 1.38)	.62	58	1	401	0.56 (0.17 to 1.89)	.35	N/A	NCT02074059[d]; NCT02528318[d]; NCT02636868[d]; EUCTR-004547-36[d]
Any ROP[35]	3	423	0.76 (0.37 to 1.54)	.44	6	3	423	0.76 (0.37 to 1.54)	.44	6	—
NEC (≥ stage 2)[36]	6	968	1.13 (0.49 to 2.63)	.78	0	2	465	1.48 (0.25 to 8.75)	.67	N/A	NCT02074059[e]; NCT02528318[e]; NCT02636868[e]; EUCTR-004547-36[d]

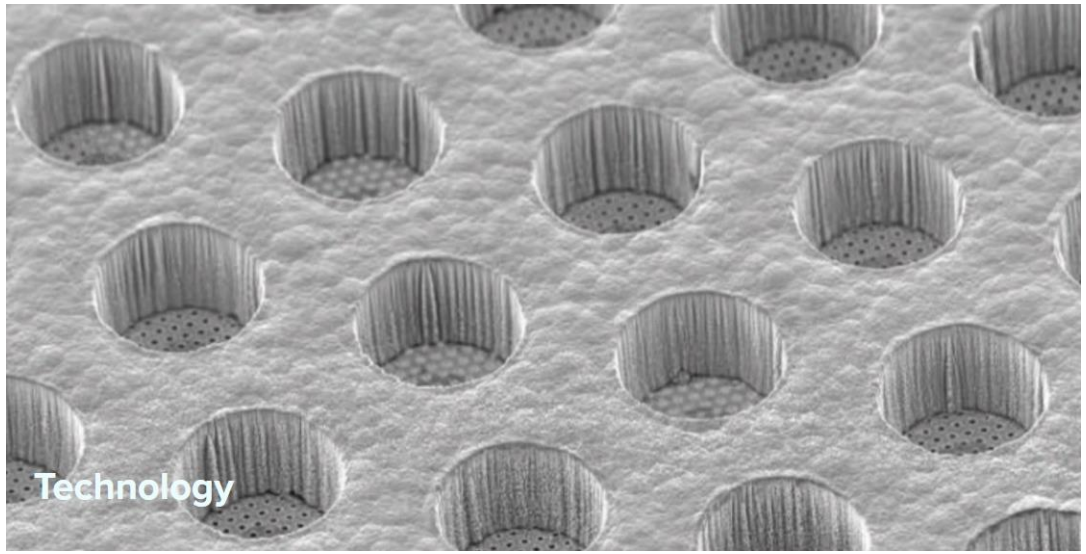


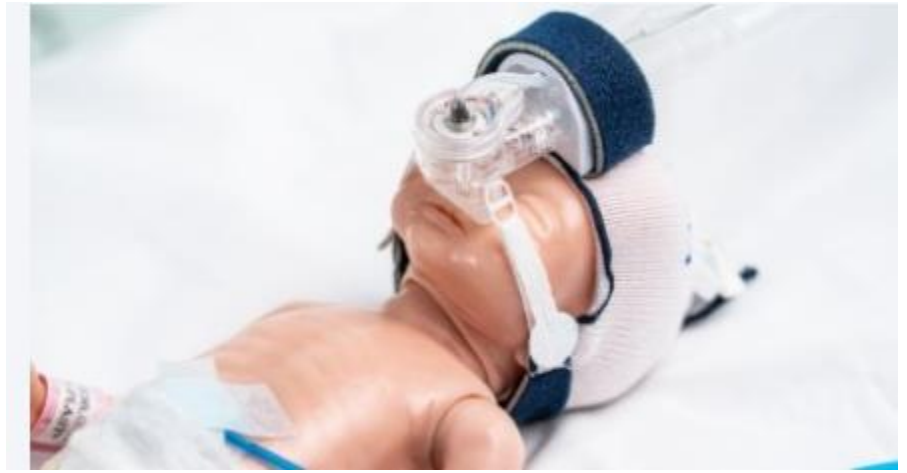

STAR WARS
THE LAST HOPE

AeroFact™ overview

For treatment of respiratory distress syndrome (RDS) in premature infants

AeroFact™ is an **investigational, biologic/device combination product**, poised to deliver a major advance in the treatment of respiratory distress syndrome (RDS) in premature infants. AeroFact™ **enables trans-nasal pulmonary delivery of surfactant replacement therapy (SRT) to infants on nasal continuous positive airway pressure (nCPAP) or non-invasive ventilation (NIV).**





- Aerofact – Technical features
  - Small aerosol droplets (1-3µm)
  - Close to the airway – custom nasal interface design
  - Synchronisation of aerosol delivery with inspiration

Trial of aerosolised surfactant for preterm infants with respiratory distress syndrome

Luke Jardine,[1,2] Kei Lui,[3,4] Helen G Liley,[1,2] Timothy Schindler ,[3,4] James Fink,[5] Jeanette Asselin,[5] David Durand [6]

Aerofact Phase-1 trial

- Infants 26-30^{+6} wks who required n-CPAP 6-8 cmH_2O and FiO_2 < 0.3 at < 2hrs old
- PART 1 – Single dose of nebulised surfactant Alveofact 216mg (n=10)
- PART 2 – Up to 4 doses of nebulised surfactant (2 then 4 hrly) (n=21)
- Compared with historical controls (3 per 1 study patient born within last 2 yrs.)
- Failure Criteria
  - RSS ≥2.4,
  - CO_2>65mm Hg,
  - pH <7.20,
  - nCPAP >8 cmH_2O
  - 3 Apn&Brady

Table 3 Outcome of AeroFact-treated infants and matched historical controls

	Part 1			Part 2		
	AeroFact	Control	P value	AeroFact	Control	P value
n	10	30		21	63	
Primary outcomes, n (%)						
Met study treatment failure criteria	4 (40)	11 (33)	0.72	6 (29)	30 (48)	0.20
Received instilled surfactant	4 (40)	14 (47)	>0.99	6 (29)	29 (46)	0.20
Survived	9 (90)	30 (100)	0.25	20 (95)	63 (100)	0.25
Survived without BPD	8 (80)	22 (73)	>0.99	16 (76)	43 (68)	0.59

BPD, bronchopulmonary dysplasia.

Jardine ADCFN 2022

Trial of aerosolised surfactant for preterm infants with respiratory distress syndrome

Luke Jardine,[1,2] Kei Lui,[3,4] Helen G Liley,[1,2] Timothy Schindler ,[3,4] James Fink,[5] Jeanette Asselin,[5] David Durand [6]

- Infants 26-30^{+6} wks who required n-CPAP 6-8 cmH_2O and FiO_2 < 0.3 at < 2hrs old
- PART 1 – Single dc (n=10)
- PART 2 – Up to 4 c (n=21)
- Compared with hi within last 2 yrs.)
- Failure Criteria
  - RSS ≥2.4,
  - CO_2>65mm Hg,
  - pH <7.20,
  - nCPAP >8 cmH_2O
  - 3 Apn&Brady

Part 2

AeroFact	Control	P value
21	63	
6 (29)	30 (48)	0.20
6 (29)	29 (46)	0.20
20 (95)	63 (100)	0.25
16 (76)	43 (68)	0.59

Met failure Criteria

Received Surfactant

				AeroFact	Control	P value
				21	63	
				6 (29)	30 (48)	0.20
Received instilled surfactant	4 (40)	14 (47)	>0.99		29 (46)	0.20
Survived	9 (90)	30 (100)	0.25	20 (95)	63 (100)	0.25
Survived without BPD	8 (80)	22 (73)	>0.99	16 (76)	43 (68)	0.59

BPD, bronchopulmonary dysplasia.

Jardine ADCFN 2022

A Dose-Ranging Study to Determine the Efficacy, Safety and Tolerability of AeroFact

ClinicalTrials.gov ID NCT03969992

Sponsor Aerogen Pharma Limited

Information provided by Aerogen Pharma Limited (Responsible Party)

Last Update Posted 2022-02-23

Study Overview

Brief Summary:
The purpose of this two-part Phase 2 study is to assess the safety, tolerability and efficacy of aerosolized SF-RI 1 (AeroFact) when delivered via nCPAP at two different doses.

Detailed Description:
Part I Primary Objective To determine an optimal dose of AeroFact administered by nasal continuous positive airway pressure (nCPAP) versus stand of care in reducing the rate of intubation/cannulation and bolus surfactant instillation in the first 7 days after birth.

Part II Primary Objective To evaluate pulmonary outcomes and respiratory utilization at 3, 6, 9, and 12 months post-menstrual age (PMA)

OFFICIAL TITLE

A Partially Blinded, Randomized, Controlled, Parallel-Group, Dose-Ranging Study to Determine the Efficacy, Safety and Tolerability of AeroFact in Preterm Infants at Risk of Worsening Respiratory Distress Syndrome

CONDITIONS

Respiratory Distress Syndrome in Premature Infant

STUDY START (ACTUAL)

2020-03-04

PRIMARY COMPLETION (ESTIMATED)

2023-08-31

STUDY COMPLETION (ESTIMATED)

2024-08-31

ENROLLMENT (ESTIMATED)

261

STUDY TYPE

Interventional

PHASE

Phase 2

Aerofact Phase-2 - USA

Inclusion Criteria:

1. Parental consent obtained prior to study procedures being performed (pre-natal consent is allowed)
2. 26 0/7 to 30 6/7 weeks of gestational age
3. Weight <2.0 Kg
4. Respiratory Severity Score (RSS) 1.4-2.0

Exclusion Criteria:

1. Apgar score less than or equal to 5 at five minutes after birth
2. Need for chest compressions or administration of epinephrine or bicarbonate in the delivery room
3. Premature rupture of membranes (PROM) > 14 days
4. Need for intubation and/or mechanical ventilation prior to enrollment
5. Active pneumothorax requiring chest tube
6. Significant congenital anomaly, chromosomal abnormality
7. Concomitant treatments with inhaled nitric oxide

Aerofact Phase-2 – USA & South Africa

Inclusion Criteria:

1. Parental consent obtained prior to study procedures being performed (pre-natal consent is allowed)
2. 26 0/7 to 30 6/7 weeks of gestational age
3. Weight <2.0 Kg
4. Respiratory Severity Score (RSS) 1.4-2.0

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Joint Program 1

BILL & MELINDA GATES foundation

AeroFact™ Proof-of-Concept Clinical Study in South Africa BMGF is supporting Aerogen Pharma in the conduct of a 232-patient clinical trial of our AeroFact™ inhaled surfactant in South Africa. This study began in April 2023 at three major Neonatal Intensive Care Units in Cape Town & Johannesburg. The enrollment of the first patients took place in May 2023Our goal for this study is to demonstrate the safety and efficacy of aerosolized surfactant in the South African clinical and public health environment, since it is unwise to assume that clinical advances can be shifted from a high income setting to a LMIC setting without thoughtful adaptation. For more information on this trial, please see the **study entry into the registry** of the South African Health Products Regulatory Agency.

Who knows where this will lead?

Thank you