Kliiniline küsimus nr 19
Kas enneaegsetel vastsündinutel kasutada parema ravitulemi saavutamiseks profülaktilist surfaktantravi võrreldes mittekasutamisega?

Tulemusnäitajad: lapse peamised tulemusnäitajad, õhktüsistused, kopsude kunstliku ventilatsiooni kestus

Ravijuhendid

Kokkuvõte ravijuhendites leiduvast:

Soovitused profülaktilise surfaktantravi kohta on leitavad kahes AGREE-ga hinnatud ravijuhendis:

European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Halliday HL; European Association of Perinatal Medicine. Neonatology. 2013;103(4):353-68. ja

AARC Clinical Practice Guideline. Surfactant replacement therapy: 2013. Walsh BK, Daigle B, DiBlasi RM, Restrepo RD; American Association for Respiratory Care. Respir Care. 2013 Feb;58(2):367-75.)

Esitatud soovitused on mõlemas juhendis koostatud GRADE süsteemi kasutades ning Ameerika ravijuhend põhineb kuni 2012. a. juulini ja Euroopa oma kuni 2012. a. lõpuni publitseeritud teaduskirjandusel.

Grades of recommendation: GRADE

A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating consistency of results or Extrapolated evidence from studies such as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating consistency of results or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+

GRADE = Grading of recommendations assessment, development and evaluation [5]; RCT = randomized controlled trial.

Mõlemas ravijuhendis soovitatakse nii profülaktilise kui selektiivse surfaktantravi kasutamist enneaegsetel vastsündinutel, kellel on RDS või risk selle kujunemiseks, kuna see vähendab õhulekete ning pulmonaalse interstitsiaalse emfüseemi esinemissagedust ja vähendab suremust antud populatsioonis.

Tugev soovitus on kasutada RDS-ga enneaegsetel vastsündinutel surfaktantravi (A) Euroopa 2013.

Varane surfaktantravi võiks olla standard. Teatud juhtudel s.h. väga enneaegsel lapsel, kelle emale ei ole manustatud antenataalselt glükokortikosteroide, ja lastel, kes vajavad esmase stabiliseerimise käigus intubatsiooni, tuleks kasutada profülaktilist surfaktantravi (A) Euroopa 2013; **(1B)** AARC 2013.

Ameerika juhendi alusel võib profülaktiline surfaktantravi olla näidustatud järgmistel juhtudel:

Surfaktandi puudulikkusega enneaegsetel vastsündinutel, kellel on kõrge risk RDS-i kujunemiseks (N: < 32 GN või sünnikaal < 1300 g)

Vastsündinutel, kelle emadel on laboratoorselt määratud lootevee letsitiin sfingomüeliin suhe < 2:1, „bubble stability" test viitab kopsude ebaküpsusele või lootevees puudub fosfatidüülglütserooli.

Süstemaatilised ülevaated

Kokkuvõte süstemaatilistest ülevaadetest

Profülaktilise surfaktantarvi kohta leidsime vastavalt otsingukriteeriumitele 2 meta-analüüsi/süstemaatilist ülevaadet (avaldatud viimase 5 aasta jooksul)

Polin RA, Carlo WA; Committee on Fetus and Newborn; American Academy of Pediatrics 2014 ja

Rojas-Reyes MX, Morley CJ, Soll R. Cochrane Database Syst Rev. 2012.

Esimene nendest ülevaadetest kaasab kokkuvõtvalt ka teise süstemaatilise ülevaate tulemusi.

Surfaktantravi on alates varastest 1990. aastatest hinnatud efektiivseks ja ohutuks ravimeetodiks surfaktandi puudulikkusega enneaegsetel vastsündinutel. (Engle WA; Pediatrics. 2008) Randomiseeritud kontrolluuringutel põhinevad süstemaatilised ülevaated on tõestanud, et surfaktandi manustamine enneaegsetele RDS-ga (respiratoorse distress sündroomiga) vastsündinutele vähendab suremust, õhulekke sündroomide (pneumotooraksi ja pulmonaalse interstitsiaalse emfüseemi) esinemissagedust ning vähendab 28 elupäevaks BPD (bronhopulmonaalse düsplaasia) kujunemise ning suremuse riski. (*Soll RF. Cochrane Database Syst Rev. 2000; (2): CD001149; Seger N, Soll R. Cochrane Database Syst Rev. 2009; Soll R, Ozek E. Cochrane Database Syst Rev. 2010; Soll RF. Cochrane Database Syst Rev. 2000; (2): CD000511*)	**Surfactant replacement therapy for preterm and term neonates with respiratory distress.** Polin RA, Carlo WA; Committee on Fetus and Newborn; American Academy of Pediatrics. Pediatrics. 2014

TABLE 1 Meta-analyses of Surfactant Replacement: Prophylaxis and Rescue Treatment With Animal-Derived and Synthetic Surfactant[2,3,8,11]

Outcome	Prophylactic Surfactant		Rescue Surfactant	
	Animal Derived	Synthetic	Animal Derived	Synthetic
	N RR (95% CI)	N RR (95% CI)	N RR (95% CI)	N RR (95% CI)
Neonatal mortality	8 0.60 (0.47–0.77)	7 0.70 (0.58–0.85)	10 0.68 (0.57–0.82)	6 0.73 (0.61–0.88)
Pneumothorax	9 0.40 (0.29–0.54)	6 0.67 (0.50–0.90)	12 0.42 (0.34–0.52)	5 0.64 (0.55–0.76)
PIE	6 0.46 (0.36–0.59)	2 0.68 (0.50–0.93)	8 0.45 (0.37–0.55)	4 0.62 (0.54–0.71)
BPD[a]	8 0.91 (0.79–1.05)	4 1.06 (0.83–1.36)	12 0.95 (0.84–1.08)	5 0.75 (0.61–0.92)
BPD/death[a]	8 0.80 (0.72–0.88)	4 0.89 (0.77–1.03)	12 0.83 (0.77–0.90)	4 0.73 (0.65–0.83)

N, number; PIE, pulmonary interstitial emphysema.
[a] Defined at 28 d.

Jan;133(1):156-63. doi: 10.1542/peds.2013-3443. Epub 2013 Dec 30.

Erinevatesse surfaktandi uuringutesse on kaasatud enneaegseid vastsündinuid, kes on sündinud 23 kuni 34 GN (gestatsiooninädalal) ja/või sünikaaluga 500 kuni 2000 g. (*Engle WA. Pediatrics 2008; Soll RF. Cochrane Database Syst Rev. 2000; (2): CD001149; Seger N, Soll R. Cochrane Database Syst Rev. 2009; Soll RF, Blanco F. Cochrane Database Syst Rev. 2001; Rojas-Reyes MX, Morley CJ, Soll R. Cochrane Database Syst Rev. 2012; Stevens TP, Harrington EW, Blennow M, Soll RF. Cochrane Database Syst Rev. 2007; Bahadue FL, Soll R. Cochrane Database Syst Rev. 2012; Soll R, Ozek E. Cochrane Database Syst Rev. 2010; Pfister RH, Soll R, Wiswell TE. Cochrane Database Syst Rev. 2009; Soll R, Ozek E. Cochrane Database Syst Rev. 2009; Soll RF. Cochrane Database Syst Rev. 2000; (2): CD000511);Suresh GK, Soll RF J Perinatol. 2005*). Nende uuringute erinevate gruppide analüüsil põhinevad tulemused näitasid, et surfaktantravi tulemusel vähenes suremus kõige enam lastel, kes sündisid enne 30 GN või sünnikaaluga <1250 g. (*Suresh GK, Soll RF J Perinatol. 2005*).
Surfaktantravi kasutamine ei ole muutnud teiste enneaegsusega seotud probleemide – BPD, IVH (intraventrikulaarne hemorraagia), NEK (nekrootiline enterokoliit), nosokomiaalsed infektsioonid, ROP (enneaegsusretinopaatia) ja PDA (avatud arterioosjuha) – esinemissagedust. Selle põhjuseks võib omakorda olla surfaktantravi tõttu vähenenud suremus enneaegsete populatsioonis (*Philip AG. J Pediatr. 1995*).

Enne rutiinse CPAP (continuous positive airway pressure – pidev positiivne rõhk hingamisteedes) ravi kasutamise ajastut läbi viidud uuringutel põhinevad metaanalüüsid on näidanud enneaegsetel vastsündinutel, kellele manustati profülaktilist surfaktanti võrreldes ravi eesmärgil manustatud surfaktanti saanutega, väiksemat suremust (RR 0,69; 95% CI 0,56-0,85; NNTB 20) ja väiksemat riski õhulekete esinemiseks (RR 0,79; 95% CI 0,63-0,98) (*Soll RF, Morley CJ. Cochrane Database Syst Rev. 2001*).

2012. a. avaldatud metaanalüüsis, mis hõlmas uuringuid (*National Institute of Child Health and Human Development SUPPORT Trial* ja *Vermont Oxford Network Delivery Room Management Trial*), kus kasutati rutiinselt CPAP ravi, ei ole enam näidatud profülaktilise

surfaktantraviga kaasnevat positiivset mõju suremusele (RR 0,89; 95% CI 0,76-1,04) ja õhulekkesündroomide esinemisele (RR 0,86; CI 0,71-1,04) (*Rojas-Reyes MX, Morley CJ, Soll R. Cochrane Database Syst Rev. 2012*). Lisaks oli profülaktilist surfaktantravi saanud laste hulgas suurem BPD esinemissagedus või suremus võrrelduna lastega, kelle stabiliseerimiseks kasutati CPAP ravi (RR 1,12; 95% CI 1,02-1,24). Samas on antud analüüsi alusel näidatud, et profülaktilise surfaktantraviga vähenes risk IVH esinemiseks (RR 0,91; 95% CI 0,82-1,00) ja raske IVH esinemiseks (RR 0,87; 95% CI 0,70-1,04), kuid ei esinenud olulisi erinevusi ROP, PDA ja PVL (periventrikulaarne leukomalaatsia) haigestumise osas. Sarnased tulemused saadi ka uuringutes, mis olid läbi viidud <30 GN sündinud lastel. Profülaktilist surfaktantravi saanud <30 GN sündinud enneaegsetel vastsündinutel oli suurem risk kroonilise kopsuhaiguse kujunemiseks (RR 1,13; 95% CI 1,00-1,28) ja oluliselt suurem suremus ja kroonilise kopsuhaiguse esinemissagedus (RR 1,13; 95% CI 1,02-1,25).	

Süstemaatiste ülevaadete kokkuvõtvad tõenduspõhised soovitused:

Profülaktiline ja ravi eesmärgil manustatud surfaktantravi vähendab RDS-i ja õhulekke sündroomide esinemssagedust ja suremust RDS-ga enneaegsetel lastel. (1) GRADE tugev soovitus

Varane CPAP ravi ja edasine selektiivne surfaktantravi võrreldes profülaktilise surfaktantravi kasutamisega väga enneaegsetel vastsündinutel vähendab BPD esinemissagedust ja suremust. (1) GRADE tugev soovitus

Kliinilised soovitused:

<30 GN sündinud enneaegsetele vastsündinutele, kes vajavad raske RDS-i tõttu mehhaanilist ventilatsiooni, tuleks manustada surfaktanti pärast esmast stabiliseerimist. (tugev soovitus)

Enneaegsetel vastsündinutel võiks vahetult sünnijärgselt alustatud CPAP ravi koos edasise selektiivse surfaktantraviga olla alternatiiviks tavapärasele intubatsioonile ja profülaktilisele või varasele surfaktantravile. (tugev soovitus)

Viited

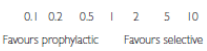
Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Background Surfactant therapy is effective in improving the outcome of very preterm infants. Trials have studied a wide variety of surfactant preparations used either to prevent or treat respiratory distress syndrome (RDS). In animalmodels, prophylactic surfactant leads to more homogeneous distribution and less evidence of lung damage. However, administration	**Prophylactic versus selective use of surfactant in preventing morbidity and mortality in**

requires intubation and treatment of infants who will not go on to develop RDS. This is of particular concern with the advent of improved approaches to providing continuous distending pressure, particularly in the form of nasal continuous positive airway pressure (NCPAP). **Objectives** To compare the effect of prophylactic surfactant administration with surfactant treatment of established RDS in very preterm infants at risk of RDS. **Search methods** We updated the search of theCochrane Central Register of Controlled Trials (*The Cochrane Library*), MEDLINE, EMBASE, CINAHL, and clinical trials.gov register in December 13, 2011. **Selection criteria** Randomized and quasi-randomized controlled trials that compared the effects of prophylactic surfactant administration with surfactant treatment of established RDS in preterm infants at risk of RDS. **Data collection and analysis** Data regarding clinical outcomes were extracted from the reports of the clinical trials by the review authors. Data analysis was done in accordance with the standards of the Cochrane Neonatal Review Group. **Main results** We identified 11 studies that met inclusion criteria (nine without routine application of continuous positive air way pressure (CPAP) in the selective treatment group; two with routine application of CPAP in the selective treatment group). The meta-analysis of studies conducted prior to the routine application of CPAP demonstrated a decrease in the risk of air leak and neonatal mortality associated with prophylactic administration of surfactant. However, the analyses of studies that allowed for routine stabilization on CPAP demonstrated a decrease in the risk of chronic lung disease or death in infants stabilized on CPAP. When all studies were evaluated together, the benefits of prophylactic surfactant could no longer be demonstrated.	**preterm infants.** Rojas-Reyes MX, Morley CJ, Soll R. Cochrane Database Syst Rev. 2012 Mar 14;3:CD000510. doi: 10.1002/14651858.CD000510.pub2. Review.

Comparison: 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants

Outcome: 1 Neonatal mortality

Study or subgroup	Prophylactic n/N	Selective n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Studies without routine application of CPAP					
Bevilacqua 1996	28/136	46/132		16.9 %	0.59 [0.39, 0.89]
Bevilacqua 1997	9/49	9/44		3.4 %	0.90 [0.39, 2.06]
Dunn 1991	9/62	8/60		3.0 %	1.09 [0.45, 2.63]
Egberts 1993	8/75	14/72		5.2 %	0.55 [0.24, 1.23]
Kattwinkel 1993	3/627	11/621		4.0 %	0.27 [0.08, 0.96]
Kendig 1991	23/235	40/244		14.2 %	0.60 [0.37, 0.97]
Merritt 1991	27/76	21/72		7.8 %	1.22 [0.76, 1.95]
Walti 1995	15/134	23/122		8.7 %	0.59 [0.33, 1.08]
Subtotal (95% CI)	**1394**	**1367**		**63.3 %**	**0.69 [0.56, 0.85]**
Total events: 122 (Prophylactic), 172 (Selective)					
Heterogeneity: Chi? = 10.60, df = 7 (P = 0.16); I? =34%					
Test for overall effect: Z = 3.54 (P = 0.00041)					
2 Studies with routine application of CPAP					
Dunn 2011	10/209	8/221		2.8 %	1.32 [0.53, 3.28]
SUPPORT 2010	114/653	94/663		33.8 %	1.23 [0.96, 1.58]
Subtotal (95% CI)	**862**	**884**		**36.7 %**	**1.24 [0.97, 1.58]**
Total events: 124 (Prophylactic), 102 (Selective)					
Heterogeneity: Chi? = 0.02, df = 1 (P = 0.88); I? =0.0%					
Test for overall effect: Z = 1.73 (P = 0.083)					
Total (95% CI)	**2256**	**2251**		**100.0 %**	**0.89 [0.76, 1.04]**
Total events: 246 (Prophylactic), 274 (Selective)					
Heterogeneity: Chi? = 22.17, df = 9 (P = 0.01); I? =59%					
Test for overall effect: Z = 1.48 (P = 0.14)					
Test for subgroup differences: Chi? = 13.11, df = 1 (P = 0.00), I? =92%					



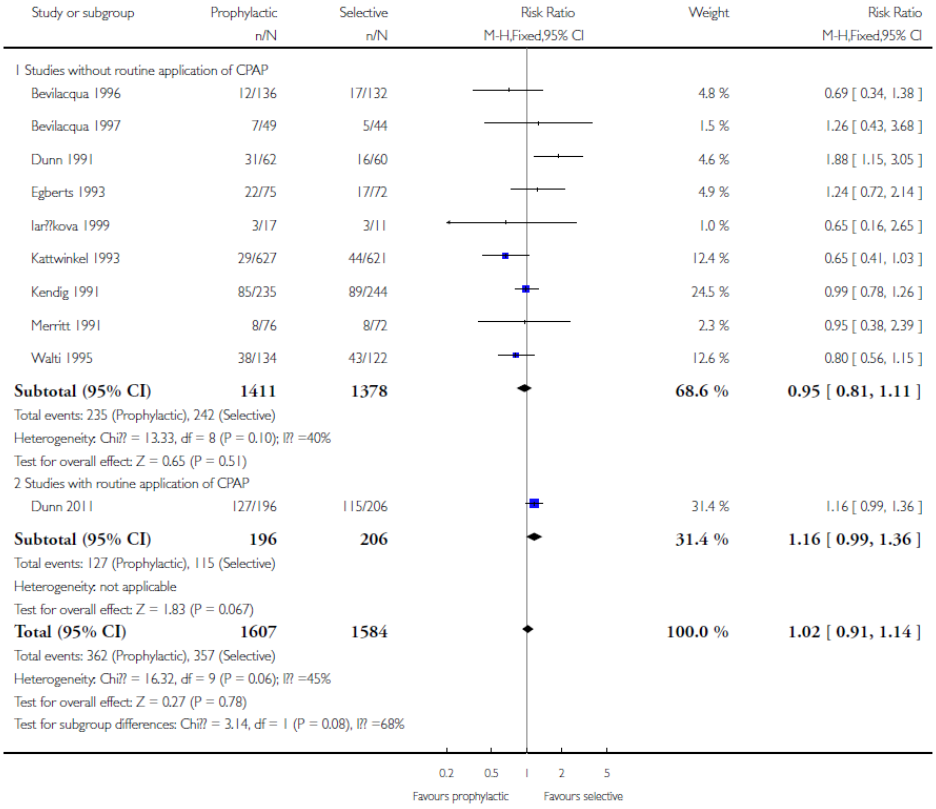
Comparison: 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants

Outcome: 2 Mortality at 36 weeks PMA or prior to hospital discharge

Study or subgroup	Prophylactic n/N	Selective n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Studies without routine application of CPAP					
Walti 1995	18/134	29/122		24.1 %	0.57 [0.33, 0.96]
Kendig 1991	29/235	49/244		38.1 %	0.61 [0.40, 0.94]
Egberts 1993	10/75	15/72		12.1 %	0.64 [0.31, 1.33]
Merritt 1991	29/76	23/72		18.7 %	1.19 [0.77, 1.86]
Subtotal (95% CI)	**520**	**510**		**93.1 %**	**0.72 [0.56, 0.93]**
Total events: 86 (Prophylactic), 116 (Selective)					
Heterogeneity: Chi? = 6.45, df = 3 (P = 0.09); I? =53%					
Test for overall effect: Z = 2.57 (P = 0.010)					
2 Studies with routine application of CPAP					
Dunn 2011	15/208	9/220		6.9 %	1.76 [0.79, 3.94]
Subtotal (95% CI)	**208**	**220**		**6.9 %**	**1.76 [0.79, 3.94]**
Total events: 15 (Prophylactic), 9 (Selective)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
Total (95% CI)	**728**	**730**		**100.0 %**	**0.79 [0.63, 1.00]**
Total events: 101 (Prophylactic), 125 (Selective)					
Heterogeneity: Chi? = 10.35, df = 4 (P = 0.03); I? =61%					
Test for overall effect: Z = 1.92 (P = 0.055)					
Test for subgroup differences: Chi? = 4.32, df = 1 (P = 0.04), I? =77%					

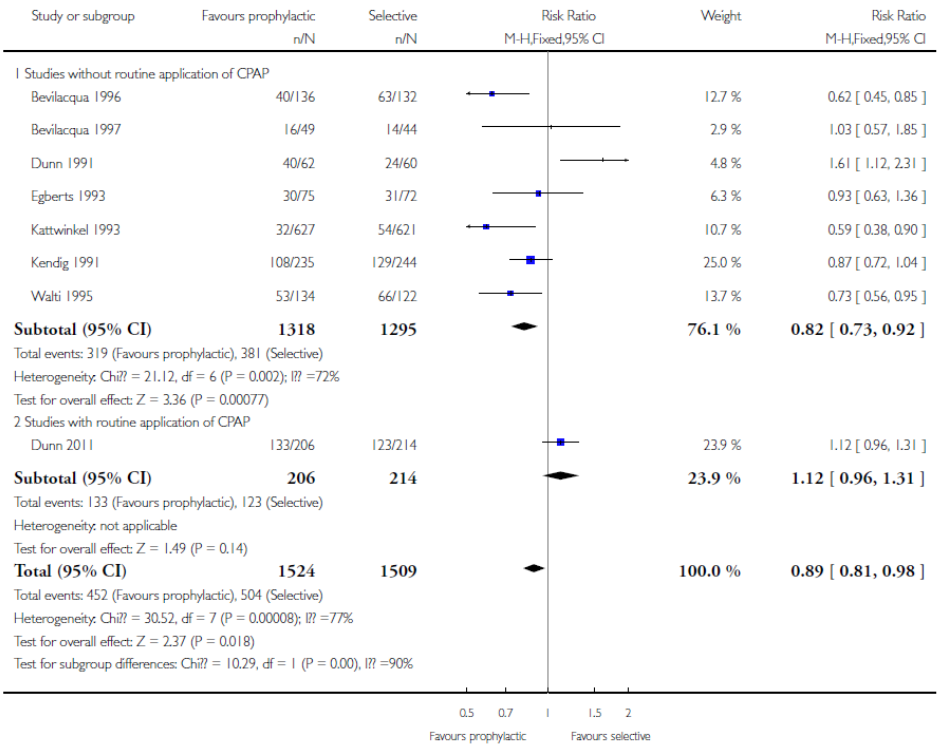
Comparison: 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants

Outcome: 3 Bronchopulmonary dysplasia (oxygen requirement at 28 to 30 days of age)



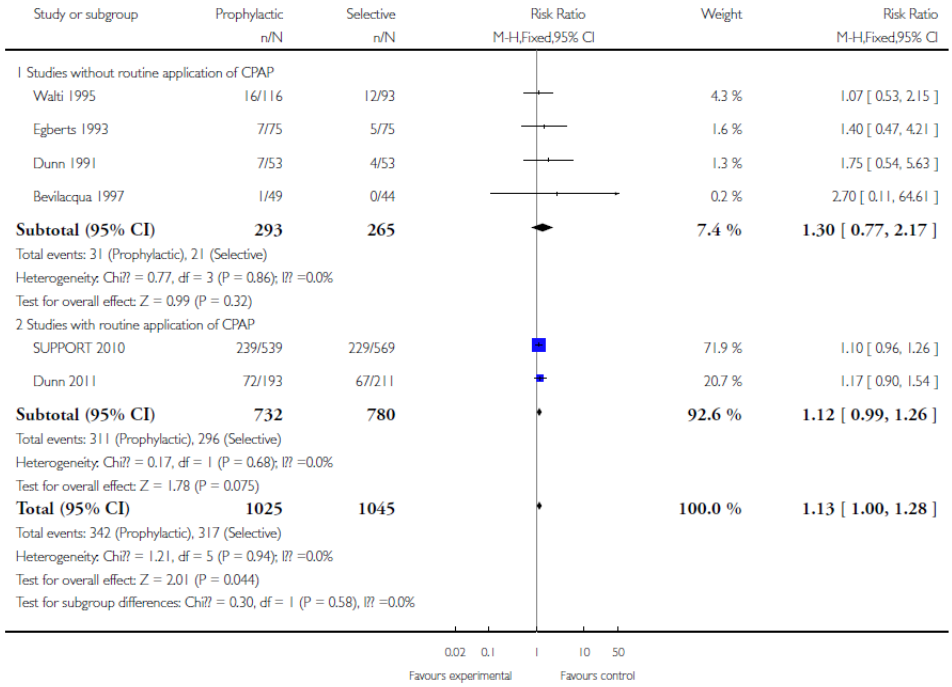
Comparison: 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants

Outcome: 4 Bronchopulmonary dysplasia or death at 28 to 30 days of age



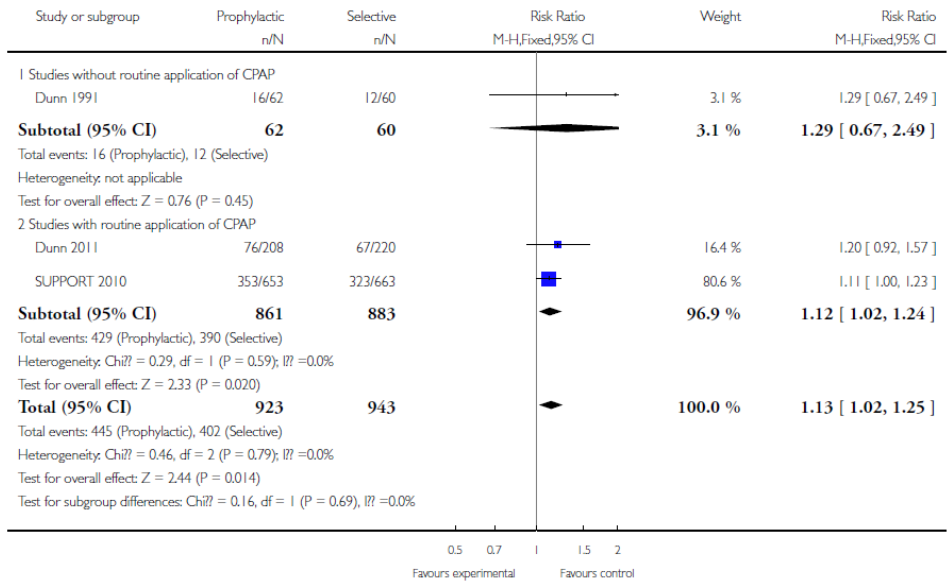
Comparison: 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants

Outcome: 5 Chronic lung disease



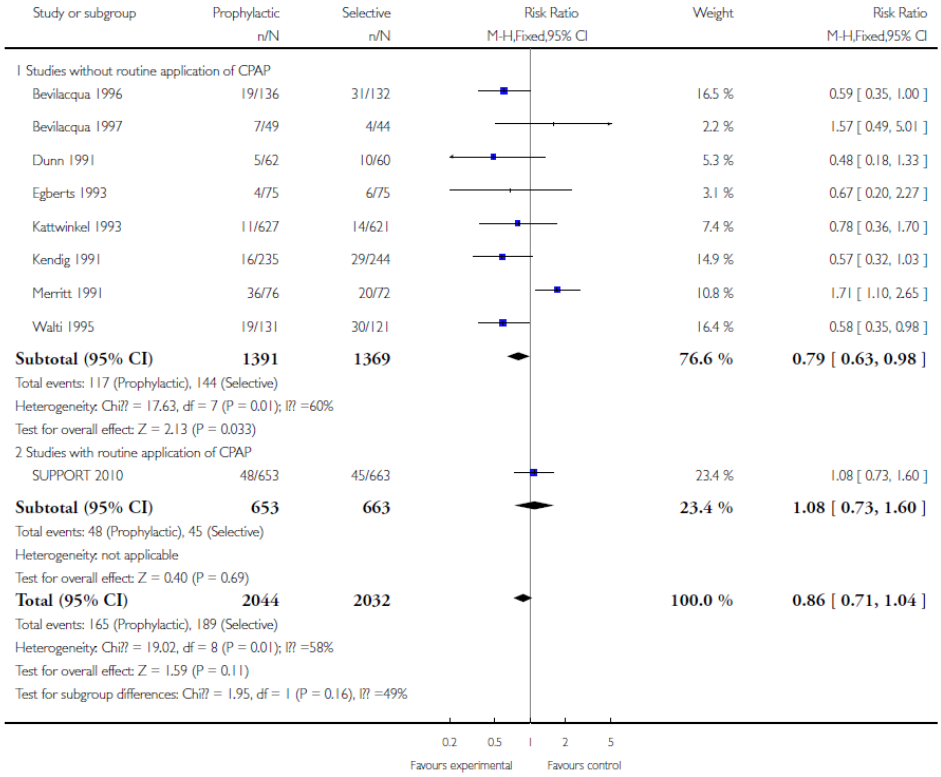
Comparison: 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants

Outcome: 6 Chronic lung disease or death



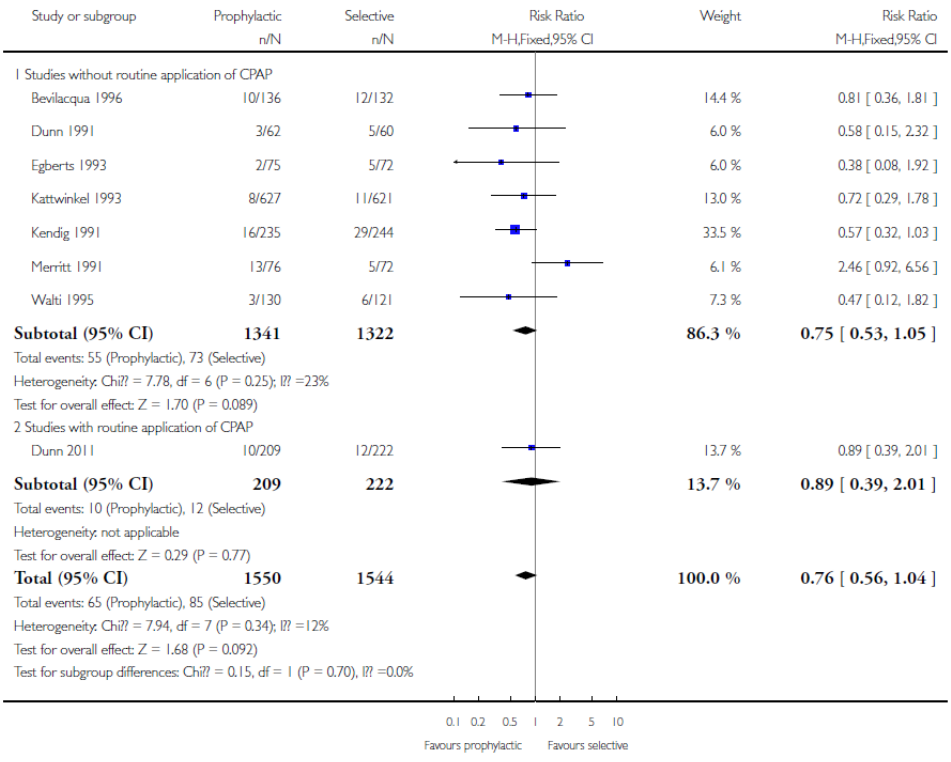
Comparison: 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants

Outcome: 7 Any air leak syndromes (including pulmonary interstitial emphysema, pneumothorax, pneumomediastinum)



Comparison: 1 Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants

Outcome: 8 Pneumothorax



Authors' conclusions **Although the early trials of prophylactic surfactant administration to infants judged to be at risk of developing RDS compared with selective use of surfactant in infants with established RDS demonstrated a decreased risk of air leak and mortality, recent large trials that reflect current practice (including greater utilization of maternal steroids and routine post delivery stabilization on CPAP) do not support these differences and demonstrate less risk of chronic lung disease or death when using early stabilization on CPAP with selective surfactant administration to infants requiring intubation.**	
OBJECTIVE: We designed a **multicenter randomized trial** to compare 3 approaches to the initial respiratory management of preterm neonates: prophylactic surfactant followed by a period of mechanical ventilation (prophylactic surfactant [PS]); prophylactic surfactant with rapid extubation to bubble nasal continuous positive airway pressure (intubate-surfactant-extubate [ISX]) or initial management with bubble continuous positive airway pressure and selective surfactant treatment (nCPAP). DESIGN/METHODS: Neonates born at **26 0/7 to 29 6/7 weeks' gestation** were enrolled at participating Vermont Oxford Network centers and randomly assigned to PS, ISX, or nCPAP groups before delivery. Primary outcome was the incidence of death or bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age. RESULTS: **648 infants** enrolled at 27 centers. The study was halted before the desired sample size was reached because of declining enrollment. When compared with the **PS group, the relative risk of BPD or death was 0.78 (95% confidence interval: 0.59 –1.03) for the ISX group and 0.83 (95% confidence interval: 0.64 –1.09) for the nCPAP group.** There were no statistically significant differences in mortality or other complications of prematurity. In the nCPAP group, 48% were managed without intubation and ventilation, and 54% without surfactant treatment.	**Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates.** Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, Ferrelli K, O'Conor J, Soll RF; Vermont Oxford Network DRM Study Group. Pediatrics. 2011 Nov;128(5):e1069-76. doi: 10.1542/peds.2010-3848. Epub 2011 Oct 24.

TABLE 2 Respiratory Support in First Hour of Life

Intervention	PS ($n = 209$)	ISX ($n = 216$)	nCPAP ($n = 223$)
NCPAP, *n*/*N* (%)	11/209 (5.3)	167/216 (77.3)	203/223 (91.0)
Intubated, *n*/*N* (%)	207/209 (99.0)	213/216 (98.6)	40/223 (17.9)
Age at intubation, median (quartile), min	3.5 (2.0–5.0)	4.0 (2.0–6.0)	4.5 (3.0–11.5)
Surfactant administration, *n*/*N* (%)	206/209 (98.6)	212/216 (98.2)	33/223 (14.8)
Extubation, *n*/*N* (%)	1/209 (0.5)	180/216 (83.3)	5/223 (2.2)

TABLE 3 Status at 36 Weeks' Postmenstrual Age

	PS	ISX	RR (95% CI)	NCPAP	RR (95% CI)
All, *N*	209	216	—	223	—
Death, %	7.2	7.0	0.97 (0.49–1.94)	4.1	0.57 (0.25–1.27)
Death or BPD, %	36.5	28.5	0.78 (0.59–1.03)	30.5	0.83 (0.64–1.09)
Gestational age 26–27⅙ wk, *N*	98	101	—	102	—
Death, %	11.2	10.1	0.90 (0.40–2.02)	5.9	0.53 (0.20–1.38)
Death or BPD, %	53.1	43.4	0.82 (0.61–1.10)	40.6	0.77 (0.57–1.03)
Gestational age 28–29⅙ wk, *N*	111	115	—	121	—
Death, %	3.6	4.4	1.20 (0.33–4.34)	2.5	0.69 (0.16–3.03)
Death or BPD, %	21.8	15.7	0.72 (0.41–1.25)	21.9	1.00 (0.61–1.64)

TABLE 5 Complications of Prematurity

	PS, *n*/*N* (%)	ISX, *n*/*N* (%)	RR vs PS (95% CI)	NCPAP, *n*/*N* (%)	RR vs PS (95% CI)
Pneumothorax	10/209 (4.8)	7/216 (3.2)	0.68 (0.26–1.75)	12/222 (5.4)	1.13 (0.50–2.56)
Pulmonary hemorrhage	6/209 (2.9)	7/216 (3.2)	1.13 (0.39–3.30)	3/222 (1.4)	0.47 (0.12–1.86)
PDA	92/208 (44.2)	74/216 (34.3)	0.77 (0.61–0.98)	101/222 (45.5)	1.03 (0.83–1.27)
NEC	14/209 (6.7)	16/216 (7.4)	1.11 (0.55–2.21)	18/222 (8.1)	1.21 (0.69–2.54)
NEC surgery	9/209 (4.3)	7/215 (3.3)	0.75 (0.29–1.98)	12/222 (5.4)	1.25 (0.54–2.90)
Gastrointestinal perforation	10/209 (4.8)	6/216 (2.8)	0.58 (0.21–1.57)	7/221 (3.2)	0.66 (0.26–1.71)
Sepsis					
Late-onset bacterial infection[a]	27/205 (13.2)	25/214 (11.7)	0.89 (0.53–1.48)	17/220 (7.7)	0.59 (0.33–1.04)
Coagulase-negative staphylococcus	18/205 (8.8)	17/214 (7.9)	0.90 (0.48–1.71)	16/221 (7.2)	0.82 (0.43–1.57)
Late-onset fungal infection	3/205 (1.5)	3/214 (1.4)	0.96 (0.20–4.69)	1/221 (0.5)	0.31 (0.03–2.95)
Received cranial ultrasound	203/209 (97.1)	207/216 (95.8)	0.99 (0.95–1.02)	218/222 (98.2)	1.01 (0.98–1.04)
With any IVH, %	46/203 (22.7)	43/206 (20.9)	0.92 (0.64–1.33)	47/218 (21.6)	0.95 (0.68–1.36)
With severe IVH, %	12/203 (5.9)	8/206 (3.9)	0.66 (0.27–1.57)	6/218 (2.8)	0.47 (0.18–1.22)
PVL	2/190 (1.1)	6/204 (2.9)	2.79 (0.57–13.68)	3/206 (1.5)	1.38 (0.23–8.19)
Any ROP	65/183 (35.5)	61/180 (33.9)	0.95 (0.72–1.27)	85/192 (44.3)	1.25 (0.97–1.60)
Severe ROP	7/183 (3.8)	4/180 (2.2)	0.58 (0.17–1.95)	13/192 (6.8)	1.77 (0.72–4.34)

PDA indicates patent ductus arteriosus; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.
[a] All bacterial pathogens, including coagulase-negative staphylococcus.

CONCLUSIONS: **Preterm neonates were initially managed with either nCPAP or PS with rapid extubation to nCPAP had similar clinical outcomes to those treated with PS followed by a period of mechanical ventilation. An approach that uses early nCPAP leads to a reduction in the number of infants who are intubated and given surfactant.**

Early CPAP versus surfactant in extremely preterm infants.

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG,

BACKGROUND
There are limited data to inform the choice between early treatment with continuous
positive airway pressure (CPAP) and early surfactant treatment as the initial support for extremely-low-birth-weight infants.
METHODS
We performed a **randomized, multicenter trial**, with a 2-by-2 factorial design, involving
infants who were born between **24 weeks 0 days and 27 weeks 6 days** of gestation. Infants were randomly assigned to
intubation and surfactant treatment (within 1 hour after birth) or to
CPAP treatment initiated in the delivery room, with subsequent use of a protocol-driven limited ventilation strategy.

Infants were also randomly assigned to one of two target ranges of oxygen saturation. The primary outcome was death or bronchopulmonary dysplasia as defined by the requirement for supplemental oxygen at 36 weeks (with an attempt at withdrawal of supplemental oxygen in neonates who were receiving less than 30% oxygen). RESULTS A total of **1316** infants were enrolled in the study. **The rates of the primary outcome did not differ significantly between the CPAP group and the surfactant group (47.8% and 51.0%, respectively; relative risk with CPAP, 0.95; 95% confidence interval [CI], 0.85 to 1.05)** after adjustment for gestational age, center, and familial clustering. The results were similar **when bronchopulmonary dysplasia was defined according to the need for any supplemental oxygen at 36 weeks (rates of primary outcome, 48.7% and 54.1%, respectively; relative risk with CPAP, 0.91; 95% CI, 0.83 to 1.01).** **Infants who received CPAP treatment, as compared with infants who received surfactant treatment, less frequently required intubation or postnatal corticosteroids for bronchopulmonary dysplasia (P<0.001), required fewer days of mechanical ventilation (P = 0.03), and were more likely to be alive and free from the need for mechanical ventilation by day 7 (P = 0.01).** The rates of other adverse neonatal outcomes did not differ significantly between the two groups.	Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Donovan EF, Newman NS, Ambalavanan N, Frantz ID 3rd, Buchter S, Sánchez PJ, Kennedy KA, Laroia N, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Bhandari V, Watterberg KL, Higgins RD. N Engl J Med. 2010 May 27;362(21):1970-9. doi: 10.1056/NEJMoa0911783. Epub 2010 May 16. Erratum in: N Engl J Med. 2010 Jun 10;362(23):2235.

Table 3. Selected Prespecified Outcomes.*

Outcome	CPAP (N=663)	Surfactant (N=653)	Relative Risk with CPAP (95% CI)	Difference in Means (95% CI)	Adjusted P Value
BPD or death by 36 wk of postmenstrual age — no. (%)					
Physiological definition of BPD†	317 (47.8)	333 (51.0)	0.95 (0.85 to 1.05)		0.30
BPD defined by need for supplemental oxygen	323 (48.7)	353 (54.1)	0.91 (0.83 to 1.01)		0.07
BPD by 36 wk of postmenstrual age — no./total no. (%)					
Physiological definition of BPD†	223/569 (39.2)	219/539 (40.6)	0.99 (0.87 to 1.14)		0.92
BPD defined by need for supplemental oxygen	229/569 (40.2)	239/539 (44.3)	0.94 (0.82 to 1.06)		0.32
Death by 36 wk of postmenstrual age — no. (%)	94 (14.2)	114 (17.5)	0.81 (0.63 to 1.03)		0.09
Need for supplemental oxygen — no. of days‡					0.12
Adjusted mean	62.2±1.6	65.3±1.6		−3.1 (−7.1 to 0.8)	
Unadjusted median	52	56			
Interquartile range	20 to 86	27 to 91			
Need for mechanical ventilation — no. of days‡§					0.03
Adjusted mean	24.8±1.0	27.7±1.1		−3.0 (−5.6 to −0.3)	
Unadjusted median	10	13			
Interquartile range	2 to 32	2 to 36			
Survival without need for high-frequency or conventional ventilation at 7 days — no./total no. (%)	362/655 (55.3)	318/652 (48.8)	1.14 (1.03 to 1.25)		0.01
Any air leak in first 14 days — no. (%)	45 (6.8)	48 (7.4)	0.89 (0.6 to 1.32)		0.56
Necrotizing enterocolitis requiring medical or surgical treatment — no./total no. (%)	83/654 (12.7)	63/636 (9.9)	1.25 (0.92 to 1.71)		0.15
Intraventricular hemorrhage grade 3 or 4 — no./total no. (%)¶	92/642 (14.3)	72/628 (11.5)	1.26 (0.94 to 1.68)		0.12
Postnatal corticosteroid therapy for BPD — no./total no. (%)	47/649 (7.2)	83/631 (13.2)	0.57 (0.41 to 0.78)		<0.001
Severe retinopathy of prematurity among survivors — no./total no. (%)	67/511 (13.1)	65/473 (13.7)	0.94 (0.69 to 1.28)		0.71

* Plus–minus values are means ±SD. BPD denotes bronchopulmonary dysplasia, CI confidence interval, and CPAP continuous positive airway pressure.
† The physiological definition of BPD includes, as a criterion, the receipt of more than 30% supplemental oxygen at 36 weeks, the need for positive-pressure support, or in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of supplemental oxygen.[16,17]
‡ Data are for 1098 infants who survived to discharge, transfer, or 120 days; the maximum follow-up was 120 days.
§ This variable includes high-frequency ventilation and conventional ventilation.
¶ There are four grades of intraventricular hemorrhage; higher grades indicate more severe bleeding.

CONCLUSIONS
The results of this study support consideration of CPAP as an alternative to intubation and surfactant in preterm infants. (ClinicalTrials.gov number, NCT00233324.)

OBJECTIVE: Early surfactant followed by extubation to nasal continuous positive airway pressure (nCPAP) compared with later surfactant and mechanical ventilation (MV) reduce the need for MV, air leaks, and bronchopulmonary dysplasia. This **randomized, controlled trial** investigated whether
prophylactic surfactant followed by nCPAP compared with
early nCPAP application with early selective surfactant would reduce the need for MV in the first 5 days of life.
METHODS: A total of **208** inborn infants who were born at 25 to 28 weeks' gestation and were not intubated at birth were randomly assigned to prophylactic surfactant or nCPAP within 30 minutes of birth. Outcomes were assessed within the first 5 days of life and until death or discharge of the infants from hospital.
RESULTS: **Thirty-three (31.4%) infants in the prophylactic**

Prophylactic or early selective surfactant combined with nCPAP in very preterm infants.

Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli S, Mosca F, Nona J, Thomson M, Verder H, Fabbri L, Halliday H;

surfactant group needed MV in the first 5 days of life compared with 34 (33.0%) in the nCPAP group (risk ratio: 0.95 [95% confidence interval: 0.64 –1.41]; P = .80). Death and type of survival at 28 days of life and 36 weeks' postmenstrual age and incidence of main morbidities of prematurity (secondary outcomes) were similar in the 2 groups. A total of 78.1% of infants in the prophylactic surfactant group and 78.6% in the nCPAP group survived in room air at 36 weeks' postmenstrual age.

TABLE 2 Primary Outcome: Need for MV Within 5 Days

GA, *n* (%)	Prophylactic Surfactant (*N* = 105)	nCPAP (*N* = 103)	RR (95% CI)
25–28 wk 6 d	33 (31.4)	34 (33.0)	0.95 (0.64–1.41)
25–26 wk 6 d	15 (46.9)	12 (38.7)	1.21 (0.68–2.16)
27–28 wk 6 d	18 (24.7)	22 (30.6)	0.81 (0.47–1.37)

TABLE 3 Death and Type of Survival

Outcome	28 d of Age			36 wk Postmenstrual Age		
	Prophylactic Surfactant, *n* (%)	nCPAP, *n* (%)	RR (95% CI)	Prophylactic Surfactant, *n* (%)	nCPAP, *n* (%)	RR (95% CI)
Survivors in room air	43 (41.0)	32 (31.1)	1.32 (0.91–1.90)	82 (78.1)	81 (78.6)	0.99 (0.86–1.14)
Survivors with oxygen only	11 (10.5)	15 (14.6)	0.72 (0.35–1.49)	5 (4.8)	5 (4.9)	0.98 (0.29–3.29)
Survivors on respiratory support (MV or nCPAP)	44 (41.9)	47 (45.6)	0.92 (0.67–1.25)	9 (8.6)	6 (5.8)	1.47 (0.54–3.99)
Death						
25–28 wk 6 d	7 (6.7)	9 (8.7)	0.76 (0.30–1.97)	9 (8.6)	11 (10.7)	0.80 (0.35–1.86)
25–26 wk 6 d	2 (6.3)	3 (9.7)	0.65 (0.13–3.10)	4 (12.5)	3 (9.7)	1.29 (0.34–4.96)
27–28 wk 6 d	5 (6.8)	6 (8.3)	0.82 (0.27–2.45)	5 (6.8)	8 (11.1)	0.71 (0.20–2.61)

TABLE 4 Secondary Outcomes

Outcomes	Prophylactic Surfactant (*N* = 105), *n* (%)	nCPAP (*N* = 103), *n* (%)	RR (95% CI)
Pneumothorax	7 (6.7)	1 (1.0)	6.82 (0.86–53.75)
Pulmonary interstitial emphysema	3 (2.9)	4 (3.9)	0.74 (0.17–3.21)
Pulmonary hemorrhage	3 (2.9)	2 (1.9)	1.47 (0.25–8.76)
Intraventricular hemorrhage grades 3–4	6 (5.7)	8 (7.8)	0.73 (0.27–2.03)
25–26 wk 6 d	3 (9.4)	4 (12.9)	0.73 (0.19–2.75)
27–28 wk 6 d	3 (4.1)	4 (5.6)	0.74 (0.19–2.89)
Patent ductus arteriosus	43 (41.0)	51 (49.5)	0.83 (0.62–1.10)
Medically treated	28 (26.7)	35 (34.0)	
Surgically ligated	6 (5.7)	3 (2.9)	
Retinopathy of prematurity			
Any	30 (28.6)	30 (29.1)	0.98 (0.65–1.48)
Stage ≥2	7 (6.7)	7 (6.8)	0.98 (0.36–2.70)
Necrotizing enterocolitis	7 (6.7)	9 (8.7)	0.76 (0.30–1.90)
Cystic periventricular leukomalacia	3 (2.9)	2 (1.9)	1.47 (0.25–8.76)
Sepsis	45 (42.9)	43 (41.7)	1.02 (0.75–1.40)
Moderate and severe BPD in survivors			
25–28 wk 6 d	14/98 (14.3)	11/94 (11.7)	1.22 (0.58–2.50)
25–26 wk 6 d	7/30 (23.3)	7/28 (25.0)	0.93 (0.38–2.30)
27–28 wk 6 d	7/68 (10.3)	4/66 (6.1)	1.70 (0.55–5.30)
Use of systemic postnatal corticosteroids	14 (13.3)	11 (10.7)	1.25 (0.59–2.62)

CONCLUSIONS: **Prophylactic surfactant was not superior to nCPAP and early selective surfactant in decreasing the need for MV in the first 5 days of life and the incidence of main morbidities of prematurity in spontaneously breathing very preterm infants on nCPAP.**

CURPAP Study Group.

Pediatrics. 2010 Jun;125(6):e1402-9. doi: 10.1542/peds.2009-2131. Epub 2010 May 3.

NB! Sponsoreeritud Chiesi Farmaceutici SpA (Parma, Italy).

Otsingustrateegia kliinilistele küsimustele 19-21.

Andmebaas	Medline (PUBMED)
Otsingustrateegia: (Key words + Mesh)	((((surfactant therapy) OR prophylactic surfactant) OR surfactant)) AND ((((((((((((("premature infant") OR "premature infants") OR "premature newborn") OR "premature newborns") OR "premature neonate") OR "premature neonates") OR "preterm infant") OR "preterm infants") OR "preterm newborn") OR "preterm newborns") OR "preterm neonate") OR "preterm neonates")) OR (("Infant, Premature"[Mesh]) OR "Infant, Low Birth Weight"[Mesh]))
Tulemuste arv	SR: 14, RCT: 17
Filtrid	Systematic Review , Meta-analysis Randomised Controlled Trial
Ajaline piirang	5 aastat
Muud piirangud	English language