Kliiniline küsimus nr 20

Kas hingamishäiretega enneaegsetel vastsündinutel kasutada parema ravitulemi saavutamiseks varast surfaktantravi võrreldes hilise surfaktantraviga:

- preparaadi valik (looduslik võrreldes sünteetiline; erinevad looduslikud)
- surfaktandi annus 200mg/kg/dosi võrreldes 100mg/kg/dosi

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

Ravijuhendid:

Soovitused surfaktani preparaatide valiku ja annustamise kohta on leitavad kahes AGREE-ga hinnatud ravijuhendis ja ühes 2014 aastal avaldatud süstemaatilises ülevaates (Clinical report 2014 AAP):

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.

AARC Clinical Practice Guideline. Surfactant replacement therapy: 2013. Walsh BK1, Daigle B, DiBlasi RM, Restrepo RD; American Association for Respiratory Care. Respir Care. 2013 Feb;58(2):367-75.)

Kokkuvõte ravijuhendites leiduvast:

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 (vt. GRADE kliiniline küsimus nr. 19).
Enneaegse vastsündinu edukaks elustamiseks on hädavajalik surfaktandi manustamine. Vajalik on fosfolopiidi 100 mg/kg [Verlato G, 2004] , aga on farmakokineetilisi ja kliinilisi uuringuid, mis näitavad, et annusel 200 mg/kg on pikem poolestusaeg [Cogo PE, 2009] ning kiirem ja efektiivsem kliiniline vastus [Singh N 2011].

Euroopas 2013 litsenseeritud surfaktandi preparaadid ja nende annused on:

Table 2. Surfactant preparations licensed in Europe in 2013

Generic name	Trade name	Source	Manufacturer	Dose (volume)
Beractant	Survanta®	bovine	Ross Laboratories (USA)	100 mg/kg/dose (4 ml/kg)
Bovactant	Alveofact®	bovine	Lyomark Pharma (Germany)	50 mg/kg/dose (1.2 ml/kg)
Poractant alfa	Curosurf®	porcine	Chiesi Farmaceutici (Italy)	100–200 mg/kg/dose (1.25–2.5 ml/kg)

Ravijuhise tugev soovitus (A) on, et poractant alfa algdoos 200 mg/kg on parem kui 100 mg/kg või beractant RDS raviks.

AARC 2013 aasta ravijuhise järgi on kättesaadavad järgmised surfaktandi preparaadid:

SURFACTANT REPLACEMENT THERAPY: 2013

Table. Currently Available Surfactants

	Trade Name	Source	Manufacturer	Dose	Surfactant Protein B
Poractant alfa	Curosurf	Porcine	Chiesi Farmaceutici	100–200 mg/kg/dose (1.25–2.5 mL/kg)	0.45
Calfactant	Infasurf	Bovine	Ony	105 mg/kg/dose (3 mL/kg)	0.26
Beractant	Survanta	Bovine	Abbott Laboratories	100 mg/kg/dose (4 mL/kg)	< 1
Lucinactant	Surfaxin	Synthetic	Discovery Labs	5.8 mL/kg	KL_4

Alates märtsist 2012 on Lucinactant esimene kasutusel olev sünteetiline surfaktant, mis kliiniliste uuringute alusel on sama efektiivne kui beractant ja poractant alfa [Engle WA.2008]. Juhises soovitatakse naturaalset eksogeenset surfaktanti kasutada rohkem kui laboris sünteesitud surfaktanti. Naturaalsel surfaktandil on parem pindaktiivsus ja parem jaotuvus alveoolide pinnal. Võrdlevates randomiseeritud kliinilistes kontrolluuringutes on naturaalse surfaktandiga ravimisel väiksem hapnikuvajadus ja madlam pneumotooraksi, BPD ja suremuse risk [Suresh GK.2005; Halliday HL.1997].
Naturaalse surfaktandiga on väike võimalus mõnede haiguste ülekandmiseks [Singh N et al 2011, *Efficacy of porcine versus bovine surfactants for preterm newborns with respiratory distress syndrome: systematic review and meta-analysis. Pediatrics 2011; 128(6):e1588-d1595*]. Võivad esineda religioossed ja kultuurilised vastuolud seoses naturaalsete loomset päritolu surfktantidega.

AARC juhise järgi soovitatakse naturaalset eksogeenset surfaktandi preparaati enam kui sünteetilist (1B).

Süstemaatilised ülevaated:

Surfactant Replacement Therapy for Preterm and Term Neonates With Respiratory Distress Richard A. Polin, MD, FAAP, Waldemar A. Carlo, MD, FAAP, and COMMITTEE ON FETUS AND NEWBORN Clinical report 2014 AAP

Kokkuvõte süstemaatilistest ülevaadetest:
*Kui võrreldi naturaalset surfaktanti (*beractant or poractant) ja sünteetilist surfaktanti (lucinactant), siis mõlema toime efektiivsus oli võrdne [Sinha SK 2005, Moya F 2007]. Neonataalne haigestumus (IVH, PVL, kopsu verejooks, sepsis, PDA, ROP, NEK ja BPD) ei erinenud statistiliselt tõepäraselt nende uuritavate gruppide vahel, keda raviti loodusliku surfaktandiga võrreldes sünteetilise surfaktandiga.

TABLE 2 Composition and Dosage of Surfactants[17]

Surfactant	Main Phospholipids	Proteins	Phospholipid Concentration	Suggested Dose	Phospholipid per Dose
Animal-derived					
Beractant (Survanta®) minced bovine lung extract	DPPC and PG	(<0.1%) SP-B and (1%) SP-C	25 mg/mL	4 mL/kg	100 mg/kg
Calfactant (Infasurf®) bovine calf lung lavage	DPPC and PG	(0.7%) SP-B and (1%) SP-C	35 mg/mL	3 mL/kg	105 mg/kg
Poractant (Curosurf®) minced porcine lung extract	DPPC and PG	(0.6%) SP-B and (1%) SP-C	80 mg/mL	2.5 mL/kg and	100-200 mg/kg
				1.25 mL/kg	100 mg/kg
Synthetic					
Colfosceril (Exosurf®)	DPPC (100%)	None	13.5 mg/mL	5 mL/kg	67.5 mg/kg
Synthetic, protein analog					
Lucinactant (Surfaxin®)	DPPC and POPG	KL4 peptide as SP-B	30 mg/mL	5.8 mL/kg	175 mg/kg

DPPC, dipalmitoyl phosphatidylcholine; PG, phosphatidylglycerol; POPG, palmitoyloleyl phosphatidylglycerol; SP-C, surfactant protein C.
[a] Abbvie Inc, North Chicago, IL.
[b] ONY Inc, Amherst, NY.
[c] Chiesi Farmaceutici, Parma, Italy.
[d] GlaxoSmithKline, Middlesex, UK.
[e] Discovery Laboratories, Warrington, PA.

Mõlemad, nii loomset päritolu surfaktant kui ka uus, sünteetiline surfaktant, vähendavad ägedat respirtoorset haigestumist ja suremust RDS-ga enneaegsetel lastel (LOE 1 – tugev soovitus).

Hiljuti avaldatud randomiseeritud kontrolluuringud kinnitavad ravijuhistes ja süstemaatilises ülevaates esitatud soovitusi:
2014 aastal Brasiilisas avaldatud RCT [*A multicenter, randomized, double-blind trial of a new porcine surfactant in premature infants with respiratory distress syndrome* , Celso Moura Rebello et al 2014], võrdles looduslikke surfaktante Butanan vs. Survanta® või Curosurf® kontrollgrupiga. Fosfolopiidide annus oli 100 mg/kg kõigil ravitud lastel. Kui hinnati suremust ja peamisi tulemusnäitajaid 72 tunni ja 28 päeva vanuselt, siis näidati, et nii uus kui ka endised mõlemad surfaktandid on efektiivsed ja turvalised vastsündinute RDS ravis.

Türgi uuringus *Neurodevelopmental Outcomes of Very Low Birth Weight Preterm Infants Treated With Poractant Alfa versus Beractant for Respiratoty Distress Syndrome* [Zeynep Eras et al,2014]
võrreldi proactant alfa vs beractant` ravi saanud RDS-ga enneaegsete laste psühhomotoorset arengut 2 aasta vanuselt. Hinnang anti Bayley II skaalaga (BSID II) kokku 215 lapsel. Uuringust järeldati, et nii proactant alfa kui beractant`ga ravitud laste kaugtulemus oli sarnane.

USA-s võrreldi 2005-2010 aastal surfaktantide beractant, calfactant või poractant alfa efektiivsust kokku 322 vastsündinute intensiivravi patsiendil [*Comparative Effectiveness of Surfactant Preparations in Premature Infants,* Trembath et al, 2013]. Uuring näitas preparaatide võrdset efektiivsust õhulekkesündroomide, suremuse ja BPD preventsioonis.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Table 2. Surfactant preparations licensed in Europe in 2013 Generic name / Trade name / Source / Manufacturer / Dose (volume) Beractant / Survanta® / bovine / Ross Laboratories (USA) / 100 mg/kg/dose (4 ml/kg) Bovactant / Alveofact® / bovine / Lyomark Pharma (Germany) / 50 mg/kg/dose (1.2 ml/kg) Poractant alfa / Curosurf® / porcine / Chiesi Farmaceutici (Italy) / 100–200 mg/kg/dose (1.25–2.5 ml/kg) At least 100 mg/kg of phospholipid is required [Verlato G, 2004] , but there are pharmacokinetic and clinical data suggesting that 200 mg/kg has a longer half-life [Cogo PE, 2009] and a better acute response [Singh N 2011]. Recommendation: Poractant alfa in an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or beractant for treatment of RDS (A).	**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.
As of March 6, 2012, Lucinactant is the first synthetic peptide-containing surfactant cleared by the FDA for use to treat neonatal RDS. When compared in clinical trials, lucinactant, was found to have similar rates of mortality and morbidity as did beractant and poractant alfa [Engle WA.2008]. A major component of animal derived surfactants (beractant, calfactant, and poractant alfa) is sur factant protein B (SP-B). SP-B has been found to reduce surface tension to a greater extent than surfactant protein-C (SP-C). Congenital absence of SP-B at birth is lethal, while SP-C deficiency is not associated with respiratory failure[Sinha S.2007]. Older generation synthetic surfactant preparations did not contain any peptidechain proteins such as SP-B, which led to the universaal practice of using animal derived surfactants, of which all contained variable amount of SP-B proteiin [Suresh GK.2005]. Current data support the use of natural exogenous surfactant over the use of laboratory derived synthetic surfactant. Natural surfactants have shown superior surface absorption and better lowering of alveolaar surface tension. In comparative randomized clinical trials, natural surfactant also showed lower oxygen requirement, lower risks of pneumothorax, bronchopulmonary dysplasia (BPD), and death[Suresh GK.2005; Halliday HL.1997]. Synthetic preparations may have better quality control than natural surfactants, due to the batch-tobatch variations in natural surfactants. The purification procedure for natural surfactants includes extraction with organic solvents to remove hydrophilic proteins SP-A and SP-D[Suresh GK.2005]. SURFACTANT REPLACEMENT THERAPY: 2013 Table. Currently Available Surfactants Trade Name / Source / Manufacturer / Dose / Surfactant Protein B Poractant alfa / Curosurf / Porcine / Chiesi Farmaceutici / 100–200 mg/kg/dose (1.25–2.5 mL/kg) / 0.45 Calfactant / Infasurf / Bovine / Ony / 105 mg/kg/dose (3 mL/kg) / 0.26 Beractant / Survanta / Bovine / Abbott Laboratories / 100 mg/kg/dose (4 mL/kg) / < 1 Lucinactant / Surfaxin / Synthetic / Discovery Labs / 5.8 mL/kg / KL_4	**AARC Clinical Practice Guideline. Surfactant replacement therapy: 2013.** Walsh BK1, Daigle B, DiBlasi RM, Restrepo RD; American Association for Respiratory Care. Respir Care. 2013 Feb;58(2):367-75.)
ANIMAL-DERIVED (natural) VERSUS SYNTHETIC SURFACTANT:	**Surfactant Replacement Therapy for Preterm and Term Neonates With Respiratory**

TABLE 2 Composition and Dosage of Surfactants[17]

Surfactant	Main Phospholipids	Proteins	Phospholipid Concentration	Suggested Dose	Phospholipid per Dose
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Calfactant (Infasurf[b]) bovine calf lung lavage	DPPC and PG	(0.7%) SP-B and (1%) SP-C	35 mg/mL	3 mL/kg	105 mg/kg
Poractant (Curosurf[c]) minced porcine lung extract	DPPC and PG	(0.6%)SP-B and (1%) SP-C	80 mg/mL	2.5 mL/kg and	100-200 mg/kg
				1.25 mL/kg	100 mg/kg
Synthetic					
Colfosceril (Exosurf[d])	DPPC (100%)	None	13.5 mg/mL	5 mL/kg	67.5 mg/kg
Synthetic, protein analog					
Lucinactant (Surfaxin[e])	DPPC and POPG	KL4 peptide as SP-B	30 mg/mL	5.8 mL/kg	175 mg/kg

DPPC, dipalmitoyl phosphatidylcholine; PG, phosphatidylglycerol; POPG, palmitoyloleyl phosphatidylglycerol; SP-C, surfactant protein C.
[a] Abbvie Inc, North Chicago, IL.
[b] ONY Inc, Amherst, NY.
[c] Chiesi Farmaceutici, Parma, Italy.
[d] GlaxoSmithKline, Middlesex, UK.
[e] Discovery Laboratories, Warrington, PA.

Both animal-derived and newer synthetic surfactants with SP-B– like activity decrease acute respiratory morbidity and mortality in preterm infants with RDS (LOE 1- strong recommendation).
When compared with animal-derived surfactant (beractant or poractant), lucinactant was shown to be equivalent [Sinha SK 2005, Moya F 2007].
Neonatal morbidities (intraventricular hemorrhage, periventricular leukomalacia, pulmonary hemorrhage, sepsis, patent ductus arteriosus, retinopathy of prematurity, necrotizing enterocolitis, and BPD) were not significantly different between preterm infants treated with animal-derived surfactants and those treated with synthetic surfactants.

Distress
Richard A. Polin, MD, FAAP, Waldemar A. Carlo, MD, FAAP, and COMMITTEE ON FETUS AND NEWBORN
Clinical report
2014 AAP

- Newborns receiving Butanan vs. Survanta® or Curosurf® comprised the control group. A dose 100 mg of phospholipids per kg was used for all newborns in all treatments.

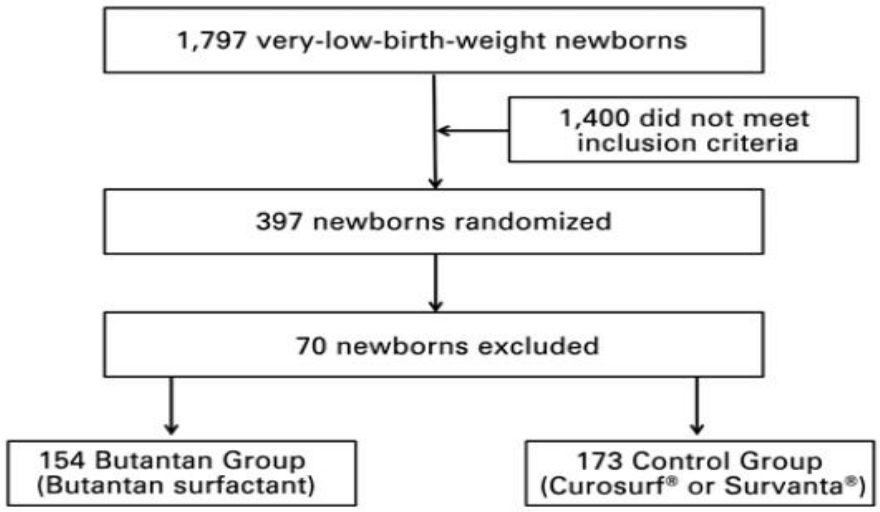


Figure 1. Patient selection flow chart

-The choice to use the 100mg/kg dose was based on the fact that, in RDS, serum-derived protein inhibitors and inflammatory mediators that inactivate the surfactant the initial phase is effective 100mg/kg dose.
No differences were observed between the Butantan vs control in relation to birth weight, gestational age, sex, and prenatal use of corticosteroids, or in mortality rates both at 72 hours and at 28 days of life.

A multicenter, randomized, double-blind trial of a new porcine surfactant in premature infants with respiratory distress syndrome
Celso Moura Rebello, Alexander Roberto Precioso, Renata Suman Mascaretti;
2014

Clinical trial register (www.clinicaltrials.gov): protocol ID: NCT02305160

Table 3. Overall mortality and by birth weight range on the 28th day of life

Secondary variables	Control group n (%)	Butantan group n (%)	p value
Overall mortality	55 (33.33)	57 (39.86)	0.24
BW <750g (n=53)	21 (67.74)	15 (68.18)	0.97
BW ≥750g and <1,000g (n=109)	23 (39.66)	26 (50.98)	0.24
BW ≥1,000g and <1,500g (n=146)	11 (14.47)	16 (22.86)	0.19

Continuous variables were analyzed using the Student's t or Mann-Whitney test, as appropriate. Qualitative variables were analyzed using the χ^2 or Fischer's exact test, as appropriate. BW: birth weight.

Butantan group newborns required more surfactant doses (mean ± standard deviation) in comparison to those of the control group (2.0±0.8 *versus* 1.5±0.7, respectively; p<0,001). No difference was found between the two groups analyzed in relation to the moment (hours of life) at which the first surfactant dose was administered: control group, at 5.35 hours (median), and Butantan group, at 4,87 hours (median) (p=0,30)

Table 5. Oxygenation index values prior to treatment and 1 and 6 hours after (values in percentiles)

Percentile	p value	10		25		50		75		90	
Group		CG	BG	CG	BG	CG	BG	CG	BG	CG	BG
Pre-treatment	0.92	5.4	5.4	7.2	6.7	10.7	10.9	16.2	17.3	24.5	25.6
1 hour after	<0.001	2.4	2.7	3.0	4.6	4.6	7.8	7.2	12.7	13.2	20.1
6 hours after	<0.001	2.0	2.3	2.6	4.0	4.0	6.8	6.4	10.1	12.0	19.3

Continuous variables were analyzed using the Student's t or Mann-Whitney test, as appropriate. Qualitative variables were analyzed using the χ^2 or Fischer's exact test, as appropriate. CG: control group; BG: Butantan group. Values expressed in percentiles.

-Comparisons between different animal-derived surfactants (with apoproteins B and C in their composition) did not show different results in relation to mortality and the main morbidities related to prematurity, including mechanical ventilation settings, incidence of pneumothorax, insterstitial emphysema, intracranial hemorrage, and persistent ductus arteriosus, when
compared at the same treatment dose.

Table 4. Frequency of secondary variables analysed on the 28th day of life

Secondary variables	Control group n (%)	Butantan group n (%)	p value
Use of oxygen at 28 days	72 (45.28)	77 (57.04)	0.05
Radiography consistent with BPD	52 (65.00)	57 (72.15)	0.33
Intracranial hemorrhage (total)	39 (24.53)	43 (31.16)	0.20
Grade I	17 (43.59)	17 (39.53)	0.94
Grade II	5 (12.82)	7 (16.28)	
Grade III	10 (25.64)	10 (23.26)	
Grade IV	7 (17.95)	9 (20.93)	
PDA (n=297)	50 (31.45)	62 (44.93)	0.02
Early sepsis (n=297)	58 (36.48)	50 (36.23)	0.97
Late sepsis (n=293)	59 (37.58)	51 (37.50)	0.99
Pulmonary hemorrhage (n=297)	20 (12.58)	16 (11.59)	0.80
Pneumothorax (n=297)	13 (8.18)	12 (8.70)	0.87
Interstitial emphysema (n=292)	12 (7.64)	23(17.04)	0.01
Necrotizing enterocolitis (n=297)	11 (6.92)	11 (7.97)	0.83
Mechanical ventilation time (days)	8	12	0.06
Total oxygen therapy time (days)	17	22	0.35

Continuous variables were analyzed using the Student's t or Mann-Whitney test, as appropriate. Qualitative variables were analyzed using the χ^2 or Fischer's exact test, as appropriate. BPD: bronchopulmonary displasia; PDA: persistent ductus arteriosus.

- **Conclusion**: The mortality rates at 72 hours and 28 days of life and the incidence of major complications of prematurity were comparable to those found with the animal-derived surfactants commercially available in Brazil, showing the efficacy and safety of the new surfactant in the treatment of respiratory distress syndrome in newborns.

The comparative effectvness study 322 neonatal intensive care units in th US from 2005-2010 who were treated with beractant, calfactant or poractant alfa.
- N 51 282; (322 NICU); GA <37; median birth weight of 1435 g (IQR 966-2065) and a median GA of 30 weeks (27-33).
- 40% (n 20 383) received beractant, 30% (n 15 748) calfactant, and 30% (n 15 151)poractant alfa.
- air leak syndromes; death; BPD or death (composite outcome).
Adjusting for gestational age (GA), antenatal steroids, discharge year, and small for GA status.
<32 weeks GA have BPD if they received supplemental oxygen or respiratory support (nasal canula, continuous positive airway pressure, or mechanical ventilation) continuously from a corrected GA of 36 0/7-36 6/7 weeks (designated as the test period).
>32 weeks GA at birth were classified as häving BPD if they received supplemental oxygen or respiratory support (nasal canula, continuous positive airway pressure, or mechanical ventilation) continuously from a postnatal age of 28-34 days.
Those who died before the test period were classified as not häving BPD.
-Air leak syndromes (calfactant vs beractant OR = 1.17 [95% CI: 0.95, 1.43]; calfactant vs poractant OR = 1.23 [0.98, 1.56]; beractant vs poractant OR = 1.06 [0.87, 1.29]), death (calfactant vs beractant OR =1.14 [0.93, 1.39]; calfactant vs poractant OR = 0.98 [0.78, 1.23]; beractant vs poractant OR = 0.86 [0.72, 1.04]), and BPD or death

Comparative Effectiveness of Surfactant Preparations in Premature Infants
Andrea Trembath, MD, MPH, Christoph P. Hornik, MD, MPH, Reese Clark, MD, P. Brian Smith, MD, MPH, MHS, Julie Daniels, PhD, MPH, and Matthew Laughon, MD, MPH, on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network*

(calfactant vs beractant OR = 1.08 [0.93, 1.26]; calfactant vs poractant OR = 1.19 [1.00, 1.41]; beractant vs poractant OR = 1.10 [0.96, 1.27]).
Beractant, calfactant, and poractant alfa demonstrated similar effectiveness in prevention of air leak syndromes, death, and BPD or death in premature infants. Air leak occurred in 3450 infants (7% overall; 8% beractant, 7% calfactant, 5% poractant alfa). Death occurred in 4576 infants (9% overall; 10% beractant, 9% calfactant, 7% poractant alfa). A total of 12 164 infants (22% overall; 27% beractant, 25% calfactant, 20% poractant alfa) had a diagnoosis of BPD or death (composite) (Table II).

Table II. Unadjusted patient outcomes during hospitalization by surfactant preparation

Outcome	Beractant	Calfactant	Poractant alfa
Total ventilator days, median (IQR)	2 (1-7)	2 (1-7)	2 (0-5)
Necrotizing enterocolitis (medical and surgical), n (%)	1384 (6.8)	1191 (7.6)	1006 (6.6)
Intraventricular hemorrhage (grade III, IV), n (%)	1008 (5.0)	835 (5.3)	657 (4.3)
Pneumothorax, n (%)	1230 (6.0)	775 (4.9)	616 (4.1)
Pulmonary interstitial emphysema, n (%)	516 (2.5)	356 (2.3)	238 (1.6)
Air leak syndrome, n (%)	1589 (7.8)	1059 (6.7)	802 (5.3)
BPD, n (%)	3475 (17.6)	2480 (16.1)	1889 (12.9)
Death, n (%)	2052 (10.1)	1438 (9.1)	1086 (7.2)
Death or BPD, n (%)	5403 (27.4)	3848 (24.9)	2913 (19.9)

Three percent of infants (n = 1514) were missing data for determining the outcome of BPD, and 3% (n = 1506) were missing data for the outcome of BPD or death. The decision regarding which surfactant preparation to use should be based on factors other than effectiveness.

Table III. Comparison of simple logistic regression and random and fixed effects mixed models, OR (95% CI)

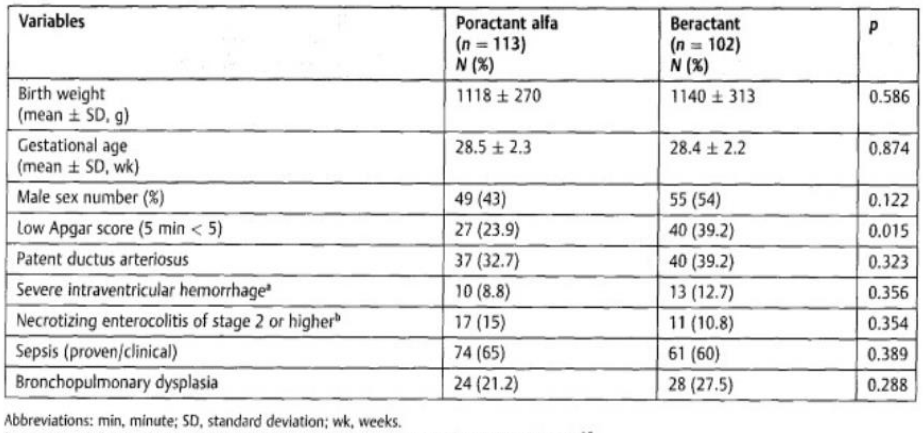
	Comparison	Logistic regression	Random effects	Fixed effects
Air leak syndromes	Calfactant vs beractant	0.85 (0.78, 0.92)*	0.94 (0.81, 1.08)	1.17 (0.95, 1.43)
	Calfactant vs poractant	1.25 (1.13, 1.40)*	1.23 (1.04, 1.44)*	1.23 (0.98, 1.56)
	Beractant vs poractant	1.47 (1.35, 1.61)*	1.31 (1.13, 1.51)*	1.06 (0.87, 1.29)
Death	Calfactant vs beractant	0.87 (0.81, 0.94)*	0.99 (0.85, 1.15)	1.14 (0.93, 1.39)
	Calfactant vs poractant	1.04 (0.95, 1.13)	1.05 (0.88, 1.24)	0.98 (0.78, 1.23)
	Beractant vs poractant	1.19 (1.09, 1.29)*	1.06 (0.91, 1.24)	0.86 (0.72, 1.04)
BPD or death	Calfactant vs beractant	0.81 (0.76, 0.85)*	1.01 (0.88, 1.16)	1.08 (0.93, 1.26)
	Calfactant vs poractant	1.10 (1.02, 1.16)*	1.15 (0.98, 1.35)	1.19 (1.00, 1.41)
	Beractant vs poractant	1.35 (1.26, 1.43)*	1.14 (1.00, 1.30)	1.10 (0.96, 1.27)

*$P < .05$.

USA 2013

GA <30 wks (25-29 W); n=33 vs n=27; RDS ravi "early rescue (keskm. 5,2 tundi)" surfactant 200 mg/kg võrreldes "late rescue (9,9 tundi)"
II doos surf. 100 mg/kg early gr. 9%, late gr. 11%.
The cost-effectiveness analysis performed in this study demonstrates how early treatment with surfactant of preterm infants with RDS is not only more effective clinically, but is also economically cheaperthan late treatment. Greater initial costs of early treatment with surfactant are compensated by subsequent lower costs required for MV.
"early" vs. "late" duration (days) of oxygen therapy 6.5 (0.3-69) vs 18.5 (0.5-64) P 0.54; NCPAP 38.5 (0.8-64) vs 39.0 (12–155)P 0.76; MV 2.5 (1.2-5.5) vs 2.1 (0.3-13.9) P 0.47.
The cost-effectiveness analysis performed in this study shows how early treatment with surfactant in preterm infants with RDS, as well as being clinically more effective, is associated with a slightly lower cost 1 lifeweek.

Analysis of the cost-effectiveness of surfactant treatment (Curosurf®) in respiratory distress syndrome therapy in preterm infants: early treatment compared to late treatment
Carlo Dani, Roberto Ravasio*,

	Leonardo Fioravanti1 and Maria Circelli (Retrospektiivne 2014)
Aim. To determine and compare the neurodevelopmental outcomes of preterm infants with RDS teated with proactant alfa or beractant at 2 years of age. **Methods**. This was a prospective, longitudinal, single-center kohort study of infants born at < 1500 g and/or <32 weeks between 2008 and 2009 who received either poractant alfa (n=113) or beractant (n=102) for RDS. Neurological and developmental assessments were performed at a corrected age of 18 to 24 months. The Bayley Scales of Infant Development II (BSID II) was used for developmental assessment; vision, hearing and neuromotor status were also evaluated. The investigators who performed the DSID II were linded to the surfactant treatment groups. The developmental assessment was performed up to 42 months of age. The mental development index (MDI) and psychomotor developmental index (PDI) were also determined.A score of 49 was assigned in cases where the child was unable to complete the developmental tests. **Defination of Outcome Variables.** The outcome of the study was neurodevelopmental impairment (NDI), which was defined as the presence of one or more of following events: (1) cerebral palsy (CP) with functional deficits, (2) bilateral hearing loss and/or blindness, and (3) MDI or PDI of < 70 on the BSID II. **CP** was defined as a nonprogressive motor disorder with abnormal muscle tone, persistent or exaggerated primitiive reflekses, or a positiive Babinski sign associated with delayed motor development. **Results.** About 33 of 113 infants (29,2%) in the poractant alfa group had neurodevelopmental impairment compared with 36 of 102 (35,2%) in the beractant group, and the results did not differ between the groups (p=0,339). Similary, no significant difference was found inthe percentage of infants with cerebral palsy (11,5 vs. 16,7% respectively; p=0,275). **Table 1** Baseline characteristics of the infants in the follow-up cohort  Abbreviations: min, minute; SD, standard deviation; wk, weeks. [a]Severe was defined as grade 3 or 4 intraventricular hemorrhage using the criteria of Papile.[16] [b]Stages 2 and 3 necrotizing enterocolitis were defined according to the Modified Bell Staging Criteria.[17]	**Neurodevelopmental Outcomes of Very Low Birth Weight Preterm Infants Treated With Poractant Alfa versus Beractant for Respiratoty Distress Syndrome** Zeynep Eras, MD, Evrim Alyamac Dizdar, MD, Gozde Kanmaz, MD, et al Turkey 2014 Am J perinatol 2014;31:463-468

Variables	Poractant alfa (n = 113) N (%)	Beractant (n = 102) N (%)	p
Birth weight (mean ± SD, g)	1118 ± 270	1140 ± 313	0.586
Gestational age (mean ± SD, wk)	28.5 ± 2.3	28.4 ± 2.2	0.874
Male sex number (%)	49 (43)	55 (54)	0.122
Low Apgar score (5 min < 5)	27 (23.9)	40 (39.2)	0.015
Patent ductus arteriosus	37 (32.7)	40 (39.2)	0.323
Severe intraventricular hemorrhage[a]	10 (8.8)	13 (12.7)	0.356
Necrotizing enterocolitis of stage 2 or higher[b]	17 (15)	11 (10.8)	0.354
Sepsis (proven/clinical)	74 (65)	61 (60)	0.389
Bronchopulmonary dysplasia	24 (21.2)	28 (27.5)	0.288

Table 2 Neurodevelopmental outcomes of the cohort at 18 to 24 months Corrected Age

Variables	Poractant alfa (n = 113) N (%)	Beractant (n = 102) N (%)	p
Age at assessment (mo)	21.1 ± 2.5	20.7 ± 2.4	0.309
NDI[a]	33 (29.2)	36 (35.2)	0.339
MDI	86.8 ± 17.2	85.9 ± 18.7	0.716
PDI	84.6 ± 20.1	81.2 ± 20.1	0.222
MDI < 70	16 (14)	21 (20.6)	0.216
PDI < 70	26 (23)	25 (24.5)	0.796
CP	13 (11.5)	17 (16.7)	0.275
Bilateral deafness	1 (0.8)	2 (1.8)	0.606
Bilateral blindness	0	0	–

Abbreviations: CP, cerebral palsy; MDI, mental developmental index; Mo, months; NDI, neurodevelopmental impairment; PDI, psychomotor developmental index.
[a]NDI was defined as one or more of the following at 18 to 24 months CA: (1) moderate-to-severe CP with functional deficits, (2) bilateral hearing loss and blindness, or (3) an MDI or PDI < 70 on the BSID II.

Conclusion. Our findnings suggest that poractant alfa and beractant are similar in terms of neurodevelopmental outcomes when used for the treatment of RDS in preterm infants.

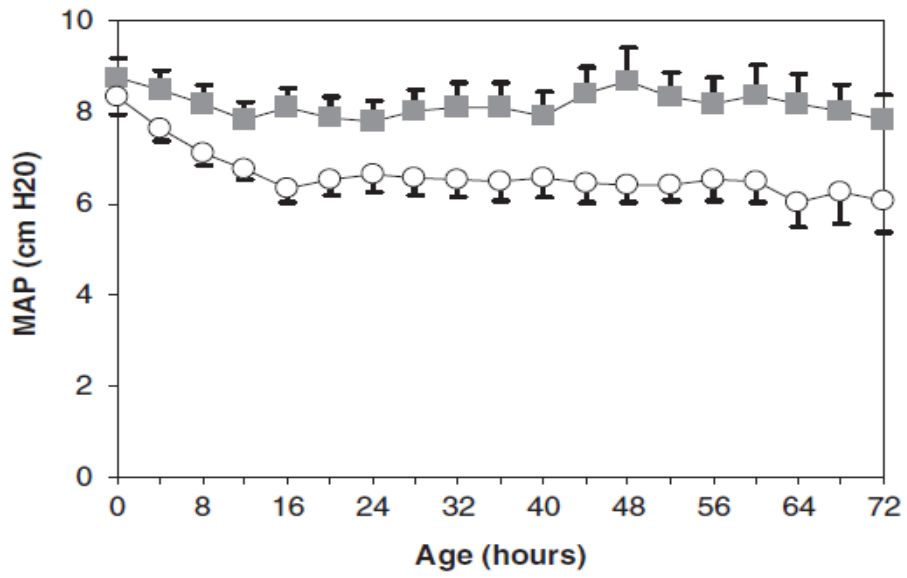
The objective of this study was to assess the short-term treatment efficacy of the two most commonly used surfactant preparations in the United States, beractant (100 mg kg–1 initial and subsequent doses) and poractant alfa (200 mg kg–1 initial and 100 mg kg–1 subsequent doses), in very premature, mechanically ventilated infants <30 weeks gestation with respiratory distress syndrome (RDS).

Study Design: Inborn infants at two institutions, open label, 1:1, randomized controlled trial. Level of respiratory support for first 72 h of life. Morbidities of prematurity observed during the neonatal intensive care unit hospitalization.

Result: We studied 52 infants 24 0/7 to 29 6/7 weeks gestation; 25 received poractant alfa (27.1±1.6 weeks, birth weight of 930±231 g) and 27 received beractant (26.7±1.7 weeks, P=0.343 and birth weight 900±271 g, P=0.668). Respiratory support for the first 72 h of life was lower in the poractant alfa than beractant group for mean airway pressure (MAP, P=0.003) and respiratory index (MAPxFiO2, P=0.032).
This study suggests significant short-term benefits to the use of the larger initial dose of poractant alfa than beractant in very premature infants with RDS. Further studies involving a larger number of preterm infants are needed to assess long-term effects.

Poractant alfa and beractant treatment of very premature infants with respiratory distress syndrome
AM Fujii, SM Patel, R Allen, G Doros, C-Y Guo and S Testa
Journal of Perinatology (2010) 30, 665–670

Conflict of interest
Dr Fujii was supported by an unrestricted research grant from Dey LP, Napa, CA and Chiesi Farmaceutici Spa, Parma, Italy.
The remaining authors declare no conflict of interest.
The funders had

 **Figure 1** Mean airway pressure (MAP, cm H_20 mean ± s.e.m.) are shown for the first 72 h of life for infants ⩽29 weeks gestation, mechanically ventilated for RDS and treated with poractant alfa (open circles) and beractant (closed squares). MAP for the first 72 h of life was less in the poractant alfa than in the beractant-treated infants ($P = 0.003$).	no involvement in study design, in data collection, analysis/ interpretation of the data, in the writing of the paper or in the decision to submit the paper for publication.

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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