Kliiniline küsimus nr 20

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

- manustamise viis (INSURE; LISA võrreldes „konventsionaalne“)
- surfaktandi korduv manustamine võrreldes ühekordne manustamine

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

Ravijuhendid

Kokkuvõte ravijuhendites leiduvast:

Soovitused 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 BK1, 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.

Hiljem hinnatud veel **Rootsi ravijuhend 2014**

Care of extremely premature infants: A guideline for the care of children born before 28 full weeks of pregnancy have passed. (originaal rootsi keeles: *Vård av extremt för tidigt födda barn. En vägledning för vård av barn födda före 28 fullgångna graviditetsveckor.)* **2014.**

<u>Kas hingamishäiretega enneaegsetel vastsündinutel kasutada parema ravitulemi saavutamiseks varast surfaktantravi võrreldes hilise surfaktantraviga?</u>

Mõlemas ravijuhendis soovitatakse RDS-ga enneaegsetel vastsündinutel kasutada surfaktantravi (s.h. nii varane kui ka hiline ravi eesmärgil manustatud surfaktant), kuna see vähendab õhulekke sündroomide esinemissagedust ja vastsündinute suremust antud populatsioonis.

RDS-ga EA vastsündinutele, kellel hingamispuudulikkus süveneb ja suureneb lisahapniku vajadus, tuleb manustada surfaktanti haiguse võimalikult varases perioodis. Surfaktandi manustamisele peab järgnema varane ekstubatsioon.

(The assessment is based on systematic charting and guidelines from a European consesus panel of neonatologists.) Rootsi 2014

RDS-ga EA vastsündinutel tuleks kasutada surfaktantravi haiguse võimalikult varases arengujärgus. Soovitav on surfaktanti manustada vastsündinule vanuses <26 GN, kui FiO_2 on >0,3 ja vanuses >26 GN, kui FiO_2 >0,4. (B) Euroopa 2013; Rootsi 2014

Kliiniliselt avalduva RDS-ga EA vastsündinutel, kes vajavad KKV, on vajalik ravi eesmärgil manustada surfaktanti. (1A) AARC 2013.

Ameerika juhendi alusel soovitatakse surfaktantravi manustada, **kui FiO2 on >0,4; kliiniliselt ja radioloogiliselt on tõestatud RDS või mekooniumi aspiratsioonisündroom (MAS) ja s.h. vastsündinutel, kellel keskmine rõhk hingamisteedes on >7 cm H_2O, et hoida adekvaatset PaO_2 või SpO_2.**

<u>Surfaktandi manustamise viis (INSURE; LISA võrreldes „konventsionaalne“)</u>

Mõlemas ravijuhendis vaadeldakse üsna põhjalikult erinavaid surfaktandi manustamise viise. Enamuses seni avaldatud uuringutes on surfaktanti manustatud **klassikalisel** ehk **standardsel meetodil** – s.t. surfaktandi manustamist intubatsioontoru kaudu, mille puhul vastsündinu on KKV-l. KKV-d saab vältida kasutades **INSURE meetodit** (INtubate-SURfactant-Extubate to CPAP s.t. intubatsioon-surfaktandi manustamine-ekstuabatsioon CPAP toetusele) ning randomiseeritud uuringutes on näidatud, et selle meetodi rakendamine vähendab vajadust KKV-ks ja edasiselt BPD esinemissagedust (*Cochrane Database Syst Rev 2007, Verder H et al 1994*). Mida varem on tehtud otsus kasutada INSURE meetodit, seda suurem on võimalus KKV-d vältida, kuigi kulub rohkem surfaktanti (*Rojas MA et al 2009*).

Hiljuti on kasutusele võetud erinevaid surfaktandi manustamise tehnikaid vältimaks traditsioonilist intubatsiooni. **LISA** (*ingl. k.* Least Invasive Surfactant Administaration – vähem invasiivne surfaktandi manustamine) puhul manustatakse surfaktanti intratrahheaalselt peenikese kateetri abil spontaanhingamisel CPAP toetusel olevale lapsele. Nimetatud metoodika rakendamine on kliiniliselt toimiv ning väheneb vajadus KKV-ks, samas ei ole näidatud paremust kaugtulemi osas (*Göpel W et al 2011; Dargaville PA 2012*).

Samuti on spontaanhingamisel CPAP toetusel olevatele RDS-ga lastele võimalik surfaktanti manustada uudsete membraan-nebulisaatorite abil, kuid selle metoodika kasutamine ei ole seni veel laialdaselt levinud ja vajab lisauuringud (*Pillow JJ et al 2012*).

Lisaks on Ameerika juhendis esitatud informatsioon loomkatsetes paljulubavaid tulemusi andnud metoodikate kohta: kõrimaski kaudu surfaktandi manustamine ja enne esimest hingetõmmet kateetriga pimesi neelu tagumisse ruumi surfaktandi manustamine.

Surfaktandi manustamisel võiks kaaluda INSURE meetodi kasutamist. Sageli on võimalik surfaktandi manustamise järgselt küpsemaid enneaegseid vastsündinud eksubeerida ja jätkata koheselt CPAP toetuse või NIPPV-ga (*ingl. k.* Nasal Intermittent Positive Pressure Ventilation – ninakaudne vahelduv positiivese rõhuga ventiatstsioon). Kliiniline otsus tuleks teha lähtuvalt hinnangust konkreetse lapse seisundile. (B) Euroopa 2013**.**

Surfaktanti ei soovitata manustada aerosoolina (2B) AARC 2013.

Rootsi ravijuhend 2014

Two strategies have been shown to be effective for the administration of surfactant during ongoing non-invasive breathing support: surfactant is given either for a short-term intubation through the tracheal tube (INSURE, intubation surfactant extubation) or without intubation through a thin catheter down in the trachea. The Swedish experiences of the catheter technique are limited thus far.

The administration of surfactant in accordance with INSURE can be repeated if the child can breathe well by itself. A birth weight of less than 750 g is an identified risk factor for a need for respirator treatment after INSURE, and these children ought as a rule not to be extubated again immediately following a second dose of surfactant.

Surfaktandi korduv manustamine võrreldes ühekordne manustamine.

Mõlema ravijuhendi alusel võib korduv surfaktandi manustamine teatud juhtudel olla vajalik. Kliiniliselt raske kuluga RDS korral on näidatud kahe doosi surfaktandi manustamisel paremat efekti kui ühe doosi kasutamisel – paranemist täheldati osügenisatsiooni osas, vähenes ventilatsiooni vajadus, risk NEK-i haigestumiseks ja vähenes suremus (*Cochrane Database Syst Rev 2009*). Ühes randomiseeritud uuringus raske kuluga RDS-ga enneaegsetel vastsündinutel poraktant alfa korduva manustamise kohta, ilmnes, et kuni kolme doosi surfaktadi manustamine võrreldes ühekordse surfaktandi kasutamisega vähendas suremust (13% vs 21%) ja õhulekete esinemissagedust (9 vs 18%) (*Speer CP et al 1992*).

Ameerika juhendi alusel võiks soovitav surfaktandi manustamisintervall olla 6-24 tundi. Euroopa juhend peab otstarbekaks surfaktanti korduvalt manustada paindliku skeemi alusel, lähtudes lapse seisundist ja lisahapnikuhapniku vajadusest; seda toetavad ka tänapäevased farmakokineetilised andmed (*Carnielli VP et al 2009*).

RDS-ga lastel, kes on CPAP toetusel, kuid esineb suurenev lisahapniku vajadus, võiks kasutada korduva(te) surfaktandi doosi(de) manustamiseks INSURE meetodit (*Dani C et al 2011*).

Rootsi ravijuhendis 2014 soovitatakse surfaktanti kordusdoosina manustada 8-12 tundi pärast eelmise surfaktandi manustamist, juhul kui püsib kopsuhaigusest tingitud oluline lisahapniku vajadus.

Kui RDS on raske kuluga ja püsib oluline lisahapniku ja/või KKV vajadus, siis võib olla vajalik manustada teine ja vahel ka kolmas surfaktandi doos (A) Euroopa 2013**.**

Korduv surfaktandi manustamine on enam soovitatud kui ühekordne surfaktandi manustamisstrateegia (1B) AARC 2013.

Süstemaatilised ülevaated

<u>Kas hingamishäiretega enneaegsetel vastsündinutel kasutada parema ravitulemi saavutamiseks varast surfaktantravi võrreldes hilise surfaktantraviga?</u>

Kokkuvõte süstemaatilistest ülevaadetest

Varase ja hilise surfaktantravi võrdluse kohta leidsime vastavalt otsingukriteeriumitele 2 meta-analüüsi/süstemaatilist ülevaadet (avaldatud viimase 5 aasta jooksul)

Polin RA, Carlo WA; Surfactant replacement therapy for preterm and term neonates with respiratory distress. Committee on Fetus and Newborn; American Academy of Pediatrics 2014 ja

Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2012.

Esimene nendest ülevaadetest kaasab kokkuvõtvalt ka teise süstemaatilise ülevaate tulemusi. Lisaks on antud teemal viimastel aastatel publitseeritud vaid üks Indias läbi viidud randomiseeritud kontrolluuring (*Kandraju et al 2013*).

Mitmed uuringud on näidanud, et surfaktandi manustamine hingamispuudulikkuse kujunemise varases järgus parandab haiguse kliinilist tulemit.
Varase surfaktantravi all mõistetakse surfaktandi manustamist 1.-2. elutunni jooksul ning **hilise surfaktantravina** surfaktandi manustamist 2 või enam tundi pärast sündi.

2012.a. avaldatud metanalüüsis järeldati, et varane surfaktantravi (surfaktant manustatud esimese 2 elutunni jooksul) võrreldes hilise surfaktantraviga vähendab oluliselt suremuse riski (RR 0,84; 95% CI 0,74–0,95), õhulekete riski (RR 0,61; 95% CI 0,48–0,78), kroonilise kopsuhaiguse riski (RR 0,69; 95% CI 0,55–0,86) ja kroonilise kopsuhaiguse esinemissagedust või suremust (RR 0,83; 95% CI 0,75–0,91). Teiste enneaegsusega seotud tüsistuste (DAP, NEK, IVH, PVL, ROP, hiline neuroloogiline tulem) osas erinevusi ei olnud. *(Bahadue FL, Soll R. Cochrane Database Syst Rev. 2012)*.
Samas tuleb märkida antud metanalüüsi negatiivseks küljeks sinna hõlmatud uuringute avaldamise aastaid (*European Study 1992; Konishi 1992, OSIRIS 1992, Gortner 1998; Plavka 2002 and Lefort 2003).*

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

Süstemaatiste ülevaadete kokkuvõtvad tõenduspõhised soovitused:

Varane ravi eesmärgil manustatud surfaktantravi (< 2 tunni vanuses) RDS-ga lastel vähendab suremuse, õhulekke sündroomide esinemssageduse ja kroonilise kopsuhaiguse esinemise riski enneaegsetel lastel. (1) GRADE tugev soovitus

Surfaktantravi kasutamine ei mõjuta enneaegsete vastsündinute neuroloogilist, arengulist, käitumuslikku, meditsiinilist või hariduslikku kaugtulemit. (2) GRADE soovitus

<u>Surfaktandi manustamise viis (INSURE; LISA võrreldes „konventsionaalne“)</u>

Kokkuvõte süstemaatilistest ülevaadetest

Erinevate surfaktandi manustamise võimaluste ja viiside võrdluse kohta leidsime vastavalt otsingukriteeriumitele 6 meta-analüüsi/süstemaatilist ülevaadet (avaldatud viimase 5 aasta jooksul)

Polin RA, Carlo WA; Surfactant replacement therapy for preterm and term neonates with respiratory distress. Committee on Fetus and Newborn; American Academy of Pediatrics 2014

More K, Sakhuja P, Shah PS; Minimally invasive surfactant administration in preterm infants: a meta-narrative review. JAMA Pediatr. 2014

Fischer HS, Bührer C; Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. Pediatrics. 2013

Abdel-Latif ME, Osborn DA; Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome. Cochrane Database Syst Rev. 2012

Abdel-Latif ME, Osborn DA.; Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome. Cochrane Database Syst Rev. 2011

Abdel-Latif ME, Osborn DA; Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome. Cochrane Database Syst Rev. 2011

Esimene nendest ülevaadetest kaasab kokkuvõtvalt ka kolme viimase süstemaatilise ülevaate (*Cochrane Database Syst Rev. 2012; Cochrane Database Syst Rev. 2011* ja *Cochrane Database Syst Rev. 2011*) tulemusi. Lisaks vastas otsingukriteeriumidele 2 RCT-d (*Göpel 2011, Kanmaz 2013*).

INSURE strateegiat kasutatakse tänapäeval laialdaselt terves maailmas. Enne 2008. aastat läbi viidud randomiseeritud uuringutes on näidatud, et RDS-ga lastel INSURE meetodi kasutamine võrreldes klassikalise surfaktandi manustamisega vähendas oluliselt KKV vajadust (RR 0,67; 95% CI 0,57-0,79) ja 28. p vanuses hapnikravi vajadust *(Stevens TP, Harrington EW, Blennow M, Soll RF. Cochrane Database Syst Rev. 2007*). Analüüsis, kus lapsed olid uuringusse arvamisel jagatud gruppidesse, lisahapniku vajaduse alusel, leiti oluliselt suurem DAP-i esinemissagedus surfaktantravi saanud lastel, kelle FiO_2 oli >0,45 (RR 2,15; 95% CI 1,09-4,23). *Vermont Oxford Network Delivery Room Management* uuringusse randomiseeriti 26-29 GN sündinud lapsed (n=648), keda raviti vastavalt uuringuprotokollile 3	**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

erinevas grupis: 1) profülaktiline surfaktantravi ja KKV, 2) INSURE või 3) nCPAP (*nasal CPAP*) surfaktantravita. Profülaktilise surfaktantravi ja KKV grupi lastega võrreldes oli RR surmaks või BPD esinemiseks INSURE grupis 0,78 (95% CI 0,59-1,03) ja CPAP gupis 0,83 (95% CI 0,64-1,09). Ainult CPAP toetusel olevatest lastest käsitleti ilma intubatsioonita 48% ja surfaktantravita 54% lastest. (*Dunn MS et al 2011*). Alternatiivsete surfaktandi manustamise viiside - surfaktandi manustamine kõrimaski kaudu, manustamine aerosoolina, surfaktandi tilgutamine neelu ja surfaktandi manustamine peenikese sondi abil trahheasse - kohta on viimastel aastatel ilmunud mitmeid kliinilisi uuringuid. Teoreetiliselt on võimalik kõiki neid meetodeid kasustada ilma intubatsiooni rakendamata lapse spontaanhingamisel olles. *(Göpel W et al 2011; Schmölzer GM et al 2013; Kribs A. 2011; Mehler K et al 2012; Cochrane Database Syst Rev. 2012; Cochrane Database Syst Rev. 2011; Cochrane Database Syst Rev. 2011; Cochrane Database Syst Rev. 2010*). Saksamaa neonataalse intensiivravi osakondades läbi viidud AVM (*Avoidance of mechanical ventilation)* uuringus randomiseeriti 220 enneaegset 26. – 28. GN sündinud last gruppidesse, kus manustati surfaktanti spontaanhingamisel lapsele peenikese kateetri abil trahheasse (LISA-meetod) või kasutati surfaktandi manustamiseks klassikalist meetodit. Kõik lapsed stabiliseeriti esmaselt CPAP toetusel. LISA rakendamine vähendas märgatavalt KKV vajadust ja lisahapniku vajadust 28 elupäeval *(Göpel W et al 2011*). Selleks, et soovitada alternatiivste surfaktandi manustamise meetodite kasutamist, on vajalik rohkem andmeid ja lisauuringuid läbi viia.	Jan;133(1):156-63.
Metaanalüüs tehti 6 randomiseeritud kontrolluuringu ja 2 vaatlusuuringu kohta, kokku osales nendes uuringutes 3081 enneaegset vastsündinut. Kõige enam oli andmeid LISA meetodi kohta – 6 uuringut (2 RCT ja 4 vaatlusuuringut). Surfaktandi manustamist aerosoolina oli uuritud 2 RCT-s ning kõrimaski kaudu ja neelu manustatud surfaktantravi käsitles kummagi teema kohta 1 vaatlusuuring. 2 RCT uuringus (*Göpel et al 2011, Kanmaz et al 2013*) LISA meetodi kohta ei näidatud olulist mõju BPD esinemisele, kuid vähenes KKV vajadus esimese 72 elutunni jooksul võrreldes klassikalise surfaktandi manustamisega.	**Minimally invasive surfactant administration in preterm infants: a meta-narrative review.** More K, Sakhuja P, Shah PS. JAMA Pediatr. 2014 Oct;168(10):901-8.
Selles metaanalüüsis vaadeldi aastatel 2008 – 2013 avaldatud 7 RCT-d (s.h. AVM 2011 s.o. *Göpel et al 2011* ja Take Care 2013 s.o *Kanmaz et al 2013* uuringud), milles oli uuritavatena kokku 3289 enneagset vastsündinut. Kombineeritud OR (95% CI) surmaks või BPD esinemiseks oli 0,83 (0,71-0,96). NNT oli 35. KKV vältimisel ei olnud mõju raske IVH esinemissagedusele. Järeldati, et <30 GN sündinud enneaegsetel vastsündinutel KKV-st hoidumiseks rakendatavatel strateegiatel (s.h. LISA), on vähene	**Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis.**

kuid siiski märkimisväärselt soodne mõju BPD ennetamisele.	Fischer HS, Bührer C. Pediatrics. 2013 Nov;132(5):e1351-60.
Cochrane 2012 metaanalüüsis nebuliseeritud surfaktantravi kohta oli võimalik vaadelda vaid üht RCT uuringut *Berggren 2000*. Nimetatud uuring oli väikese patsientide arvuga (36) ja kahjuks ka arvestatavate veavõimalustega. Seetõttu ei saa soovitada surfaktandi manustamist nebuliseerituna enneaegsetele RDS-ga lastele. Vajalik on kaalu omavate kliiniliste uuringute jätkamine antud teemal.	**Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome.** Abdel-Latif ME, Osborn DA. Cochrane Database Syst Rev. 2012 Oct 17;10:CD008310.
Cochrane 2011 metaanalüüsis kõrimaski kaudu manustatud surfaktantravi kohta enneaegsetel RDS-ga lastel oli võimalik vaadelda vaid üht RCT uuringut *Attridge 2010*. Nimetatud uuring oli väikese patsientide arvuga (26) ja kahjuks ka arvestatavate veavõimalustega. Seetõttu ei saa käesoleva metaanalüüsi alusel soovitada surfaktandi manustamist kõrimaski kaudu enneaegsetele RDS-ga lastele. Vajalik on kaalu omavate kliiniliste uuringute jätkamine antud teemal.	**Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome.** Abdel-Latif ME, Osborn DA. Cochrane Database Syst Rev. 2011 Jul 6;(7):CD008309. doi: 10.1002/14651858.CD008309.pub2. Review.
Cochrane 2011 metaanalüüsis enne esimest hingetõmmet neelu manustatud surfaktantravi kohta enneaegsetel RDS-ga lastel ei olnud võimalik analüüsida ühtegi RCT uuringut, kuna neid ei ole seni publitseeritud, samuti ei olnud 2010 a. antud teemal käigusolevaid uuringuid. Loomkatsetele ja inimestel läbi viidud vaatlusuuringutele tuginedes võiks arvata, et enne esimest hingetõmmet neelu manustatud surfaktantravi on potentsiaalselt turvaline, teostatav ja võib-olla efektiivne. Antud teema kohta on vajalikud põhjalikumad uuringud.	**Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome.** Abdel-Latif ME, Osborn DA.

	Cochrane Database Syst Rev. 2011 Mar 16;(3):CD008311. doi: 10.1002/14651858.CD008311.pub2. Review.

Süstemaatiste ülevaadete kokkuvõtvad tõenduspõhised soovitused:

Surfaktandi manustamisel võiks kaaluda INSURE meetodi kasutamist. LISA meetodi kasutamine võib olla efektiivne ja potentsiaalselt turvaline meetod surfaktandi manustamiseks. Kindlasti on vajalikud suuremat jõudu omavad lisauuringud antud metoodika kohta.

Teisi minimaalselt invasiivseid metoodikaid surfaktandi manustamiseks praegustele andmetele tuginedes soovitada ei saa. Vajalikud on põhjalikud kliinilised uuringud.

<u>Surfaktandi korduv manustamine võrreldes ühekordne manustamine.</u>

Kokkuvõte süstemaatilistest ülevaadetest

Kordusdoosidena või ühekordselt manustatud surfaktantravi võrdluse kohta on leidsime vastavalt otsingukriteeriumitele 1 süstemaatilise ülevaate (avaldatud viimase 5 aasta jooksul)

Polin RA, Carlo WA; Surfactant replacement therapy for preterm and term neonates with respiratory distress. Committee on Fetus and Newborn; American Academy of Pediatrics 2014.

Lisaks käsitlesime siinkohal ka infot, mis on esitatud antud teema kohta *Cochrane Database Syst Rev. 2009* metaanalüüsis. Viimasesse analüüsi on hõlmatud järgmised RCT-d (*Corbet 1995* /sünteetiline surfaktant/, *Dunn 1990, Speer 1992* /mõlemad looduslik surfactant/). Hilisemaid teemakohaseid RCT-sid ei ole tehtud/avaldatud.

Käesolevas ülevaateartiklis on antud teema kohta välja toodud järgmised aspektid: RDS raviks kindlatel näidustustel (kliiniliselt raske haiguskulg - KKV vajadus, lisahapniku vajadus) korduvate doosidena manustatud surfaktantravi võrreldes ühekordse surfaktandi või platseebo manustamisega on vähendanud suremust ja haigestumust enneaegsete hulgas. Loodusliku surfaktandi korduval manustamisel on näidatud paranemist oksügenisatsiooni osas, vähenes ventilatsiooni vajadus ja risk pneumotooraksi esinemiseks, sünteetilise surfaktandi korduval manustamisel näidati paranemist oksügenisatsiooni osas, vähenes ventilatsiooni vajadus ja risk NEK-i haigestumiseks ning vähenes suremus (*Soll R, Ozek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2009*). *Dunn 1990* ja *Speer 1992* kasutasid oma uuringutes looduslikku surfaktanti kordusdoosina 100 mg/kg. Reeglina ei peaks surfaktandi kordusdoose manustama väiksema intervalliga kui 12 tundi, välja arvatud juhtudel, kus surfactant on	**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 Jan;133(1):156-63. doi: 10.1542/peds.2013-3443. Epub 2013 Dec 30.

inaktiveeritud infektsiooni, mekooniumi või vere poolt (*Cogo PE, Facco M, Simonato M, et al. Pharmacokinetics and clinical predictors of surfactant redosing in respiratory distress syndrome. Intensive Care Med. 2011;37(3):510–517*)	

Süstemaatiste ülevaadete kokkuvõtvad tõenduspõhised soovitused:

Raske kuluga RDS ravis on soovitav korduvalt manustasda surfaktanti.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
<u>Kas hingamishäiretega enneaegsetel vastsündinutel kasutada parema ravitulemi saavutamiseks varast surfaktantravi võrreldes hilise surfaktantraviga?</u>	
Background Clinical trials have confirmed that surfactant therapy is effective in improving the immediate need for respiratory support and the clinical outcome of premature newborns. Trials have studied a wide variety of surfactant preparations used either to prevent (prophylactic or delivery room administration) or treat (selective or rescue administration) respiratory distress syndrome (RDS). Using either treatment strategy, significant reductions in the incidence of pneumothorax, as well as significant improvement in survival, have been noted. It is unclear whether there are any advantages to treating infants with respiratory insufficiency earlier in the course of RDS. **Objectives** To compare the effects of early versus delayed selective surfactant therapy for newborns intubated for respiratory distress within the first two hours of life. Planned subgroup analyses included separate comparisons for studies utilizing natural surfactant extract and synthetic surfactant. **Search methods** We searched the Oxford Database of Perinatal Trials, MEDLINE (MeSH terms: pulmonary surfactant; text word: early; limits: age, newborn: publication type, clinical trial), PubMed, abstracts, conference and symposia proceedings, expert informants, and journal handsearching in the English language. For the updated search in April 2012 we searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, 2012, Issue 1) and PubMed (January 1997 to April 2012). **Selection criteria** Randomized and quasi-randomized controlled clinical trials comparing early selective surfactant administration (surfactant administration via the endotracheal tube in infants intubated for respiratory distress, not specifically for surfactant dosage) within the first two hours of life versus delayed selective surfactant administration to infants with established RDS were considered for review. **Data collection and analysis**	**Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome.** Bahadue FL, Soll R. Cochrane Database Syst Rev. 2012;11(11):CD001456

Data regarding clinical outcomes were excerpted from the reports of the clinical trials by the review authors. Subgroup analyses were performed based on type of surfactant preparation, gestational age, and exposure to prenatal steroids. Data analysis was performed in accordance with the standards of the Cochrane Neonatal Review Group. **Main results** Six randomized controlled trials met selection criteria. Two of the trials utilized synthetic surfactant (ExosurfNeonatal) and four utilized animal-derived surfactant preparations. The meta-analyses demonstrate significant reductions in the risk of neonatal mortality (typical risk ratio (RR) 0.84; 95% confidence interval (CI) 0.74 to 0.95; typical risk difference (RD) -0.04; 95% CI -0.06 to -0.01; 6 studies; 3577 infants), chronic lung disease (typical RR 0.69; 95% CI 0.55 to 0.86; typical RD -0.04; 95% CI -0.06 to -0.01; 3 studies; 3041 infants), and chronic lung disease or death at 36 weeks (typical RR 0.83; 95% CI 0.75 to 0.91; typical RD -0.06; 95% CI -0.09 to -0.03; 3 studies; 3050 infants) associated with early treatment of intubated infants with RDS. Intubated infants randomized to early selective surfactant administration also demonstrated a decreased risk of acute lung injury including a decreased risk of pneumothorax (typical RR 0.69; 95% CI 0.59 to 0.82; typical RD -0.05; 95% CI -0.08 to -0.03; 5 studies; 3545 infants), pulmonary interstitial emphysema (typical RR 0.60; 95% CI 0.41 to 0.89; typical RD -0.06; 95% CI -0.10 to -0.02; 3 studies; 780 infants), and overall air leak syndromes (typical RR 0.61; 95% CI 0.48 to 0.78; typical RD -0.18; 95% CI -0.26 to -0.09; 2 studies; 463 infants). A trend toward risk reduction for bronchopulmonary dysplasia (BPD) or death at 28 days was also evident (typical RR 0.94; 95% CI 0.88 to 1.00; typical RD -0.04; 95% CI -0.07 to -0.00; 3 studies; 3039 infants). No differences in other complications of RDS or prematurity were noted. Only two studies reported on infants under 30 weeks' gestation. Decreased risk of neonatal mortality and chronic lung disease or death at 36 weeks' postmenstrual age was noted.	

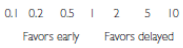
Analysis 1.1. Comparison 1 Early versus delayed selective surfactant treatment, Outcome 1 Neonatal mortality.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early versus delayed selective surfactant treatment

Outcome: 1 Neonatal mortality

Study or subgroup	Early treatment n/N	Late treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
European Study 1992	37/212	55/208		13.1 %	0.66 [0.46, 0.96]
OSIRIS 1992	296/1344	337/1346		79.7 %	0.88 [0.77, 1.01]
Subtotal (95% CI)	**1556**	**1554**		**92.8 %**	**0.85 [0.75, 0.96]**
Total events: 333 (Early treatment), 392 (Late treatment)					
Heterogeneity: Chi² = 2.04, df = 1 (P = 0.15); I² =51%					
Test for overall effect: Z = 2.51 (P = 0.012)					
2 Animal-derived surfactant					
Gortner 1998	3/154	2/163		0.5 %	1.59 [0.27, 9.37]
Konishi 1992	1/16	2/16		0.5 %	0.50 [0.05, 4.98]
Lefort 2003	14/35	21/40		4.6 %	0.76 [0.46, 1.26]
Plavka 2002	2/21	7/22		1.6 %	0.30 [0.07, 1.28]
Subtotal (95% CI)	**226**	**241**		**7.2 %**	**0.69 [0.44, 1.09]**
Total events: 20 (Early treatment), 32 (Late treatment)					
Heterogeneity: Chi² = 2.33, df = 3 (P = 0.51); I² =0.0%					
Test for overall effect: Z = 1.58 (P = 0.11)					
Total (95% CI)	**1782**	**1795**		**100.0 %**	**0.84 [0.74, 0.95]**
Total events: 353 (Early treatment), 424 (Late treatment)					
Heterogeneity: Chi² = 4.84, df = 5 (P = 0.44); I² =0.0%					
Test for overall effect: Z = 2.82 (P = 0.0048)					
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² =0.0%					



Analysis 1.2. Comparison 1 Early versus delayed selective surfactant treatment, Outcome 2 Mortality at discharge.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early versus delayed selective surfactant treatment

Outcome: 2 Mortality at discharge

Study or subgroup	Early treatment n/N	Late treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
OSIRIS 1992	354/1344	398/1346		92.7 %	0.89 [0.79, 1.01]
Subtotal (95% CI)	**1344**	**1346**		**92.7 %**	**0.89 [0.79, 1.01]**
Total events: 354 (Early treatment), 398 (Late treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.86 (P = 0.062)					
2 Animal-derived surfactant					
Gortner 1998	5/154	3/163		0.7 %	1.76 [0.43, 7.26]
Konishi 1992	1/16	2/16		0.5 %	0.50 [0.05, 4.98]
Lefort 2003	14/35	21/40		4.6 %	0.76 [0.46, 1.26]
Plavka 2002	2/21	7/22		1.6 %	0.30 [0.07, 1.28]
Subtotal (95% CI)	**226**	**241**		**7.3 %**	**0.74 [0.47, 1.15]**
Total events: 22 (Early treatment), 33 (Late treatment)					
Heterogeneity: Chi² = 3.07, df = 3 (P = 0.38); I² =2%					
Test for overall effect: Z = 1.34 (P = 0.18)					
Total (95% CI)	**1570**	**1587**		**100.0 %**	**0.88 [0.78, 0.99]**
Total events: 376 (Early treatment), 431 (Late treatment)					
Heterogeneity: Chi² = 3.63, df = 4 (P = 0.46); I² =0.0%					
Test for overall effect: Z = 2.14 (P = 0.032)					
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² =0.0%					

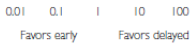
Analysis 1.5. Comparison 1 Early versus delayed selective surfactant treatment, Outcome 5 Chronic lung disease.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early versus delayed selective surfactant treatment

Outcome: 5 Chronic lung disease

Study or subgroup	Early treatment n/N	Late treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
OSIRIS 1992	106/1344	151/1346		89.1 %	0.70 [0.55, 0.89]
Subtotal (95% CI)	**1344**	**1346**		**89.1 %**	**0.70 [0.55, 0.89]**
Total events: 106 (Early treatment), 151 (Late treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.92 (P = 0.0035)					
2 Animal-derived surfactant					
Gortner 1998	7/154	12/163		6.9 %	0.62 [0.25, 1.53]
Plavka 2002	4/21	7/22		4.0 %	0.60 [0.20, 1.75]
Subtotal (95% CI)	**175**	**185**		**10.9 %**	**0.61 [0.30, 1.22]**
Total events: 11 (Early treatment), 19 (Late treatment)					
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² =0.0%					
Test for overall effect: Z = 1.39 (P = 0.16)					
Total (95% CI)	**1519**	**1531**		**100.0 %**	**0.69 [0.55, 0.87]**
Total events: 117 (Early treatment), 170 (Late treatment)					
Heterogeneity: Chi² = 0.15, df = 2 (P = 0.93); I² =0.0%					
Test for overall effect: Z = 3.21 (P = 0.0013)					
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² =0.0%					



Analysis 1.6. Comparison 1 Early versus delayed selective surfactant treatment, Outcome 6 CLD or death at 36 weeks' PMA.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early versus delayed selective surfactant treatment

Outcome: 6 CLD or death at 36 weeks' PMA

Study or subgroup	Early treatment n/N	Late treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
OSIRIS 1992	429/1344	514/1346		94.8 %	0.84 [0.75, 0.93]
Subtotal (95% CI)	**1344**	**1346**		**94.8 %**	**0.84 [0.75, 0.93]**
Total events: 429 (Early treatment), 514 (Late treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.39 (P = 0.00069)					
2 Animal-derived surfactant					
Gortner 1998	12/154	15/163		2.7 %	0.85 [0.41, 1.75]
Plavka 2002	6/21	14/22		2.5 %	0.45 [0.21, 0.95]
Subtotal (95% CI)	**175**	**185**		**5.2 %**	**0.65 [0.39, 1.10]**
Total events: 18 (Early treatment), 29 (Late treatment)					
Heterogeneity: Chi² = 1.46, df = 1 (P = 0.23); I² =32%					
Test for overall effect: Z = 1.60 (P = 0.11)					
Total (95% CI)	**1519**	**1531**		**100.0 %**	**0.83 [0.75, 0.91]**
Total events: 447 (Early treatment), 543 (Late treatment)					
Heterogeneity: Chi² = 2.62, df = 2 (P = 0.27); I² =24%					
Test for overall effect: Z = 3.68 (P = 0.00023)					
Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.37), I² =0.0%					

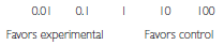
Analysis 1.7. Comparison 1 Early versus delayed selective surfactant treatment, Outcome 7 Any air leak syndrome.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early versus delayed selective surfactant treatment

Outcome: 7 Any air leak syndrome

Study or subgroup	Early treatment n/N	Late treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic Surfactant					
European Study 1992	65/212	102/208		96.8 %	0.63 [0.49, 0.80]
Subtotal (95% CI)	**212**	**208**		**96.8 %**	**0.63 [0.49, 0.80]**
Total events: 65 (Early treatment), 102 (Late treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.75 (P = 0.00018)					
2 Animal-derived surfactant					
Plavka 2002	0/21	3/22		3.2 %	0.15 [0.01, 2.73]
Subtotal (95% CI)	**21**	**22**		**3.2 %**	**0.15 [0.01, 2.73]**
Total events: 0 (Early treatment), 3 (Late treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
Total (95% CI)	**233**	**230**		**100.0 %**	**0.61 [0.48, 0.78]**
Total events: 65 (Early treatment), 105 (Late treatment)					
Heterogeneity: Chi^2 = 0.94, df = 1 (P = 0.33); I^2 =0.0%					
Test for overall effect: Z = 3.96 (P = 0.000075)					
Test for subgroup differences: Chi^2 = 0.93, df = 1 (P = 0.34), I^2 =0.0%					



Analysis 1.8. Comparison 1 Early versus delayed selective surfactant treatment, Outcome 8 Pneumothorax.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early versus delayed selective surfactant treatment

Outcome: 8 Pneumothorax

Study or subgroup	Early treatment n/N	Late treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
European Study 1992	38/212	55/208		18.1 %	0.68 [0.47, 0.98]
OSIRIS 1992	160/1344	232/1346		75.5 %	0.69 [0.57, 0.83]
Subtotal (95% CI)	**1556**	**1554**		**93.6 %**	**0.69 [0.58, 0.81]**
Total events: 198 (Early treatment), 287 (Late treatment)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 4.40 (P = 0.000011)					
2 Animal-derived surfactant					
Gortner 1998	6/154	6/163		1.9 %	1.06 [0.35, 3.21]
Lefort 2003	8/35	11/40		3.3 %	0.83 [0.38, 1.83]
Plavka 2002	0/21	3/22		1.1 %	0.15 [0.01, 2.73]
Subtotal (95% CI)	**210**	**225**		**6.4 %**	**0.78 [0.42, 1.45]**
Total events: 14 (Early treatment), 20 (Late treatment)					
Heterogeneity: Chi^2 = 1.56, df = 2 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 0.79 (P = 0.43)					
Total (95% CI)	**1766**	**1779**		**100.0 %**	**0.69 [0.59, 0.82]**
Total events: 212 (Early treatment), 307 (Late treatment)					
Heterogeneity: Chi^2 = 1.85, df = 4 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 4.45 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 =0.0%					

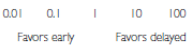
Analysis 1.9. Comparison 1 Early versus delayed selective surfactant treatment, Outcome 9 Pulmonary interstitial emphysema.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 1 Early versus delayed selective surfactant treatment

Outcome: 9 Pulmonary interstitial emphysema

Study or subgroup	Early treatment n/N	Late treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
European Study 1992	29/212	46/208		79.2 %	0.62 [0.40, 0.94]
Subtotal (95% CI)	**212**	**208**		**79.2 %**	**0.62 [0.40, 0.94]**
Total events: 29 (Early treatment), 46 (Late treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.22 (P = 0.026)					
2 Animal-derived surfactant					
Gortner 1998	6/154	9/163		14.9 %	0.71 [0.26, 1.94]
Plavka 2002	0/21	3/22		5.8 %	0.15 [0.01, 2.73]
Subtotal (95% CI)	**175**	**185**		**20.8 %**	**0.55 [0.22, 1.39]**
Total events: 6 (Early treatment), 12 (Late treatment)					
Heterogeneity: Chi² = 1.01, df = 1 (P = 0.32); I² =1%					
Test for overall effect: Z = 1.27 (P = 0.20)					
Total (95% CI)	**387**	**393**		**100.0 %**	**0.60 [0.41, 0.89]**
Total events: 35 (Early treatment), 58 (Late treatment)					
Heterogeneity: Chi² = 0.99, df = 2 (P = 0.61); I² =0.0%					
Test for overall effect: Z = 2.56 (P = 0.010)					
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² =0.0%					



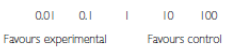
Analysis 2.1. Comparison 2 Early versus delayed selective surfactant treatment in infants less than 30 weeks' gestation, Outcome 1 Neonatal mortality.

Review: Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome

Comparison: 2 Early versus delayed selective surfactant treatment in infants less than 30 weeks' gestation

Outcome: 1 Neonatal mortality

Study or subgroup	Early treatment n/N	Late treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Synthetic surfactant					
European Study 1992	37/212	55/208		89.0 %	0.66 [0.46, 0.96]
Subtotal (95% CI)	**212**	**208**		**89.0 %**	**0.66 [0.46, 0.96]**
Total events: 37 (Early treatment), 55 (Late treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.20 (P = 0.028)					
2 Animal-derived surfactant					
Plavka 2002	2/21	7/22		11.0 %	0.30 [0.07, 1.28]
Subtotal (95% CI)	**21**	**22**		**11.0 %**	**0.30 [0.07, 1.28]**
Total events: 2 (Early treatment), 7 (Late treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.63 (P = 0.10)					
Total (95% CI)	**233**	**230**		**100.0 %**	**0.62 [0.43, 0.89]**
Total events: 39 (Early treatment), 62 (Late treatment)					
Heterogeneity: Chi² = 1.07, df = 1 (P = 0.30); I² =7%					
Test for overall effect: Z = 2.62 (P = 0.0089)					
Test for subgroup differences: Chi² = 1.07, df = 1 (P = 0.30), I² =6%					



Authors' conclusions

Early selective surfactant administration given to infants with RDS requiring assisted ventilation leads to a decreased risk of acute pulmonary injury (decreased risk of pneumothorax and pulmonary interstitial emphysema) and a decreased risk of neonatal mortality

and chronic lung disease compared to delaying treatment of such infants until they develop worsening RDS.	
Abstract BACKGROUND: Preterm neonates with respiratory distress syndrome (RDS) benefit from early application of nasal continuous positive airway pressure (nCPAP). However, it is not clear whether surfactant should be administered early as a routine to all such infants or later in a selective manner. OBJECTIVE: It was the aim of this study **to compare the efficacy of early routine versus late selective surfactant treatment in reducing the need for mechanical ventilation (MV) during the first week of life among moderate-sized preterm infants** with RDS being supported by nCPAP. METHODS: Infants born at **28(0/7) to 33(6/7) weeks of gestation with** RDS and on nCPAP were randomly assigned within the first 2 h of life to early routine surfactant administration by the InSurE technique **(early surfactant group)** or to late selective administration of surfactant **(late surfactant group).** The primary outcome was need for MV in the first 7 days of life. RESULTS: Among **153 infants** randomized to early (n = 74) or late surfactant (n = 79) groups, the **need for MV was significantly lower in the early surfactant group (16.2 vs. 31.6%; relative risk 0.41, 95% confidence interval 0.19-0.91).** The incidence of pneumothorax (1.9 vs. 2.3%) and the need for supplemental O2 at 28 days (2.7 vs. 8.9%) were similar in the two groups. **Table 2.** Primary and other major outcomes Outcome | Early surfactant (n = 74) | Late surfactant (n = 79) | RR | p value Ventilation till day 7 | 12 (16.2) | 25 (31.6) | 0.41 [0.19–0.91] | 0.03 Mortality | 9 (12.2) | 11 (13.9) | 0.87 [0.33–2.22] | 0.74 Patent ductus arteriosus | 20 (27) | 24 (30.4) | 0.85 [0.42–1.72] | 0.64 Culture-positive sepsis | 18 (24.3) | 14 (17.7) | 1.49 [0.68–3.33] | 0.31 Necrotizing enterocolitis | 2 (2.7) | 3 (3.8) | 0.70 [0.11–4.34 | 0.70 Retinopathy of prematurity | 10 (13.5) | 12 (15.2) | 0.88 [0.35–2.17] | 0.76 Cystic PVL or grade III or grade IV IVH | 3 (4.1) | 3 (3.8) | 0.93 [0.18–5.00] | 0.93 Duration of CPAP, h | | | – | 0.99 Median | 24 | 28 | | IQR | 18–48 | 16.5–51.5 | | Duration of MV, h | | | – | 0.77 Median | 32.5 | 42 | | IQR | 25–95.2 | 24.5–90.5 | | Pneumothorax | 1 (1.9) | 2 (2.3) | – | 0.59 Supplementation with O_2 at 28 days | 2 (2.7) | 7 (8.9) | – | 0.11 BPD (O_2 dependency at 36 weeks) | 0 | 2 (2.5) | – | – Length of hospital stay (survivors), days | | | – | 0.47 Median | 25 | 19 | | IQR | 11–38.5 | 11–33 | | Figures in parentheses are percentages; figures in brackets are 95% CIs. PVL = Periventricular leukomalacia; IVH = intraventricular hemorrhage; BPD = bronchopulmonary dysplasia. **CONCLUSION:** **Early routine surfactant administration within 2 h of life as compared to late selective administration significantly reduced the need for MV in the first week of life among preterm infants with RDS on nCPAP.**	**Early routine versus late selective surfactant in preterm neonates with respiratory distress syndrome on nasal continuous positive airway pressure: a randomized controlled trial.** Kandraju H, Murki S, Subramanian S, Gaddam P, Deorari A, Kumar P. Neonatology. 2013;103(2):148-54.
Abstract **Background:** The best criteria for surfactant treatment in the perinatal	**Analysis of the cost-effectiveness**

period are unknown and this makes it of interest to consider the possible economic implications of lessening the use of more restrictive criteria.
Objective: The objective of this study is the evaluation of the costs of respiratory care for preterm infants with Respiratory Distress Syndrome (RDS) treated with "early rescue" surfactant compared to a "late rescue" strategy.
Methods: The study was carried out applying the costs of materials used, of staff and pharmacological therapy calculated in the Neonatal Intensive Care Unit (NICU) of an Italian hospital to the Verder et al. study (Pediatrics 1999) clinical data.
Results: The cost for patients **treated with early strategy was slightly lower than for patients treated with läte strategy (Euro 4,901.70 vs. Euro 4,960.07).** The cost of treatment with surfactant was greater in the early group (Euro 458.49 vs. Euro 311.74), but this was compensated by the greater cost of treatment with Mechanical Ventilation (MV) in the late group (respectively Euro 108.85 vs. Euro 259.25).

Table 6 Comparison of cost-effectiveness (€) in "*early*" and "*late*" treatment groups

	Early treatment	*Late* treatment	Difference
Primary Endpoint			
MV and/or death < 7 days, (%)	21	63	42
Average cost per patient treated			
- surfactant (1st dose)	438.56	287.76	150.80
- surfactant (2nd dose)	19.93	23.98	4.05
- NCPAP	4,334.36	4,389.08	54.72
- MV	108.85	259.25	150.40
Total	4,901.70	4,960.07	58.37

Conclusions: 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.

of surfactant treatment (Curosurf®) in respiratory distress syndrome therapy in preterm infants: early treatment compared to late treatment.

Dani C, Ravasio R, Fioravanti L, Circelli M.
Ital J Pediatr. 2014 May 2;40:40. doi: 10.1186/1824-7288-40-40.

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<u>Surfaktandi manustamise viis (INSURE; LISA võrreldes „konventsionaalne")</u>

IMPORTANCE Surfactant administration by minimally invasive methods that allow for spontaneous breathing might be safer and more effective than administration with endotracheal intubation and mechanical ventilation; however, the efficacy and safety of minimally invasive methods have not been reviewed.
OBJECTIVE To conduct a meta-narrative review of the efficacy and safety of minimally invasive surfactant administration using a thin catheter, aerosolization, a laryngeal mask airway, and pharyngeal

Minimally invasive surfactant administration in preterm infants: a meta-narrative review.

More K, Sakhuja P,

administration in preterm infants with or at risk for respiratory distress syndrome.
DATA SOURCES We searched the PubMed, EMBASE, Cochrane, and CINAHL databases, published journals, and conference proceedings from inception to June 30, 2013.
STUDY SELECTION Randomized clinical trials or observational studies of preterm infants who were given surfactant for respiratory distress syndrome by minimally invasivemethods.
DATA EXTRACTION AND SYNTHESIS An overall meta-narrative review was conducted encompassing the evolution of noninvasive surfactant therapy. Risk ratios and 95% confidence intervals are reported when appropriate.
MAIN OUTCOMES AND MEASURES Chronic lung disease diagnosed by the need for oxygen therapy at a postmenstrual age of 36 weeks, need for mechanical ventilation within the first 72 hours of birth, need for mechanical ventilation any time during the hospital stay, and adverse events associated with administration of surfactant by various methods.
RESULTS We included 10 studies (6 randomized and 4 observational) of 3081 neonates. Thin catheter administration was evaluated in 6 studies (2 randomized and 4 observational); aerosolization, in 2 randomized studies; and laryngeal mask and pharyngeal administration, in 1 observational study each.

Table 1. Characteristics of Included Studies

Source	Design and Population	Comparison Treatment	Participants and Intervention	Results
Method 1: Administration of Surfactant via Thin Catheter				
Kribs et al,[14] 2007	Nonrandomized feasibility study; ELBW infants with GA, 23-27 wk	ET instillation	29 I and 34 C; F_{IO_2}, >0.4: 100 mg/kg surfactant	BPD: 14% I vs 15% C (NS); mortality: 12% I vs 35% C (P = .025)
Kribs et al,[30] 2010	Prospective cohort study; VLBW infants or GA, <31 wk	ET instillation	319 I and 1222 C	MV in first 72 h: 29% I vs 53% C (P < .001); BPD: 11% I vs 18% C (P = .004)
Göpel et al,[12] 2011	RCT; VLBW infants or GA, 26-28^6 wk, age <12 h	CPAP followed by ET instillation	108 I and 112 C	MV on day 2-3: RR, 0.68 (95% CI, 0.42-0.88); MV at any time: RR, 0.42 (95% CI, 0.31-0.59); BPD: RR, 0.62 (95% CI, 0.27-1.40)
Dargaville et al,[31] 2013	Nonrandomized study (historical controls); GA, 25-34 wk, age, <24 h	Routine CPAP and ET instillation	38 I and 41 C: GA, 25-28 wk; 23 I and 56 C: GA, 29-34 wk	MV at 72 h, GA, 25-28 wk: OR, 0.21 (95% CI, 0.08-0.55); MV at 72 h, GA, 29-34 wk: OR 0.34 (95% CI, 0.11-1.0); BPD: 29% I vs 29% C (P = .85)
Klebermass-Schrehof et al,[17] 2013	Nonrandomized study (historical controls); GA, 23-27 wk, at birth	CPAP, ET instillation	224 I and 182 C	MV need at 3 d: 23% I vs 52% C (P < .001); BPD: 16% I vs 12% C (NS)
Kanmaz et al,[16] 2013	RCT; GA, <32 wk; age, <72 h	INSURE method	100 C and 100 I (porcine surfactant, 100 mg/kg[a])	MV within 72 h: 30% I vs 45% C (P = .02) (reported); MV at any time: 40% I vs 49% C (P = .08); BPD: 10% I vs 20% C (P = .009)
Method 2: Surfactant Administration via Aerosol[b]				
Berggren et al,[18] 2000	RCT; GA, 27-36 wk; randomized at 2-36 h; F_{IO_2} >0.4	CPAP	16 C and 16 I (porcine surfactant, 480 mg[a])	Need for MV: 38% C vs 31% I (NS); BPD: 12.5% C vs 0% I (NS)
Minocchieri et al,[32] 2013	RCT; GA, 29-33 wk; F_{IO_2}, 0.22-0.30 in first 6 h after birth	CPAP	N = 64; I (porcine surfactant[a]) vs C	Need for intubation in the first 72 h: RR, 0.56 (95% CI, 0.34-0.93); BPD: no difference (numbers not given)
Method 3: Surfactant Administration via LMA				
Attridge et al,[33] 2013	RCT; BW, ≥1200 g; age at inclusion, ≤72 h	ET instillation	13 I (calfactant surfactant, 3 mL/kg) and 13 C	MV need within 96 h: RR, 1.0 (95% CI, 0.25-4.07)
Method 4: Surfactant Administration via Nasopharyngeal Instillation				
Ten Centre Study Group,[34] 1987	RCT; GA, 25-29 wk	Saline	43 I and 32 C: 25-26 wk; 116 I and 117 C: 27-29 wk	Mortality: 19% I vs 30% C (P < .01); respiratory support in first 10 d: I group, 19 h less in >30% oxygen (P < .05) and 20 h less ventilation (P < .05)

Abbreviations:
BPD, bronchopulmonary dysplasia; BW, birth weight; C, comparison; CPAP, continuous positive airway pressure; ELBW, extremely low birth weight; ET, endotracheal; F_{IO_2}, fraction of inspired oxygen; GA, gestational age; I, intervention; INSURE, intubation, surfactant administration during brief mechanical ventilation, and extubation; LMA, laryngeal mask airway; MV, mechanical ventilation; NS, not significant; OR, odds ratio; RCT, randomized clinical trial; RDS, respiratory distress syndrome; RR, relative risk; VLBW, very low birth weight.
[a] Indicates Curosurf (Chiesi USA, Inc).
[b] Indicates CPAP plus nebulized surfactant.

The meta-narrative review confirmed the slow evolution and challenges of the different modes of administration, with thin catheter administration being the most studied intervention. Two randomized studies of surfactant administration using a thin catheter revealed no significant

Shah PS.

JAMA Pediatr. 2014 Oct;168(10):901-8.

difference in the outcome of bronchopulmonary dysplasia but a potential reduction in the need for mechanical ventilation within 72 hours of birth when compared with standard care.
CONCLUSIONS AND RELEVANCE Surfactant administration via a thin catheter may be an efficacious and potentially safe method; however, further studies are needed. Further studies are also needed for other methods of minimally invasive surfactant administration.

Abstract
BACKGROUND AND OBJECTIVE: Mechanical ventilation via an endotracheal tube is a risk factor for bronchopulmonary dysplasia (BPD), one of the most common morbidities of very preterm infants. Our objective was **to investigate the effect that strategies to avoid endotracheal mechanical ventilation (eMV) have on the incidence of BPD in preterm infants <30 weeks' gestational age (GA)**.
METHODS: In February 2013, we searched the databases Medline, Embase, and the Cochrane Central Register of Controlled Trials. Study selection criteria **included randomized controlled trials published in peer-reviewed journals since the year 2000 that compared preterm infants <30 weeks' GA treated by using a strategy aimed at avoiding eMV with a control group in which mechanical ventilation via an endotracheal tube was performed at an earlier stage.** Data were extracted and analyzed by using the standard methods of the Cochrane Neonatal Review Group. The authors independently assessed study eligibility and risk of bias, extracted data and calculated odds ratios and 95% confidence intervals, employing RevMan version 5.1.6.
RESULTS: We identified **7 trials that included a total of 3289 infants.**

TABLE 1 Characteristics of Included Studies

Author	Study Name	Year	Intervention	Any eMV Except INSURE, %	GA	Randomization	*n*	Recruitment
Morley et al[13]	COIN	2008	nCPAP versus mechanical ventilation	59 vs 100	$25^{0}/_{7}$–$28^{6}/_{7}$	At 5 min of age	610	1999–2006
Rojas et al[37] [a]	CNRN	2009	nCPAP versus INSURE	43 vs 39	$27^{0}/_{7}$–$29^{6}/_{7}$	15–60 min of age	146[b]	2004–2006
Finer et al[14]	SUPPORT	2010	nCPAP versus mechanical ventilation	83 vs 100	$24^{0}/_{7}$–$27^{6}/_{7}$	<1 h of age	1316	2005–2009
Sandri et al[16]	CURPAP [d]	2010	nCPAP versus INSURE	31 vs 33[c]	$25^{0}/_{7}$–$28^{6}/_{7}$	<30 min of age	208	2007–2008
Dunn et al[15]	DRM	2011	3 groups: nCPAP versus INSURE versus mechanical ventilation	52 vs 59 vs 96	$26^{0}/_{7}$–$29^{6}/_{7}$	Before delivery	648	2003–2009
Göpel et al[36]	AMV	2011	nCPAP ± surfactant during spontaneous breathing versus nCPAP ± mechanical ventilation	33 vs 73	$26^{0}/_{7}$–$28^{6}/_{7}$	<12 h of age	220	2007–2009
Kanmaz et al[19] [a]	Take Care	2013	nCPAP ± surfactant during spontaneous breathing versus nCPAP ± INSURE	42 vs 52[a]	$\leq 29^{6}/_{7}$	<2 h of age	141[b]	2010–2011

[a] Previously unpublished, stratified data for infants $<30^{0}/_{7}$ weeks' GA.
[b] Number of infants $<30^{0}/_{7}$ weeks' GA only.
[c] Need for any eMV except INSURE in the first 5 d of live.
[d] Combining prophylactic surfactant and early nasal continuous positive airway pressure study.

The combined odds ratio (95% confidence interval) of death or BPD was 0.83 (0.71–0.96). The number needed to treat was 35.

Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis.

Fischer HS, Bührer C.

Pediatrics. 2013 Nov;132(5):e1351-60.

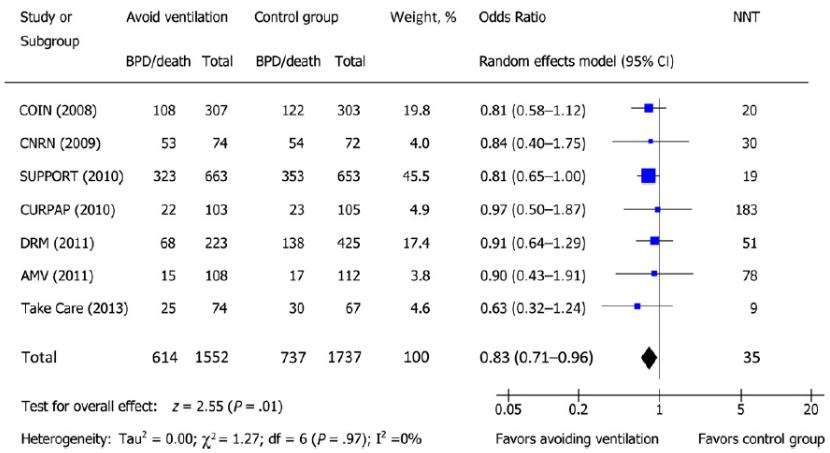

FIGURE 2
Effect of avoiding eMV on death or BPD.

The study results were remarkably homogeneous. **Avoiding eMV had no influence on the incidence of severe intraventricular hemorrhage.**

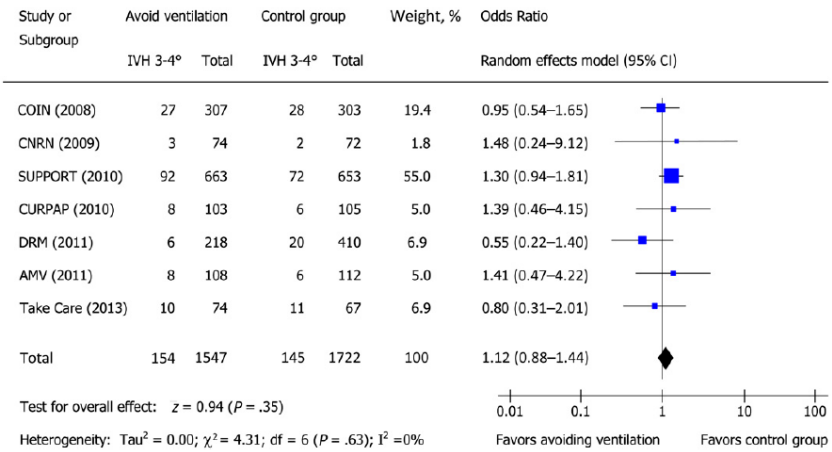

FIGURE 3
Effect of avoiding eMV on IVH.

CONCLUSIONS: Strategies aimed at avoiding eMV in infants <30 weeks' GA have a small but significant beneficial impact on preventing BPD.

A B S T R A C T

Background

Nebulised surfactant has the potential to deliver surfactant to the infant lung with the goal of avoiding endotracheal intubation and ventilation, ventilator-induced lung injury and bronchopulmonary dysplasia (BPD).

Objectives

To determine the effect of nebulised surfactant administration either as prophylaxis or treatment compared to placebo, no treatment or intratracheal surfactant administration on morbidity and mortality in preterm infants with, or at risk of, respiratory distress syndrome (RDS).

Search methods

Searches were performed of CENTRAL (The Cochrane Library, January 2012), MEDLINE and PREMEDLINE (1950 to January 2012), EMBASE (1980 to January 2012) and CINAHL (1982 to January 2012), as well as proceedings of scientific meetings, clinical trial registries,

Nebulised surfactant in preterm infants with or at risk of respiratory distress syndrome.

Abdel-Latif ME, Osborn DA.

Cochrane Database Syst Rev. 2012 Oct 17;10:CD008310.

Google Scholar and reference lists of identified studies. Expert informants and surfactant manufacturers were contacted. **Selection criteria** Randomised, cluster-randomised or quasi-randomised controlled trials of nebulised surfactant administration compared to placebo, no treatment, or other routes of administration (laryngeal, pharyngeal instillation of surfactant before the first breath, thin endotracheal catheter surfactant administration or intratracheal surfactant instillation) on morbidity and mortality in preterm infants at risk of RDS. We considered published, unpublished and ongoing trials. **Data collection and analysis** Two review authors independently assessed studies for eligibility and quality, and extracted data. **Main results** **No studies of prophylactic or early nebulised surfactant administration were found. A single small study of late rescue nebulised surfactant was included. The study is of moderate risk of bias. The study enrolled 32 preterm infants born < 36 weeks' gestation with RDS on nasal continuous positive airway pressure (nCPAP).** The study reported no significant difference between nebulised surfactant administration compared to no treatment groups in chronic lung disease (risk ratio (RR) 5.00; 95% confidence interval (CI) 0.26 to 96.59) or other outcomes (oxygenation 1 to 12 hours after randomisation, need for mechanical ventilation, days of mechanical ventilation or continuous positive airways pressure (CPAP) or days of supplemental oxygen). No side effects of the nebulised surfactant therapy or aerosol inhalation were reported. **Authors' conclusions** **There are insufficient data to support or refute the use of nebulised surfactant in clinical practice. Adequately powered trials are required to determine the effect of nebulised surfactant administration for prevention or early treatment of RDS in preterm infants. Nebulised surfactant administration should be limited to clinical trials.**	
A B S T R A C T **Background** Laryngeal mask airway (LMA) administration is one way of delivering surfactant to the infant lung, with the potential benefit of avoiding endotracheal intubation and ventilation, ventilator induced lung injury and bronchopulmonary dysplasia (BPD). **Objectives** To determine the effect of LMA surfactant administration either as prophylaxis or treatment compared to placebo, no treatment, or intratracheal surfactant administration on morbidity and mortality in preterm infants with, or at risk of, respiratory distress syndrome (RDS). **Search strategy** We searched CENTRAL (*The Cochrane Library*, October 2010), MEDLINE and PREMEDLINE (1950 to October 2010), EMBASE (1980	**Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome.** Abdel-Latif ME, Osborn DA. Cochrane Database Syst Rev. 2011 Jul

to October 2010) and CINAHL (1982 to October 2010). We also searched proceedings of scientific meetings, clinical trial registries, Google Scholar and reference lists of identified studies, as well as contacting expert informants and surfactant manufacturers. **Selection criteria** Randomised, cluster-randomised or quasi-randomised controlled trials of laryngeal mask surfactant administration compared to placebo, no treatment, or other routes of administration (nebulised, pharyngeal instillation of surfactant before the first breath, thin endotracheal catheter surfactant administration or intratracheal surfactant instillation) on morbidity and mortality in preterm infants at risk of RDS. We considered published, unpublished and ongoing trials. **Data collection and analysis** Two review authors independently assessed studies for eligibility and quality, and extracted data. **Main results** **We found no studies of prophylactic or early LMA surfactant administration. A single small study of late rescue LMA surfactant was identified as eligible for inclusion.** The study enrolled **26 preterm infants born ≥1200 g with RDS** on continuous positive airway pressure (nCPAP). LMA surfactant administration compared to no treatment resulted in a reduction in mean FiO2 required to maintain oxygen saturation between 88% and 92% for 12 hours after the intervention. No significant difference was reported in subsequent mechanical ventilation and endotracheal surfactant, pneumothorax, days on intermittent positive airway pressure (IPPV), and days on IPPV or oxygen. **Authors' conclusions** **There is evidence from a single small trial that LMA surfactant administration in preterm infants ≥1200 g with established RDS may have a short term effect in reducing oxygen requirements although the study is underpowered to detect important clinical effects.** **Adequately powered trials are required to determine the effect of LMA surfactant administration for prevention or treatment of RDS in preterm infants. LMA surfactant administration should be limited to clinical trials.**	6;(7):CD008309.
A B S T R A C T **Background** Intrapartum pharyngeal instillation of surfactant before the first breath may result in surfactant administration to the infant lung, with the potential benefit of avoiding endotracheal intubation and ventilation, ventilator induced lung injury and bronchopulmonary dysplasia. **Objectives** To determine the effect of pharyngeal instillation of surfactant before the first breath compared to placebo, no treatment or intratracheal surfactant administration followed by intermittent positive pressure ventilation (IPPV) on morbidity and mortality in preterm infants at risk of respiratory distress syndrome (RDS). **Search strategy**	**Pharyngeal instillation of surfactant before the first breath for prevention of morbidity and mortality in preterm infants at risk of respiratory distress syndrome.** Abdel-Latif ME, Osborn DA.

Searches were made of CENTRAL (*The Cochrane Library*, to September 2010), MEDLINE and PREMEDLINE (1950 to September 2010), EMBASE (1980 to 2010) and CINAHL (1982 to 2010). This strategy was supplemented by searches of proceedings of scientific meetings, Google Scholar and reference lists of identified studies, as well as contact with expert informants and surfactantmanufacturers. **Selection criteria** Published, unpublished and ongoing randomised controlled or quasi-randomised trials (using individual or cluster allocation) of pharyngeal instillation of surfactant before the first breath compared to placebo or no treatment, or intratracheal surfactant instillation followed by IPPV, on morbidity and mortality in preterm infants at risk of RDS. **Data collection and analysis** Two authors independently assessed study eligibility and quality. **Main results** **No published, unpublished or ongoing trials that met the inclusion criteria for this review were found.** Authors' conclusions There were no data from randomised controlled or quasi-randomised trials that evaluated the effect of intrapartum instillation of pharyngeal surfactant before the first breath. Evidence from animal and observational human studies suggest that pharyngeal instillation of surfactant before the first breath is potentially safe, feasible and may be effective.Well designed trials are needed.	Cochrane Database Syst Rev. 2011 Mar 16;(3):CD008311. doi: 10.1002/14651858. CD008311.pub2. Review.
Summary BACKGROUND Surfactant is usually given to mechanically ventilated preterm infants via an endotracheal tube to treat respiratory distress syndrome. We tested a new method of surfactant application to spontaneously breathing preterm infants to avoid mechanical ventilation. METHOD In a parallel-group, randomised controlled trial, **220 preterm infants** with a gestational age between **26 and 28 weeks** and a birthweight **less than 1·5 kg** were enrolled in **12 German neonatal intensive care units.** Infants were independently randomised in a 1:1 ratio with variable block sizes, to **standard treatment or intervention**, and randomisation was stratified according to centre and multiple birth status. Masking was not possible. Infants were stabilised with continuous positive airway pressure and received rescue intubation if necessary. In the intervention group, infants received surfactant treatment during spontaneous breathing via a thin catheter inserted into the trachea by laryngoscopy if they needed a fraction of inspired oxygen more than 0·30. The **primary endpoint was need for any mechanical ventilation**, or **being not ventilated but having a partial pressure of carbon dioxide more than 65 mm Hg (8·6 kPa) or a fraction of inspired oxygen more than 0·60, or both, for more than 2 h between 25 h and 72 h of age.** Analysis was by intention to treat. This study is registered, number ISRCTN05025922. FINDINGS 108 infants were assigned to the intervention group and 112 infants to the standard treatment group. All infants were analysed. On day	**Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial.** Göpel W, Kribs A, Ziegler A, et al; German Neonatal Network. Lancet. 2011;378(9803):1627– 1634 **Funding:** **German Ministry**

2 or 3 after birth, **30 (28%) infants in the intervention group were mechanically ventilated versus 51 (46%) in the standard treatment group (number needed to treat 6, 95% CI 3–20, absolute risk reduction 0·18, 95% CI 0·30–0·05, p=0·008).**

	Intervention group (n=108)	Standard treatment group (n=112)	Absolute risk reduction (95% CI)	Number needed to treat (95% CI)	p value*
All infants (%)	30 (28%)	51 (46%)	−0·18 (−0·30 to −0·05)	6 (3 to 20)	0·008
26 weeks' gestation (%)	11/26 (42%)	11/26 (42%)	0·00 (−0·27 to 0·27)	..	1·000
27 weeks' gestation (%)	12/41 (29%)	21/44 (48%)	−0·18 (−0·39 to 0·03)	..	0·119
28 weeks' gestation (%)	7/41 (17%)	19/42 (45%)	−0·28 (−0·47 to −0·08)	4 (2 to 13)	0·009

The primary outcome was any mechanical ventilation, or being not ventilated but having a partial pressure of carbon dioxide more than 65 mm Hg (8·6 kPa) or a fraction of inspired oxygen more than 0·60, or both, for more than 2 h between 25 h and 72 h of age. Data are n (%) or n/N (%), unless otherwise stated. *Calculated with Fisher's exact test.

Table 2: Primary outcome

36 (33%) infants in the intervention group were mechanically ventilated during their stay in the hospital compared with 82 (73%) in the standard treatment group (number needed to treat: 3, 95% CI 2–4, p<0·0001). The intervention group had significantly fewer median days on mechanical ventilation, (0 days. IQR 0–3 vs 2 days, 0–5) and a lower need for oxygen therapy at 28 days (30 infants [30%] vs 49 infants [45%], p=0·032) compared with the standard treatment group. We recorded no differences between groups for mortality (seven deaths in the intervention group vs five in the standard treatment group) and serious adverse events (21 vs 28).

	Intervention group (n=108)	Standard treatment group (n=112)	Absolute risk reduction (95% CI)	Number needed to treat (95% CI)	p value
Any mechanical ventilation					
All infants (%)	36 (33%)	82 (73%)	−0·40 (−0·52 to −0·27)	3 (2 to 4)	<0·0001
26 weeks' gestation (%)	11/26 (42%)	19/26 (73%)	−0·31 (−0·55 to −0·29)	4 (2 to 34)	0·048
27 weeks' gestation (%)	18/41 (44%)	33/44 (75%)	−0·31 (−0·50 to −0·08)	4 (2 to 12)	0·004
28 weeks' gestation (%)	7/41 (17%)	30/42 (71%)	−0·54 (−0·71 to −0·34)	2 (2 to 3)	<0·0001
Other pulmonary outcomes					
Duration of mechanical ventilation (days)	0 (0–3)	2 (0–5)	..	..	<0·0001
Any respiratory support (mechanical ventilation or CPAP) (days)	25 (11–38)	29 (16–41)	..	..	0·069
Supplemental O_2 (days)	5 (2–32)	19 (2–42)	..	..	0·059
Pulmonary haemorrhage	1 (1%)	3 (3%)	..	..	0·622
Pneumothorax	4 (4%)	8 (7%)	..	..	0·375
Supplemental O_2 at age 28 days*	30 (30%)	49 (45%)	..	..	0·032
Death or supplemental O_2 at 28 days	37 (34%)	52 (46%)	..	..	0·075
Bronchopulmonary dysplasia at 36 weeks postmenstrual age*	8 (8 %)	14 (13%)	..	..	0·268
Discharged home, treated with O_2	1 (1%)	1 (1%)	..	..	1·000
Death or bronchopulmonary dysplasia at 36 weeks postmenstrual age	15 (14%)	17 (15%)	..	..	0·850
Oxygen saturation (%)					
Day 1	93% (91–96)	93% (91–96)	..	..	0·339
Day 2	93% (91–96)	94% (92–96)	..	..	0·299
Day 3	95% (92–97)	95% (92–97)	..	..	0·907
FiO_2					
Day 1	0·25 (0·22–0·29)	0·24 (0·21–0·30)	..	..	0·901
Day 2	0·22 (0·21–0·28)	0·22 (0·21–0·27)	..	..	0·973
Day 3	0·21 (0·21–0·23)	0·21 (0·21–0·25)	..	..	0·857

Data are n (%), n/N (%), or median (IQR) unless otherwise stated. O_2=oxygen. CPAP=continuous positive airway pressure. FiO_2=fraction of inspired oxygen. *Data restricted to infants who were alive (intervention group n=101, standard treatment group n=109).

Table 3: Secondary outcomes—pulmonary outcomes

INTERPRETATION The application of surfactant via a thin catheter to spontaneously breathing preterm infants receiving continuous positive airway pressure reduces the need for mechanical ventilation.

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of Research and Technology, University of Lübeck,

and Chiesi Pharmaceuticals !!!

Confl icts of interest

EH has received speaking fees and travel grants from the surfactant-producing companies Abbot, Chiesi, Nycomed, Boehringer, and Altana. EH has participated in clinical trials sponsored by Abbott, Boehringer, Chiesi, Byk Gulden, Altana, and Nycomed. EH has worked on advisory boards for Chiesi, Nycomed, and Draeger Medical, a company working in the fi eld of neonatal ventilation, monitoring, and thermal care.

EH received no money personally for this study, the support was institutional to cover insurance and other regulatory costs of the trial.

Acknowledgments

The trial was supported by grants from Chiesi

surfaktantravi kasutati sagedamini ja KKV vajadus oli väiksem kui teistes seni avaldatud uuringutes. Samuti oli AMV uuringus väiksem BPD esinemissagedus või suremus võrreldes teiste uuringutega. Seega võiks tulevikus kaaluda LISA kasutamist individualiseeritud käsitlusena enneaegsetel vastsündinutel. Kindlate soovituste andmiseks on aga kindlasti vajalikud lisauuringud.

	AMV (26–28 weeks)		SUPPORT[1] (26–27 week stratum)		COIN[2] (27–28 week stratum)		CURPAP[3] (25–28 weeks)	
	CPAP, surfactant without intubation (n=108)	CPAP with rescue intubation (n=112)	CPAP with rescue intubation (n=378)	Intubation (n=373)	CPAP with rescue intubation (n=207)	Intubation (n=198)	CPAP with rescue intubation (n=103)	Intubation, early extubation (n=105)
Birthweight (g; mean [SD])	975 (244)	938 (205)	834 (188)*	825 (198)*	964 (212)*	952 (217)*	913 (200)	967 (221)
Surfactant treatment (%)	74%	65%	67%*	99%*	38%*	77%*	49%	100%
Mechanical ventilation (%)	33%	73%	83%*	100%*	59%*	100%*	33%	100%
Days on mechanical ventilation (median [IQR])	0 (0-3)	2 (0-5)	4 (0-15)	6 (2-21)	3 (0-11)*	4 (1-14)*	6 (1-112)†	5 (1-61)†
Pneumothorax (%)	4%	7%	6%	6%	9%*	3%*	1%	7%
Bronchopulmonary dysplasia at 36 weeks or death (%)	14%	15%	38%	44%	25%	31%	21%	22%

CPAP=continuous positive airway pressure. CPAP with rescue intubation was the intervention in the SUPPORT and COIN trials, but was the control in the AMV and CURPAP trials. *Data are for all infants in the trial (gestational age 24–27 weeks in SUPPORT, 25–28 weeks in COIN). †In the CURPAP trial, days on mechanical ventilation are medians (range) for intubated infants.

Table 5: **CPAP, surfactant treatment, and outcome data from published trials**

Pharmaceuticals, Lubeck University, and the German Ministry of Research and Technology (grant number 01ER0805, The German Neonatal Network). Chiesi Pharmaceuticals is a manufacturer of surfactant. We thank all the staff in participating hospitals and especially the parents and infants who participated in the trial.

Ühekeskuseline randomiseeritud kontrolluuring Türgis Zekai Tahir Burak NICU 2010 -2011, Take Care=LISA vs INSURE. 200 last <32 GN, 100 Take Care grupis ja 100 LISA grupis.

Abstract

BACKGROUND: The primary aim of this randomized study was to describe the feasibility of early administration of surfactant via a thin catheter during spontaneous breathing (Take Care) and compare early mechanical ventilation (MV) requirement with the InSurE (Intubate, Surfactant, Extubate) procedure.

METHODS: Preterm infants, who were, **<32 weeks** and stabilized with nasal continuous positive airway pressure (nCPAP) in the delivery room, were randomized to receive **early surfactant treatment either by the Take Care or InSurE technique**. Tracheal instillation of 100 mg/kg poractant a via 5-F catheter during spontaneous breathing under nCPAP was performed in the intervention group. In the InSurE procedure, infants were intubated, received positive pressure ventilation for 30 seconds after surfactant instillation, and placed on nCPAP immediately.

RESULTS: One hundred infants in each group were analyzed. **The MV requirement in the first 72 hours of life was significantly lower in the Take Care group when compared with the InSurE group (30% vs 45%, P = .02, odds ratio –0.52, 95% confidence interval –0.94 to –0.29).**

Surfactant administration via thin catheter during spontaneous breathing: randomized controlled trial.

Kanmaz HG, Erdeve O, Canpolat FE, Mutlu B, Dilmen U.

Pediatrics. 2013 Feb;131(2):e502-9

TABLE 3 The Rates of BPD and MV Requirements among Groups

Primary Outcome	Take Care *n* = 100	InSurE *n* = 100	*P*	RR	95% CI	NNT	*P**
All infants							
Early MV, %	30	45	.02	−0.52	−0.94 to −0.29	6	.02
Any MV, %	40	49	.12	−0.56	−1 to −0.29		.08
BPD, *n* (%)	9 (10.3)	17 (20.2)	.009	−0.27	−0.72 to −0.1	10	.005
≤28 wk	*n* = 59	*n* = 55					
Early MV, %	32	52	.02	−0.43	−0.91 to −0.19		.02
Any MV, %	45	59	.09	−0.42	−0.94 to −0.47		.03
BPD, *n* (%)	6 (13.6)	16 (26.2)	.008	−0.21	−0.65 to −0.07	7	.004

NNT, number needed to treat. Early MV: MV requirement in first 72 h of life. Any MV: MV requirement during hospitalization. BPD, *n* (%): Moderate to severe BPD rates among survivors to discharge.
* *P* for relative risk.

Mean duration of both nCPAP and MV were significantly shorter in the Take Care group (P values .006 and .002, respectively). Bronchopulmonary dysplasia rate was significantly lower among the infants treated with the Take Care technique (relative risk –0.27, 95% confidence interval –0.1 to –0.72)

TABLE 2 Pulmonary Outcomes among Both Groups

	Take Care	InSurE	*P*
Surfactant administration time, min	44.9 ± 24.6	48.8 ± 30.3	.22
pH levels before treatment, mean ± SD	7.14 ± 0.49	7.27 ± 0.54	.21
pH levels after treatment, mean ± SD	7.20 ± 0.68	7.27 ± 0.65	.51
Radiologic scoring before treatment, median	3 (2 – 4)	3 (2 – 4)	.28
Radiologic scoring after treatment, median	2(1-3)	1(1-2)	.28
Second dose of surfactant	22 (22)	21 (21)	1
Early intubation	30 (30)	45 (45)	.02
Surfactant after intubation	7 (7)	10 (10)	.68
Late intubation	19 (19)	29 (29)	.1
Pneumothorax, *n* (%)	7 (7)	10 (10)	.61
Pulmonary interstitial emphysema, *n* (%)	2 (2)	3 (3)	1
Atelectasis	6 (6)	5 (5)	.5
Pulmonary hemorrhage, *n* (%)	5 (5)	7 (7)	.76
Any MV, *n* (%)	40 (40)	49 (49)	.12
nCPAP duration, h, (min-max), median	78 (24-720)	116(24-489)	.002
MV duration, h, (min-max), median	35.6 (0-756)	64.1(0-489)	.006
Supplemental O_2 duration, h, median	40.5(0-480)	60.7(0-960)	.07

Early Intubation: Intubation in first 72 h of life. Late Intubation: Intubation after 72 h of life during hospitalization. Any MV: Mechanical ventilation requirement during hospitalization.

CONCLUSIONS: The Take Care technique is feasible for the treatment of respiratory distress syndrome in infants with very low birth weight. It significantly reduces both the need and duration of MV, and thus the bronchopulmonary dysplasia rate in preterm infants.

<u>Surfaktandi korduv manustamine võrreldes ühekordne manustamine.</u>

Abstract

BACKGROUND:

Randomized controlled trials have demonstrated the efficacy of surfactant therapy in the treatment of infants at risk for or having respiratory distress syndrome (RDS). Due to surfactant inactivation, multiple doses of surfactant may lead to improved outcome.

OBJECTIVES:

To determine the effect of multiple doses of exogenous surfactant compared to single doses of exogenous surfactant on mortality and

Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory

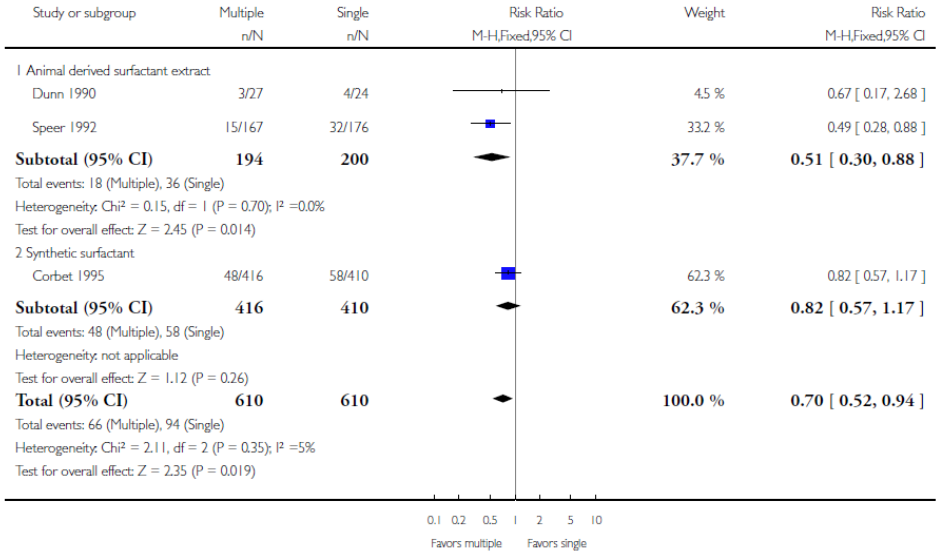
complications of prematurity in premature infants at risk for or having respiratory distress syndrome. SEARCH STRATEGY: For the initial search in 1999, searches were made of the Oxford Database of Perinatal Trials, Medline (MeSH terms: pulmonary surfactant; limits: age groups, newborn infant; publication type, clinical trials), previous reviews including cross references, abstracts, conference and symposia proceedings, expert informants, and journal hand searching in the English language.In June 2008, the searches were updated including Medline, Cinhal and Embase using similar terms as the original search. SELECTION CRITERIA: Randomized controlled trials comparing a policy of multiple doses of surfactant to a policy of single doses of surfactant extract in premature infants at risk for or having respiratory distress syndrome were considered for this review. DATA COLLECTION AND ANALYSIS: Data on clinical outcomes including pneumothorax, patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage (all intraventricular hemorrhage and severe intraventricular hemorrhage), bronchopulmonary dysplasia, retinopathy of prematurity, and mortality were excerpted by the both reviewers (R. Soll; E. Ozek). For this update additional data were sought on pulmonary hemorrhage, periventricular leukomalacia, neurodevelopmental follow-up, rehospitalization for pulmonary reasons, and reactive airway disease. Data were analyzed according to the standards of the Cochrane Neonatal Review Group. MAIN RESULTS: Three trials (Corbet 1995 /sünteetiline surfaktant/, Dunn 1990, Speer 1992 /mõlemad looduslik surfactant/) were identified that met study criteria. Two studies were randomized controlled trials of multiple vs. single dose animal derived surfactant extract in infants with established respiratory distress syndrome. **Meta-analysis of these trials suggests a reduction in the risk of pneumothorax (typical relative risk 0.51, 95% CI 0.30, 0.88; typical risk difference-0.09, 95% CI -0.15, -0.02)**	**distress syndrome.** Soll R, Ozek E. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD000141. doi: 10.1002/14651858.CD000141.pub2.

Analysis 1.1. Comparison 1 Multiple vs single dose surfactant for severe RDS, Outcome 1 Pneumothorax.

Review: Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome

Comparison: 1 Multiple vs single dose surfactant for severe RDS

Outcome: 1 Pneumothorax



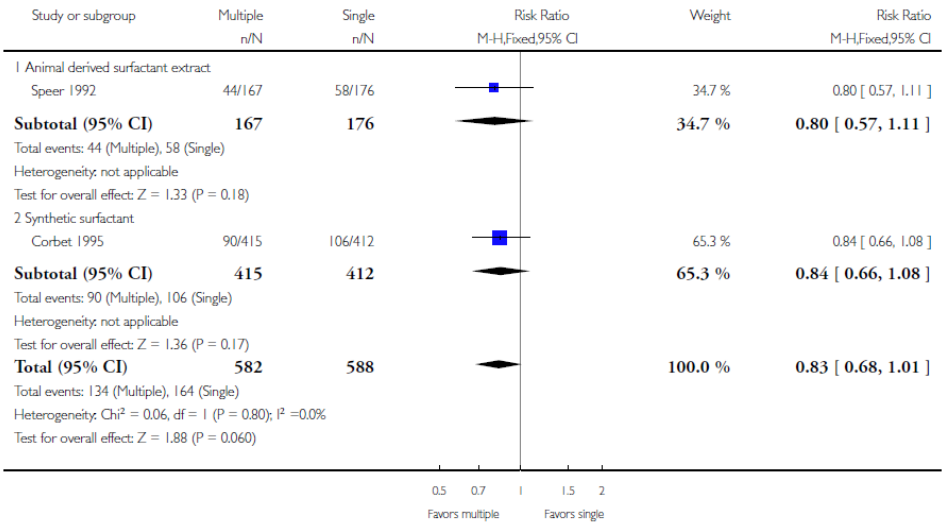
and a trend towards a reduction in the risk of mortality (typical relative risk 0.63, 95% CI 0.39, 1.02; typical risk difference -0.07, 95% CI -0.14, 00.00).

Analysis 1.10. Comparison 1 Multiple vs single dose surfactant for severe RDS, Outcome 10 BPD or death.

Review: Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome

Comparison: 1 Multiple vs single dose surfactant for severe RDS

Outcome: 10 BPD or death



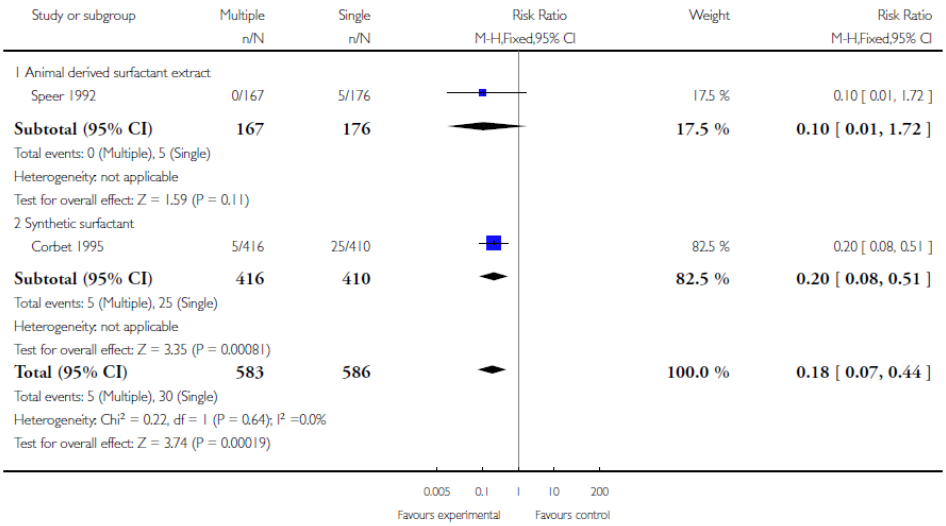
One study of multiple vs. single dose synthetic surfactant in infants at high risk of respiratory distress syndrome was identified. **This study reported a decrease in NEC (relative risk 0.20, 95% CI 0.08, 0.51; risk difference-0.05, 95% CI -0.07, -0.02) and mortality (relative risk 0.56, 95% CI 0.39, 0.81; risk difference-0.07, 95% CI -0.12, -0.03)**.

Analysis 1.4. Comparison 1 Multiple vs single dose surfactant for severe RDS, Outcome 4 Necrotizing Enterocolitis.

Review: Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome

Comparison: 1 Multiple vs single dose surfactant for severe RDS

Outcome: 4 Necrotizing Enterocolitis

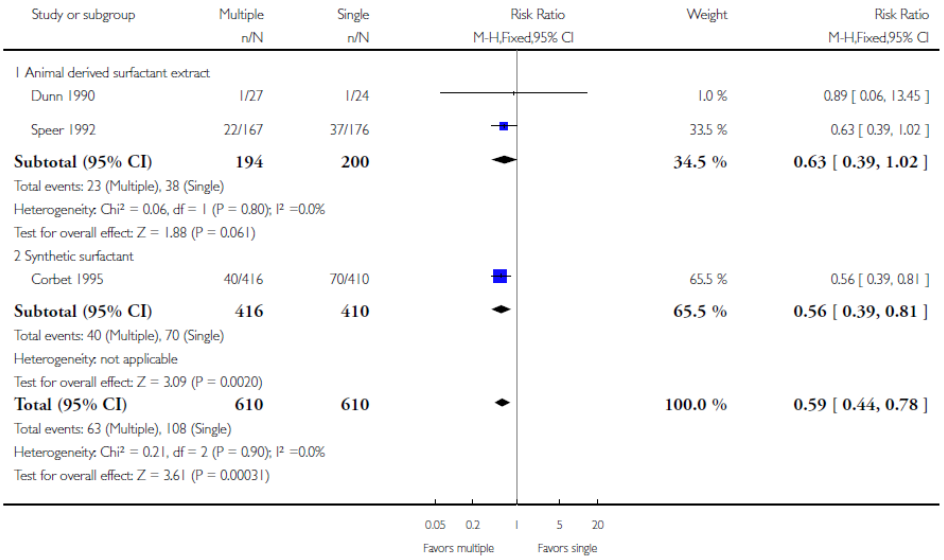


Analysis 1.9. Comparison 1 Multiple vs single dose surfactant for severe RDS, Outcome 9 Mortality.

Review: Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome

Comparison: 1 Multiple vs single dose surfactant for severe RDS

Outcome: 9 Mortality



No data on long-term neurological or pulmonary outcome were reported. No complications associated with multiple dose treatment were reported in the identified trials.

AUTHORS' CONCLUSIONS:

In infants with established respiratory distress, a policy of multiple doses of animal derived surfactant extract resulted in greater improvements regarding oxygenation and ventilatory requirements, a decreased risk of pneumothorax and a trend toward improved survival. In infants at high risk of respiratory distress, a policy of multiple doses of synthetic surfactant resulted in greater improvements regarding oxygenation and ventilatory requirements,

a decreased risk of NEC and decreased mortality.The ability to give multiple doses of surfactant to infants with ongoing respiratory insufficiency leads to improved clinical outcome and appears to be the most effective treatment policy.	
Abstract **Rationale** Limited data are available on predictors for surfactant retreatment in preterm infants with respiratory distress syndrome (RDS). **Objective** To study the pharmacokinetics of exogenous surfactant and the clinical parameters associated with surfactant redosing. **Methods** Exogenous surfactant pharmacokinetics was studied in 125 preterm infants (birth weight 997 ± 432 g; gestational age 28.0 ± 2.6 weeks) with moderate to severe RDS requiring mechanical ventilation. Clinical and respiratory parameters were recorded hourly, and surfactant disaturated-phosphatidylcholine (DSPC) half-life, pool size, and endogenous synthesis were calculated by stable isotope tracing of surfactant DSPC isolated from serial tracheal aspirates. Univariate and multiple logistic regression were used to study the effects of clinical and surfactant kinetic variables on the need for redosing. **Results** Fifty-three infants (42.4%) received one dose, 51 (40.8%) two doses, and 21 (16.8%) three doses. **Median (interquartile range, IQR) DSPC half-life was 21 (13–39), 11 (7–17), and 10 (7–16) h after the first, second, and third dose, respectively ($p = 0.07$).** Univariate analysis showed a significantly shorter DSPC half-life in infants requiring more surfactant doses. On logistic analysis, risk of redosing was higher with lower birth weight, worse radiological score, shorter DSPC half-life, and surfactant dose of 100 mg/kg, whilst it was lower with elective high-frequency ventilation at time of intubation, instead of conventional ventilation. **Conclusions** **When optimizing surfactant replacement therapy and its cost–benefit ratio, pharmacokinetics and clinical variables associated with need of redosing should be taken into account.**	**Pharmacokinetics and clinical predictors of surfactant redosing in respiratory distress syndrome.** Cogo PE, Facco M, Simonato M, De Luca D, De Terlizi F, Rizzotti U, Verlato G, Bellagamba MP, Carnielli VP. Intensive Care Med. 2011 Mar;37(3):510-7. doi: 10.1007/s00134-010-2091-2. Epub 2010 Dec 10.

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