Kliiniline küsimus nr 21

Kas hingamishäiretega enneaegsetel vastsündinutel kasutada parema ravitulemi saavutamiseks varast CPAP-ravi võrreldes varase surfaktantraviga?

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

Ravijuhendid

Kokkuvõte ravijuhenditest:

Soovitused varase CPAP versus surfaktantravi kohta on leitav ühes 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. Esitatud soovitused on juhendis koostatud GRADE süsteemi kasutades, juhend põhineb 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.

Vastsündinute surfaktantravi kliinilised uuringud on keskendunud selle optimaalse doosi, manustamise aja ja viisi ning parima preparaadi kindlaks määramisele [Soll RF,2000, 2010].

Mitteinvasiivne hingamise toetus on defineeritud kui hingamise toetus ilma intubatsioonita: CPAP, erinevad ventilatsiooni tüübid läbi ninakanüülide ja maskide, mida nimetatakse „nasaalne vahelduv positiivse rõhuga ventilatsioon“ – NIPPV ja niisutatud doseeritud hapnik sissehingatavas õhus [Bancalari E, 2013].

Hiljutised kliinilised uuringud näitavad, et varane CPAP ravi alustamine ja pigem selektiivne kui rutiinne profülaktilise surfaktandi manustamine võib olla parem, sest aitab

hoiduda intubatsioonist ja vähendab kroonilise kopsuhaiguse ja surmade sagedust CPAP`i grupi vastsündinutel [SUPPORT Study 2010; Sandri F, 2010, Rojas-Reyes MX ,2012].

Seejuures vajab märkimist, et nende uuringute enneaegsed vastsündinud värvati uurimisgruppi juba antenataalselt, enamus neist oli saanud enne sündi kopsude ettevalmistust steroidiga ja nad sündisid optimaalsetes tingimustes. Nende uuringute tulemused ei ole seetõttu üldistatavad spetsiifiliste erakorraliste olukordadega [Rich W,2012].

Euroopa 2013 ravijuhise tugev soovitus on, et CPAP ravi peaks alustama kõigil vastsündinutel, kellel on risk RDS tekkimiseks, nagu <30 rasedusnädala sündinud enneaegsed, kes ei vaja mehhaanilist ventilatsiooni, kuni nende kliinilise seisundi hindamiseni (A).

Süstemaatilised ülevaated

Noninvasive Ventilation With vs Without Early Surfactant to Prevent Chronic Lung Disease in Preterm Infants: A Systematic Review and Meta-analysis.
Isayama T, Chai-Adisaksopha C, McDonald SD
JAMA Pediatr. 2015 Jun 8. doi: 10.1001/jamapediatrics.2015

Respiratory Support in Preterm Infants at Birth
COMMITTEE ON FETUS AND NEWBORN
Waldemar A. Carlo, MD, FAAP Richard A. Polin, MD, FAAPPediatrics 2014;133:171–174

Avoiding Endotracheal Ventilation to Prevent Bronchopulmonary Dysplasia: A Meta-analysis
Hendrik S. Fischer, MD, and Christoph Bührer, MD, PhD Department of Neonatology, Charité University Medical Center, Berlin, Germany
PEDIATRICS Volume 132, Number 5, November 2013

See metaanalüüs hõlmab ka uuringuid „**Early CPAP versus Surfactant in Extremely Preterm Infants“** SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network* N Engl J Med 2010;362:1970-9 ja
„**Prophylactic or Early Selective Surfactant Combined With nCPAP in Very Preterm Infants“** *Fabrizio Sandri, MD, Richard Plavka, MD, Gina Ancora, MD, Umberto Simeoni, MD, Zbyneˇk Stranak, MD, Stefano Martinelli, MD, Fabio Mosca, MD, Jose' Nona, MD, Merran Thomson, MD, Henrik Verder, MD, Laura Fabbri, PhD, and Henry Halliday, MD, for the CURPAP Study Group PEDIATRICS Volume 125, Number 6,* June 2010

Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Rojas-Reyes MX, Morley CJ, Soll R. Cochrane Database Syst Rev.2012**.**

Kokkuvõte süstemaatilistest ülevaadetest
CPAP- ravi ja profülaktilise surfaktantarvi kohta leidsime vastavalt otsingukriteeriumitele 4 metaanalüüsi/süstemaatilist ülevaadet (avaldatud viimase 5 aasta jooksul). Lisatud on 3 randomiseeritud kontrolluuringut, mis avaldati 2012 ja 2014 aastal.

Hiljutised randomiseeritud kontrolluuringud (RCT) uuringud viitavad, et CPAP võib osutuda efektiivseks alternatiiviks profülaktilisele või varasele surfaktantravile [Sandri F 2004, Finer NN 2004, Rojas MA 2009, Morley CJ 2008, Finer NN 2010, Dunn MS 2011, Tapia JL 2012]. CPAP hingamistoetust saab rakendada kõige kiiremini ja vähem invasiivselt juba sünnitustoas võrreldes INSURE meetodiga [Pfister RH, Soll RF 2012 Clin. Perinatol]. Mõeldav on alustada CPAP sünnitustoas isegi kõige väiksematele enneaegsetele (24-27 GN), kuigi mida ebaküpsem on vastsündinu, seda sagedamini võib ta vajada intubatsiooni [Finer NN 2004].Mitteinvasiivsed ventilatsioonimeetodid, nagu NIV, ei ole eelistatumad kui CPAP [Kirpalani H, 2013].

Austraalia COIN (CPAP or INtubation) uuring (Australasian Trial Network) võrdles nCPAP (8 cm H2O) ja eMV enneaegseid vastsündinuid, kellel oli spontaanne hingamine 5. eluminutil [Morley CJ 2008].Selles uuringus oli surmajuhtumite, BPD ja postnataalsete kortikosteroidide kasutamisesagedus väiksem neil, kes said CPAP`i. Keskmine KKV aeg oli lühem CPAP`i grupis, vastavalt 3 päeva ja 4 päeva eMV grupis. Samas pneumotooraksit esines sagedamini CPAP grupis kui eMV grupis (9% vs 3%; P < .001).

Suurim uuring (N = 1310) - Surfactant Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT), mis viidi läbi Eunice Kennedy Shriver National Institutes of Health and Human Development Neonatal Research Network`s, võrdles nCPAP`i, mis alustati kohe pärast sündi ja kasutati limiteeritud ventilatsiooni strateegiat, profülaktilise surfaktantravi ja ja MV 60 minuti jooksul pärast sündi 24-27 GN-l sündinud enneaegsetel [Finer NN 2010]. BPD esinemissagedus CPAP-grupis oli 48% võrreldes 51% surfaktandi grupis (RR: 0.91; 95% CI: 0.83–1.01; P = .07). 24-25 rasedusnädalal sündinud vastsündinute suremus oli madalam CPAP grupis kui surfaktandi grupis (20% vs 29%; RR: 0.68; 95% CI: 0.5– 0.92; P = .01). Kaks kolmandikku CPAP grupi lastest küll vajasid lõpuks siiski surfaktanti, kuid nende KKV aeg oli lühem (25 vs 28 päeva) ja neil kasutati vähem postnataalseid steroide võrreldes surfaktandi grupiga (7% vs 13%). Õhulekete tekkimise suhtes gruppide vahel erinevust ei olnud. See uuring näitas, et nCPAP, alustatuna kiiresti pärast sündi, on efektiivne ja ohutualternatiiv profülaktilisele või varasele surfaktantrvile ja peaks olema parem. Vanuses 18-22 kuud korrigeeritud vanuse järgi esines suremust või neuroloogilist kahjustust 28% CPAP grupi lastel ja 30% surfaktant/ventilatsiooni grupi lastel (RR: 0.93; 95% CI: 0.78–1.10; P = .38).CPAP grupi lastel esines selles vanuses vähem ka respiratoorseid haigestumisi [Stevens TP 2013].

Dunn MS et al 2011 uuringus Vermont Oxford Network Delivery Room Management Trial randomiseerisid vastsündinud 26-29 GN kolme gruppi: profülaktiline surfaktant ja eMV; profülaktiline surfaktant, ekstubatsioon ja CPAP; ning CPAP ilma surfaktandita. Nende gruppide vahel ei olenud statistiliselt olulist erinevust. BPD või surmajuhtumite RR oli 0,83 (95% CI: 0,64-1,09) CPAP grupis ja 0,78 (95% CI 0,59-1,03) INSURE grupis.

Uuringutes CURPAP Colombian Network ja Colombian Network [Rojas MA 2009] ei näidatud BPD esinemissageduse erinevust CPAP ja INSURE strateegiate vahel. Colombian Network`i uuringus olis CPAP grupis pneumotooraksi risk suurem kui INSURE grupis vastavalt 9% ja 2%.
Lõuna-Ameerika Neocosur uuringus [Tapia JL 2012] näidati, et varane CPAP ja selektiivne INSURE, kui vaja, vähendas KKV ja surfaktandi vajadust.

Hendrik S. et al 2013 eesmärgiks oli uurida endotraheaalset mehhaanilist ventilatsiooni (eMV) vältivate strateegiate mõju BPD esinemissagedusele enneaegsete grupis 30

gestatsioonināda lat (GN). Veebruaris 2013 vaadati läbi Medline, Embase, Cochrane Central Register `andmebaasidest ja eel-retsenseeritud ajakirjadest sellesisulised uuringud alates aastast 2000. See ajaperiood valiti, sest peegeldab paremini kaasaegset olukorda, eriti antenataalsete asteroidide kasutamist prinataalabis. Andmed koguti ja analüüsiti vastavalt Cochrane Neonatal Review Group`i standarditele.
Tulemused: Analüüs hõlmas kokku 7 uuringut ja kokku 3289 vastsündinut.

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.

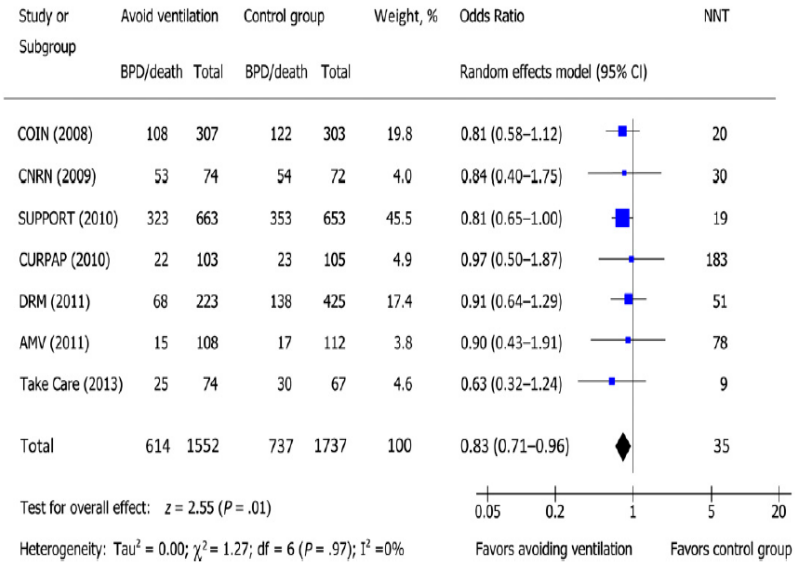

FIGURE 2
Effect of avoiding eMV on death or BPD.

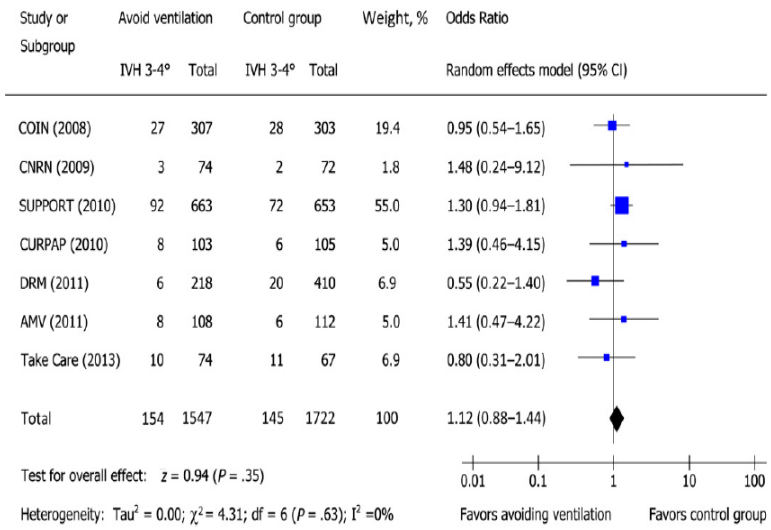

FIGURE 3
Effect of avoiding eMV on IVH.

Kokkuvõtteks nendel lastel, kelle hoiduti eMV oli väiksem risk surra või haigestuda BPD`sse (95% CI 0.83 (0.71–0.96) ilma et suureneks raske IVH risk. Edasised uuringud peaks olema suunatud NIPPV ja nHFOV kasutamisele sünnitustoas ja alternatiivsete surfaktandi manustamise viiside leidmisele.
Viimati avaldatud süstemaatilises metaanalüüsis [*Isayama T, Chai-Adisaksopha C, McDonald SD* 2015] on kokkuvõtteks öeldud, et ei kumbki, INSURE ega ainult nCPAP, ei ole teisest parem. Tundub, et INSURE kasutamisel ei suurene krooniline kopsuhaigus ja/või suremus, õhktüsistuste ja kroonilise kopsuhaiguse esinemissagedus üksi. Seetõttu võib INSURE olla eelistatud nCPAP´ga võrreldes. Edasisied adekvaatsemad uuringud on vajalikud.

Süstemaatiste ülevaadete kokkuvõtvad tõenduspõhised soovitused:

Metaanalüüsides profülaktiline surfactant vs CPAP, kui ka uuringutes selektiivne varane surfactant vs CPAP, varase CPAP kasutamine koos vajadusel selektiivse surfaktandiga väga enneaegsetele vastsündinutele realiseerub madalamas BPD/suremuse esinemises võrreldes profülaktilise või varase surfaktantraviga (Level of Evidence - LOE 1 ehk A).

Ainult varase CPAP-ga ravitud enneaegsetel vastsündinutel ei ole tõusnud järeltulemi risk võrreldes hilisema surfaktantraviga või selle mittekasutamisega (LOE 1).

Varase CPAP ravi alustamine võib vähendada edaspidi kopsude kunstlikku ventilatsiooni kestvust ja postnataalse kortikosteroidravi vajadust (LOE 1).

Kuna respiratoorse distressiga enneaegsed vastsündinud erinevad küpsusastmelt ja RDS raskusastmelt, siis on vajalik individualiseerida patsientide käsitlus.

Kasutada CPAP`i kiiresti pärast sündi, koos vajadusel selektiivse surfaktantraviga, võiks olla rutiinne alternatiiv intubatsioonile ja profülaktilise surfaktandi manustamisele (LOE 1 – tugev soovitus)[AAP,2004].
Kui hingamise toetuseks on vajalik kopsude kunstlik ventilatsioon, siis pärast varse surfaktandi manustamist on eelistatud kiire ekstubtsioon prolongeeritud mehhaanilisele ventiltsioonile (LOE 1 – tugev soovitus) [AAP,2004].

Randomiseeritud uuringud , mis on avaldatud 2012 ja 2014 aastal kinnitavad eelpool tehtud kokkuvõtteid süstemaatilistest ülevaadetest ja metaanalüüsidest:

Varane CPAP ja vajadusel selektiivne INSURE vähendavad surfaktantravi vajadust ja KKV kestvust väga väikese sünnikaaluga enneaegsetel vastsündinutel suurendamata haigestumise ja suremuse riski [Timothy P.et al (SUPPORT),2014; Maryam Nakhshab et al 2014; Jose L. Tapia et al,2012; Roehr CC. et al (COIN) 2011]

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Surfactant therapy, whether given prophylactically [Soll RF,2000] or as rescue therapy [Soll RF,2010] to babies with or at risk of developing RDS, reduces the risk of pneumothorax (pulmonary air leak) and neonatal death. Clinical trials have focused on determining the optimal dose, the timing of dosing, the best method of administration and the best surfactant preparation. More recent clinical trials show that with a policy of early initiation of CPAP and selective surfactant administration rather than routine prophylaxis babies may do better, with some avoiding intubation altogether and reduced rates of death or chronic lung disease in the CPAP group [SUPPORT Study 2010; Sandri F 2010, Rojas-Reyes MX 2012]. However, it must be borne in mind that babies in these trials were recruited antenatally and were therefore delivered in optimal condition, with a high rate of antenatal steroid use. These results may not be generalizable to all babies nor to specific situations within individual institutions [Rich W,2012]. Non-invasive respiratory support can be defined as any form of respiratory support that is not delivered via an endotracheal tube. It includes CPAP, various types of ventilation provided through soft nasal prongs or masks which are collectively called 'nasal intermittent positiive pressure ventilation' (NIPPV) and humidified oxygen delivered by high-flow nasal cannulae [Bancalari E, 2013] **Recommendations** (1) CPAP should be started from birth in all babies at risk of RDS, such as those <30 weeks` gestation who do not need MV , until their clinical status can be assessed (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
However, recent multicenter randomized controlled trials indicate that nasal continuous positive airway pressure (CPAP) may be an effective alternative to prophylactic or early surfactant administration [*Sandri F 2004, Finer NN 2004, Rojas MA 2009, Morley CJ 2008, Finer NN 2010, Dunn MS 2011, Tapia JL 2012*]. Respiratory support is being achieved more frequently with CPAP and other less invasive approaches, such as the technique of intubation, surfactant, and extubation (INSURE) [*Pfister RH, Soll RF 2012 Clin. Perinatol.*]. It is feasible to proovide noninvasive nasal CPAP starting in the delivery room, even in extremely preterm infants (24–27 weeks' gestation), but the most immature infants had the highest risk of failure [*Finer NN 2004*]. Noninvasive modes of ventilation, such as nasal intermittent ventilation, do not appear to provide further benefiits compared with CPAP [*Kirpalani H 2013*].	**Respiratory Support in Preterm Infants at Birth** COMMITTEE ON FETUS AND NEWBORN Waldemar A. Carlo, MD, FAAP Richard A. Polin, MD, FAAP Pediatrics 2014;133:171–174

The COIN (CPAP or INtubation) Trial of the Australasian Trial Network compared the effectiveness of nasal CPAP (8 cm of water pressure) to intubation and mechanical ventilation in preterm infants who were breathing spontaneously at 5 minutes after birth [*Morley CJ 2008*]. There was a trend for a lower rate of death or BPD in infants who received CPAP and used fewer corticosteroids postnatally. The mean duration of ventilation was shorter in the CPAP group (3 days in the CPAP group and 4 days in the ventilator group). However, the CPAP group had a higher rate of pneumothorax than the ventilator group (9% vs 3%; P < .001).

The largest CPAP trial (N = 1310), the Surfactant Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT) conducted by the Eunice Kennedy Shriver National Institutes of Health and Human Development Neonatal Research Network investigators, was designed to evaluate nasal CPAP started immediately after birth by using a limited-ventilation strategy compared with prophylactic surfactant therapy and ventilator support started within 60 minutes after birth by using a limited ventilation strategy in infants born at 24 to 27 weeks' gestation [*Finer NN 2010*]. This trial used prospectively defined criteria for intubation and extubation. The rate of death or BPD in the CPAP group was 48% compared with 51% in the surfactant group (relative risk [RR]: 0.91; 95% confidence interval [CI]: 0.83–1.01; P = .07). Among infants born at 24 and 25 weeks' gestation, the death rate was lower in the CPAP group than in the surfactant group (20% vs 29%; RR: 0.68; 95% CI: 0.5– 0.92; P = .01). Two-thirds of the infants in the CPAP group ultimately received surfactant. In addition, duration of mechanical ventilation was shorter (25 vs 28 days), and use of postnatal corticosteroid therapy was reduced in the CPAP group (7% vs 13%). The rate of air leaks did not differ between the groups, and there were no averse effects of the CPAP strategy despite a reduction in the use of surfactant. This trial demonstrated that nasal CPAP started immediately after birth is an effective and safe alternative to prophylactic or early surfactant administration and may be superior. A follow-up study at 18 to 22 months' corrected age showed that death or neurodevelopmental impairment occurred in 28% of the infants in the CPAP group compared with 30% of those in the surfactant/ventilation group (RR: 0.93; 95% CI: 0.78–1.10; P = .38).CPAP and the limitedventilation strategy, rather than intubation and surfactant, resulted in less respiratory morbidity by 18 to 22 months' corrected age [*Stevens TP 2013*].

The Vermont Oxford Network Delivery Room Management Trial randomly assigned infants born at 26 to 29 weeks' gestation to 1 of 3 treatment groups: prophylactic surfactant and continued ventilation, prophylactic surfactant and extubation to CPAP, or CPAP (without surfactant). There were no statistically significant differences between the 3 groups, but when compared with the prophylactic surfactant group, the RR of BPD or death was 0.83 (95% CI: 0.64–1.09) for the CPAP group and 0.78 (95% CI: 0.59–1.03) for the INSURE group [*Dunn MS 2011*].

Other trials have compared early CPAP with prophylactic or early surfactant administration. The CURPAP [*Sandri F 2004*] and Colombian Network [*Rojas MA 2009*] trials did not demonstrate a difference in the rate of BPD between the 2 treatment strategies. Moreover, in the Columbian Network trial,3 infants randomly assigned to prophylactic CPAP had a higher risk of pneumothorax (9%) than infants randomly assigned to INSURE (2%).
Infants in the South American Neocosur Network treial were randomly assigned to early CPAP (with rescue using an INSURE strategy) or oxygen hood (with rescue using mechanical ventilation). The early CPAP strategy (and selective of INSURE, if needed) reduced the need for mechanical ventilation and surfactant [*Tapia JL 2012]*.
Standard but diverse CPAP systems have been used in these and ohter large randomized controlled trials reviewed, including bubble CPAP and ventilator CPAP. A detailed description of the practical aspects of using CPAP systems are beyond the scope of this statement but are available in the published literatuure [*Polin RA 2008, Sahni R 1998*].
A meta-analysis of prophylactic surfactant versus prophylactic stabilization with CPAP and subsequent selective surfactant administration in preterm infants showed that prophylactic administration of surfactant compared with stabilization with CPAP and selective surfactant administration was associated with a higher risk of death or BPD (RR: 1.12; 95% CI: 1.02–1.24; P < 0.05) [*Bahadue FL 2012*].
The previously reported benefiits of prophylactic surfactant could no longer be demonstrated. It is notable that infants as immatureas 24 weeks' gestational age were enrolled in many of the trials. In a subgroup analysis in the SUPPORT trial, the most immature infants (born at 24 and 25 weeks' gestation) benefited the most from the CPAP strategy. Many extremely preterm infants can be managed with CPAP only; early application of nasal CPAP (without surfactant administration) was successful in 50% of infants weighing ≤750 g at birth in 1 retrospective review [*Ammari A 2005*].
Surfactant administration can be expensive, particularly in low-resource settings. Additionally, intubation and mechanical ventilation may not be possible or desirable in institutions with limited resources. CPAP proovides an alternative for early respiratory support in resource-limited settings. Emerging evidence indicates that early CPAP is an effective strategy for respiratory support in extremely preterm infants, including very immature infants. CPAP appears to be at least as safe and effective as early surfactant therapy with mechanical ventilation [*Pfister RH 2012*].

CONCLUSIONS
1. Based on a meta-analysis of prophylactic surfactant versus CPAPas well as on other trials of more selective early use of surfactant versus CPAP not included in the meta-analysis, the early use of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death when compared with treatment with prophylactic or early surfactant therapy (Level of

Evidence: 1). 2. Preterm infants treated with early CPAP alone are not at increased risk of adverse outcomes if treatment with surfactant is delayed or not given (Level of Evidence: 1). 3. Early initiation of CPAP may lead to a reduction in duration of mechanical ventilation and postnatal corticosteroid therapy (Level of Evidence: 1). 4. Infants with RDS may vary markedly in the severity of the respiratory disease, maturity, and presence of other complications, and thus it is necessary to individualize patient care. Care for these infants is provided in a variety of care settings, and thus the capabilities of the health care team need to be considered. RECOMMENDATION 1. Using CPAP immediately after birth with subsequent selective surfactant administration may be considered as an alternative to routine intubation with prophylactic or early surfactant administration in preterm infants (Level of Evidence: 1, Strong Recommendation) [*American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. Pediatrics.2004;114(3):874–877*]. If it is likely that respiratory support with a ventilator will be needed, early administration of surfactant followed by rapid extubation is preferable to prolonged ventilation (Level of Evidence: 1, Strong Recommendation) [*American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. Pediatrics. 2004;114(3):874–877*].	
Controversy exists regarding which of the 2 major strategies currently used to prevent chronic lung disease (CLD) in preterm infants is optimal: noninvasive continuous positive airway pressure (NCPAP) or intubate-surfactant-extubate (INSURE). Preterm infants often require surfactant administration because of respiratory distress syndrome. To evaluate whether early INSURE or NCPAP alone is more effective in preventing CLD, death, or both. **Data Sources:** MEDLINE, EMBASE, Cochrane Controlled Trials Register, and Cumulative Index to Nursing and Allied Health Literature databases from their inception to January 2, 2015, along with conference proceedings and trial registrations. **Study Selection:** Randomized clinical trials that compared early INSURE with NCPAP alone in preterm infants who had never been intubated before the study entry were selected. Among 1761 initially identified articles, 9 trials (1551 infants) were included. **Data Extraction and Synthesis:** Duplicate study selection and data extraction were performed. Meta-analysis was conducted using random-effects models with quality-of-evidence assessment according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. **Main Outcomes and Measures:** Seven main outcomes were selected a priori to be assessed according to GRADE, including a composite	**Noninvasive Ventilation With vs Without Early Surfactant to Prevent Chronic Lung Disease in Preterm Infants: A Systematic Review and Meta-analysis.** Isayama T, Chai-Adisaksopha C, McDonald SD. JAMA Pediatr. 2015 Jun 8. doi:10.1001/jamapediatrics.2015

outcome of CLD and/or death, CLD alone, death alone, air leakage, severe intraventricular hemorrhage, neurodevelopmental impairment, and a composite outcome of death and/or neurodevelopmental impairment. **Results:** There were no statistically significant differences between early INSURE and NCPAP alone for all outcomes assessed. However, the relative risk (RR) estimates appeared to favor early INSURE over NCPAP alone, with a 12% RR reduction in CLD and/or death (RR, 0.88; 95% CI, 0.76-1.02; risk difference [RD], -0.04; 95% CI, -0.08 to 0.01; moderate quality of evidence), a 14% decrease in CLD (RR, 0.86; 95% CI, 0.71-1.03; RD, -0.03; 95% CI, -0.06 to 0.01; moderate quality of evidence), and a 50% decrease in air leakage (RR, 0.50; 95% CI, 0.24-1.07; RD, -0.03; 95% CI, -0.06 to 0.00; very low quality of evidence). The sample size was less than the optimal information size. **Conclusions and Relevance:** Currently, no evidence suggests that either early INSURE or NCPAP alone is superior to the other. INSURE does not appear to increase CLD and/or death, CLD alone, and air leakage and may reduce these adverse outcomes compared with NCPAP alone. Further adequately powered trials are required.	
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.	**Avoiding Endotracheal Ventilation to Prevent Bronchopulmonary Dysplasia: A Meta-analysis** Hendrik S. Fischer, MD, and Christoph Bührer, MD, PhD Department of Neonatology, Charité University Medical Center, Berlin, Germany PEDIATRICS Volume 132, Number 5, November 2013

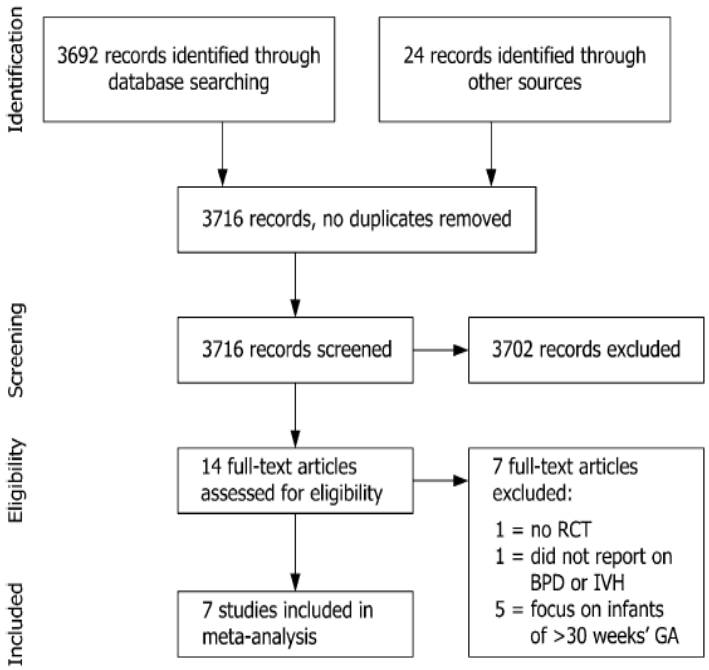

FIGURE 1
Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram.[4]

We included studies publisher in 2000 and thereafter because they were considered to better reflect current practice, especially with regard to the use of antenatal steroids.

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).

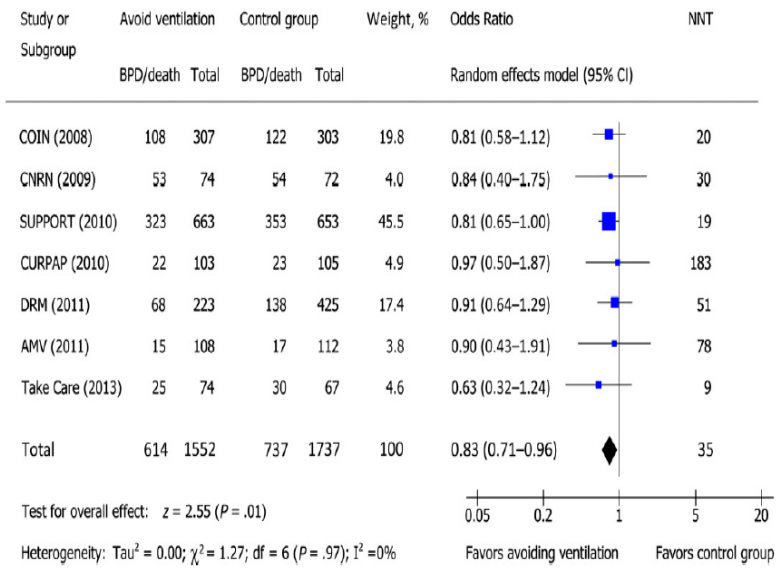

FIGURE 2
Effect of avoiding eMV on death or BPD.

The number needed to treat (NNT)was 35. The study results were remarkably homogeneous. Avoiding eMV had no influence on the incidence of severe intraventricular hemorrhage.

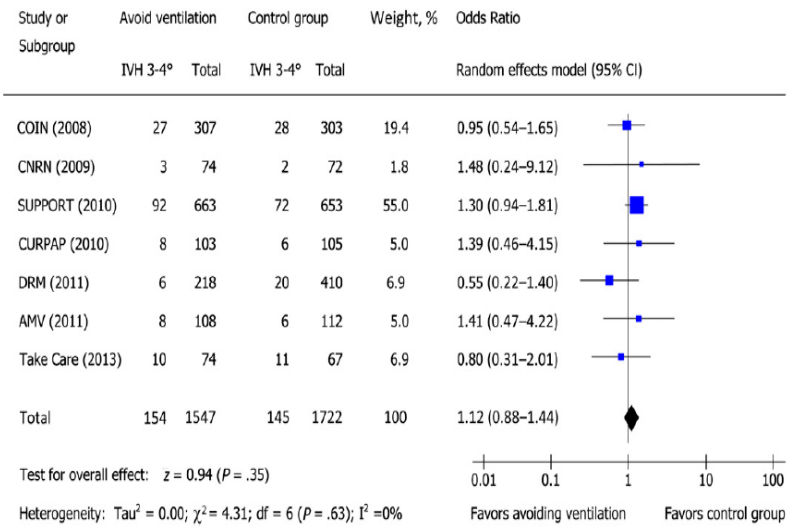

FIGURE 3
Effect of avoiding eMV on IVH.

CONCLUSIONS: Strategies aimed at avoiding eMV in infants ,30 weeks' GA have a small but significant beneficial impact on preventing
BPD. Pediatrics 2013;132:e1351–e1360.
The present meta-analysis indicates that avoiding eMV reduces the incidence of death or BPD in premature infants ,30 weeks' GA without increasing the risk of IVH. However, with an number need to treat of 35, the beneficial effect was small. Avoiding intubation and subsequent ventilation through an endotracheal tube may only be one component of a comprehensive strategy to reduce BPD in this population. Future studies need to explore the role of nIPPV and nHFOV in the primary treatment of neonates in the delivery room and to investigate alternatiive methods of administering surfactant.

Neonatal mortality in studies with routine application of continuous positive airway pressure to control infants. Two studies routinely placed control infants onCPAP (SUPPORT 2010; Dunn 2011).Neither trial reported a significant effect of prophylactic surfactant on neonatal mortality. Meta-analysis of these two studies, demonstrated a concerning trend towards an increase in the risk of neonatal mortality associated with the use prophylactic surfactant when compared with early stabilization on CPAP with selective use of surfactant in infants with respiratory failure [2 trials, 1746 infants; typical RR 1.24, 95% CI 0.97 to 1.58, (I^2 0%); typical RD 0.03, 95% CI -0.00 to 0.06; (I^2 0%)]. **Mortality at 36 weeks PMA in studies with routine application of continuous positive airway pressure to control infants.** Dunn 2011 was the only study that routinely placed control infants on CPAP that reported on mortality at 36 weeks PMA. This study did not find a statistically significant difference on 36 weeks PMA mortality between surfactant treatment groups [1 trial, 428 infants, RR 1.76, 95% CI 0.79 to 3.94; RD 0.03, 95% CI -0.01 to 0.08]. Test for heterogeneity not applicable. **Air leak in studies with routine application of continuous positive airway pressure to control infants** Only SUPPORT 2010 reported on air leak and did not find a statistically significant difference on the risk of air leak between prophylactic administration of surfactant group and selective administration of surfactant in infants with respiratory failure early stabilized on CPAP group [1 trial, 1316 infants; RR 1.08, 95% CI 0.73 to 1.60; RD 0.01, 95% CI -0.02 to 0.03]. Test for heterogeneity not applicable. **Pneumothorax and pulmonary hemorrhage in studies with routine application of continuous positive airway pressure to control infants** Only Dunn 2011 reported on this outcome, and did not find a statistically significant difference on the risk of pneumothorax and pulmonary hemorrhage between treatment groups [one trial, 431 infants; RR 0.89, 95% CI 0.39 to 2.01; RD -0.01, 95% CI -0.05 to 0.04]. Test for heterogeneity not applicable.	**Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants.** Review. Rojas-Reyes MX, Morley CJ, Soll R Cochrane Database Syst Rev.2012 Mar 14;3:CD000510
To explore the early childhood pulmonary outcomes of infants who participated in the National Institute of Child Health and Human Development's Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT), using a factorial design that randomized extremely preterm infants to lower vs higher oxygen saturation targets and delivery room continuous positive airway pressure (CPAP) vs intubation/surfactant. Study design The Breathing Outcomes Study, a prospective secondary study to the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial, assessed respiratory morbidity at 6-month intervals from hospital discharge to 18-22 months corrected age (CA). Two prespecified primary outcomes—wheezing more than twice per week during the worst 2-week period and cough longer than 3 days without a	**Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial 2014 (SUPPORT)** Timothy P. Stevens, MD, MPH, Neil N. Finer, MD et al. SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of

cold— were compared for each randomized intervention. Results: One or more interviews were completed for 918 of the 922 eligible infants. **Table I. Demographic and neonatal characteristics of follow-up cohorts** 		Low oxygen saturation (n = 439)	High oxygen saturation (n = 479)	CPAP (n = 474)	Intubation/surfactant (n = 444)
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Birth weight, g, mean ± SD	858 ± 186	844 ± 190	850 ± 184	851 ± 193
Gestational age, w, mean ± SD	25.9 ± 1.0	25.9 ± 1.0	25.9 ± 1.0	25.9 ± 1.0
Gestational age 24 wk 0 d to 25 wk 6 d, n (%)	158 (35.5)	184 (37.5)	183 (37.7)	159 (35.3)
Gestational age 25 wk 0 d to 27 wk 6 d, n (%)	287 (64.5)	307 (62.5)	303 (62.4)	291 (64.7)
Male sex, n (%)	222 (49.7)	264 (53.8)	238 (49.0)	248 (54.9)
Race/ethnicity, n (%)				
Non-Hispanic black	168 (37.6)	157 (32.0)	173 (35.6)	152 (33.6)
Non-Hispanic white	176 (39.4)*	226 (46.0)	196 (40.3)	206 (45.6)
Hispanic	88 (19.7)	91 (18.5)	98 (20.2)	81 (17.9)
Other/unknown	15 (3.4)	17 (3.5)	19 (3.9)	13 (2.9)
Length of hospitalization, d, median (range)	90 (39-365)	93 (46-366)	91 (44-366)	93 (39-365)
BPD (traditional definition), n (%)	160 (36.3)†	221 (45.8)	187 (39.1)	194 (43.5)
BPD (physiological definition), n (%)	165 (37.4)	193 (40.0)	183 (38.3)	175 (39.2)
Discharged home on oxygen, n (%)	105 (24.0)	111 (23.2)	108 (22.8)	108 (24.4)
Discharged home on respiratory medications, n (%)	101 (27.3)	106 (27.1)	110 (27.8)	97 (26.6)
Discharged home October-March, n (%)	232 (52.9)	227 (47.5)	232 (48.8)	227 (51.4) | *Low oxygen saturation vs high oxygen saturation, $P < .05$. †Low oxygen saturation vs high oxygen saturation, $P < .01$. The incidences of wheezing and cough were 47.9% and 31.0%,respectively, anddidnot differbetween the study armsof either randomized intervention. Infants randomized to lower vs higher oxygen saturation targets had a similar risk of death or respiratory morbidity (except for croup and treatmentwith oxygen or diuretics at home).	Child Health and Human Development Neonatal Research Network

Table IV. Respiratory outcomes in lower vs higher oxygen saturation target groups and early CPAP vs intubation/surfactant groups at the 6-mo interview and for the first 18-22 mo CA (combined responses to the 6-, 12-, and 18- to 22-mo interviews)

Outcome	Low oxygen saturation, n (%)	High oxygen saturation, n (%)	ARR (95% CI)	*P* value	CPAP	Intubation/surfactant	ARR (95% CI)	*P* value
Primary outcomes								
Has your child's chest sounded wheezy or whistling more than twice in 1 wk?								
6 months	94 (22.0)	129 (27.7)	0.73 (0.53-1.01)	.06	107 (23.2)	116 (26.9)	0.79 (0.58-1.09)	.16
6-22 months	203 (46.7)	233 (49.1)	0.92 (0.70-1.22)	.57	224 (47.7)	212 (48.2)	0.90 (0.68-1.19)	.47
Has your child had a cough for more than 3 days without a cold?								
6 months	63 (16.9)	76 (19.3)	0.84 (0.57-1.22)	.35	63 (16.2)	76 (20.2)	0.77 (0.53-1.12)	.17
6-22 months	127 (30.8)	141 (31.1)	1.01 (0.75-1.37)	.93	127 (28.4)	141 (33.7)	0.81 (0.60-1.10)	.18
Secondary outcomes								
Symptoms								
Wheezing/whistling more than twice in 1 wk or cough for more than 3 d								
6 months*	162 (43.5)	195 (49.5)	0.78 (0.58-1.05)	.10	178 (45.8)	179 (47.5)	0.95 (0.70-1.28)	.72
6-22 months	276 (66.8)	316 (69.5)	0.87 (0.65-1.18)	.37	303 (67.8)	289 (68.7)	0.95 (0.70-1.29)	.74
Has your child's chest sounded wheezy or whistling?								
6 months	135 (36.3)	171 (43.4)	0.73 (0.54-1.00)	<.05	151 (38.8)	155 (41.1)	0.89 (0.66-1.21)	.47
6-22 months	245 (59.3)	286 (62.9)	0.85 (0.64-1.13)	.27	269 (60.2)	262 (62.2)	0.86 (0.64-1.15)	.31
Has your baby's chest sounded wheezy or whistling apart from colds?								
6 months	61 (16.4)	84 (21.3)	0.73 (0.50-1.06)	.10	66 (17.0)	79 (21.0)	0.77 (0.53-1.11)	.16
6-22 months	117 (28.4)	165 (36.3)	0.67 (0.49-0.91)	.01	129 (28.9)	153 (36.5)	0.68 (0.50-0.92)	.01
Illnesses								
Has your child had asthma, reactive airway disease, or BPD exacerbation or flare-up diagnosed by a doctor?								
6 months*	51 (13.7)	62 (15.7)	0.84 (0.56-1.27)	.41	48 (12.3)	65 (17.2)	0.66 (0.44-1.00)	<.05
6-22 months*	140 (33.9)	158 (35.0)	1.01 (0.75-1.37)	.93	144 (32.2)	154 (36.8)	0.81 (0.60-1.09)	.16
Has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?								
6 months	72 (19.4)	78 (19.8)	0.98 (0.67-1.41)	.90	70 (18.0)	80 (21.2)	0.82 (0.57-1.19)	.30
6-22 months	161 (39.0)	183 (40.4)	0.96 (0.72-1.28)	.79	167 (37.4)	177 (42.2)	0.81 (0.61-1.09)	.17
Any of asthma, reactive airway disease, BPD exacerbation, or flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor								
6 months	95 (25.5)	109 (27.7)	0.91 (0.65-1.27)	.58	96 (24.7)	108 (28.7)	0.81 (0.58-1.13)	.22
6-22 months	204 (49.4)	241 (53.1)	0.91 (0.69-1.21)	.52	213 (47.7)	232 (55.2)	0.71 (0.53-0.95)	.02
Has your child had croup diagnosed by a doctor?								
6 months†	9 (2.4)	11 (2.8)	0.87 (0.36-2.08)	.75	7 (1.8)	13 (3.5)	0.52 (0.21-1.30)	.16
6-22 months*	46 (11.2)	39 (8.6)	1.35 (0.84-2.16)	.21	40 (9.0)	45 (10.8)	0.77 (0.49-1.23)	.28
Health services								
Has your child ever had to visit the doctor or emergency room for breathing or wheezing problems?								
6 months	167 (44.9)	188 (47.8)	0.82 (0.60-1.11)	.20	173 (44.6)	182 (48.3)	0.81 (0.60-1.10)	.18
6-22 months	292 (70.1)	319 (70.1)	0.98 (0.72-1.34)	.89	304 (68.0)	307 (72.9)	0.73 (0.53-1.00)	<.05
Has your child had to stay in a hospital overnight?								
6 months	105 (28.2)	118 (30.0)	0.89 (0.64-1.23)	.47	106 (27.3)	117 (31.0)	0.79 (0.57-1.10)	.17
6-22 months	169 (41.0)	199 (43.7)	0.90 (0.68-1.20)	.48	182 (40.7)	186 (44.3)	0.87 (0.66-1.16)	.35

(*continued*)

Table IV. Continued

Outcome	Low oxygen saturation, n (%)	High oxygen saturation, n (%)	ARR (95% CI)	*P* value	CPAP	Intubation/surfactant	ARR (95% CI)	*P* value
Has your child had to stay in a hospital overnight for wheezing/breathing problems?								
6 months	69 (18.6)	73 (18.6)	0.98 (0.67-1.44)	.93	64 (16.5)	78 (20.7)	0.72 (0.49-1.05)	.09
6-22 months	129 (31.3)	140 (30.8)	1.04 (0.77-1.40)	.80	130 (29.1)	139 (33.1)	0.82 (0.61-1.11)	.21
Medications								
Treated with a diuretic medication?								
6 months*	27 (6.3)	24 (5.2)	1.29 (0.72-2.32)	.39	23 (5.0)	28 (6.5)	0.72 (0.40-1.29)	.27
6-22 months*	31 (7.1)	24 (5.0)	1.50 (0.85-2.64)	.16	24 (5.1)	31 (7.0)	0.68 (0.39-1.20)	.18
Treated with an inhaled steroid medication?								
6 months	51 (11.9)	53 (11.4)	1.12 (0.73-1.71)	.61	54 (11.7)	50 (11.6)	1.00 (0.66-1.53)	.99
6-22 months	112 (25.6)	129 (26.9)	0.97 (0.71-1.32)	.82	128 (27.1)	113 (25.5)	1.10 (0.80-1.50)	.56
Treated with a nebulized medication?								
6 months†	5 (1.2)	18 (3.9)	0.30 (0.11-0.81)	.02	13 (2.8)	10 (2.3)	1.22 (0.54-2.75)	.63
6-22 months*	29 (6.6)	42 (8.8)	0.73 (0.44-1.22)	.23	39 (8.3)	32 (7.2)	1.11 (0.67-1.84)	.69
Treated with a systemic steroid medication?								
6 months†	11 (2.6)	8 (1.7)	1.50 (0.61-3.70)	.38	12 (2.6)	7 (1.6)	1.61 (0.64-4.04)	.31
6-22 months	44 (10.1)	42 (8.8)	1.13 (0.71-1.80)	.62	48 (10.2)	38 (8.6)	1.22 (0.77-1.95)	.40
Treated with oxygen at home?								
6 months†	90 (24.3)	80 (20.3)	1.22 (0.83-1.79)	.31	80 (20.6)	90 (23.9)	0.82 (0.56-1.21)	.32
6-22 months	104 (25.2)	96 (21.1)	1.31 (0.92-1.88)	.14	94 (21.0)	106 (25.3)	0.80 (0.56-1.15)	.23
Family								
Have you had to change your plans because of your child's breathing problems?								
6 months	58 (15.5)	69 (17.5)	0.85 (0.57-1.27)	.43	50 (12.9)	77 (20.4)	0.58 (0.39-0.87)	<.01
6-22 months	139 (33.7)	170 (37.4)	0.87 (0.65-1.17)	.36	145 (32.4)	164 (39.0)	0.74 (0.55-1.00)	<.05

ARR, adjusted relative risk, with adjustments for stratification factors (study center and gestational age group) and familial clustering.
*Where models did not converge, adjustments are limited to center and gestational age.
†If the 2 adjustment model failed to converge, unadjusted relative risks are reported.

Infants randomized to CPAP vs intubation/surfactant had fewer episodes of wheezing without a cold (28.9% vs 36.5%; P < .05), respiratory illnesses diagnosed by a doktor (47.7% vs 55.2%; P < .05), and physician or emergency room visits for breathing problems (68.0%vs 72.9%; P < .05) by 18-22 months CA.

Table V. Combined outcomes of death or respiratory morbidity for lower vs higher oxygen saturation target groups and early CPAP vs intubation/surfactant groups for the first 18-22 mo CA (combined responses to the 6-, 12-, and 18- to 22-mo interviews)

Outcomes with death	Low saturation (n = 586)	High saturation (n = 569)	ARR (95% CI)	*P* value	CPAP (n = 583)	Intubation/surfactant (n = 572)	ARR (95% CI)	*P* value
Primary outcomes								
Has your child's chest sounded wheezy or whistling more than twice in 1 wk?	337 (59.5)	344 (59.0)	1.06 (0.83-1.37)	.62	337 (58.0)	344 (60.6)	0.86 (0.67-1.11)	.26
Has your child had a cough for more than 3 days without a cold?	262 (47.9)	254 (45.0)	1.18 (0.91-1.51)	.21	240 (42.9)	276 (49.9)	0.78 (0.60-1.00)	.05
Secondary outcomes								
Symptoms								
Wheezing/whistling more than twice in 1 wk or cough for more than 3 d	410 (75.0)	425 (75.2)	0.99 (0.74-1.32)	.96	414 (74.1)	421 (76.1)	0.92 (0.69-1.23)	.56
Has your child's chest sounded wheezy or whistling?	379 (69.3)	395 (69.9)	0.98 (0.75-1.29)	.90	380 (68.0)	394 (71.2)	0.84 (0.64-1.10)	.21
Has your baby's chest sounded wheezy or whistling apart from colds?	252 (46.1)	275 (48.7)	0.91 (0.71-1.17)	.48	241 (43.1)	286 (51.7)	0.70 (0.54-0.90)	<.01*
Illnesses								
Has your child had asthma, reactive airway disease, or BPD exacerbation or flare-up diagnosed by a doctor?	274 (50.1)	270 (47.9)	1.17 (0.91-1.50)	.23	256 (45.8)	288 (52.2)	0.76 (0.59-0.98)	.03*
Has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?	295 (53.9)	295 (52.3)	1.12 (0.87-1.44)	.39	279 (49.9)	311 (56.3)	0.78 (0.60-1.00)	.05
Any of asthma, reactive airway disease, BPD exacerbation or flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?	339 (62.0)	351 (62.2)	1.05 (0.81-1.36)	.71	326 (58.3)	364 (65.9)	0.71 (0.54-0.92)	<.01*
Has your child had croup diagnosed by a doctor?	180 (32.9)	153 (27.1)	1.35 (1.03-1.77)	.03*	154 (27.5)	179 (32.4)	0.78 (0.60-1.03)	.08
Health services								
Has your child ever had to visit the doctor or emergency room for breathing or wheezing problems?	427 (78.1)	430 (76.1)	1.11 (0.82-1.50)	.49	417 (74.6)	440 (79.6)	0.73 (0.54-0.99)	<.05*
Has your child had to stay in a hospital overnight?	303 (55.5)	310 (54.9)	1.06 (0.82-1.37)	.64	294 (52.6)	319 (57.8)	0.84 (0.65-1.08)	.17
Has your child had to stay in a hospital overnight for wheezing/breathing problems?	263 (48.2)	252 (44.6)	1.20 (0.93-1.54)	.17	242 (43.3)	273 (49.5)	0.78 (0.61-1.01)	.06
Medications								
Treated with a diuretic medication?	165 (29.0)	137 (23.4)	1.42 (1.07-1.88)	.02*	137 (23.5)	165 (28.8)	0.74 (0.56-0.98)	.04*
Treated with an inhaled steroid medication?	246 (43.2)	240 (41.0)	1.15 (0.89-1.47)	.29	241 (41.3)	245 (42.8)	0.96 (0.75-1.24)	.76
Treated with a nebulized medication?	16 3 (28.6)	155 (26.5)	1.15 (0.87-1.52)	.33	152 (26.1)	166 (29.0)	0.85 (0.64-1.13)	.27
Treated with a systemic steroid medication?	178 (31.3)	156 (26.6)	1.28 (0.98-1.68)	.07	162 (27.8)	172 (30.1)	0.88 (0.68-1.16)	.38
Treated with oxygen at home?	238 (43.5)	206 (36.5)	1.46 (1.11-1.91)	<.01*	206 (36.9)	238 (43.1)	0.76 (0.58-1.00)	.05*
Family								
Have you had to change your plans because of your child's breathing problems?	273 (49.9)	281 (49.7)	1.04 (0.81-1.34)	.74	257 (46.0)	297 (53.7)	0.72 (0.56-0.92)	.01*

*$P < .05$.

Table VI. Respiratory outcomes for infants with traditional BPD (oxygen requirement at 36 wk postmenstrual age) for the first 18-22 mo CA (combined responses to the 6-, 12-, and 18- to 22-mo interviews)

Outcome	Traditional BPD (n = 377)	No traditional BPD (n = 539)	ARR (95% CI)	*P* value
Primary outcomes				
Has your child's chest sounded wheezy or whistling more than twice in 1 wk?	194 (52.0)	242 (45.1)	1.52 (1.15, 2.01)	<.01
Has your child had a cough for more than 3 days without a cold?	119 (33.7)	149 (29.0)	1.17 (0.86, 1.60)	.31
Secondary outcomes				
Symptoms				
Wheezing/whistling more than twice in 1 wk or cough more than 3 d	262 (74.2)	330 (64.1)	1.76 (1.27, 2.43)	<.01
Has your child's chest sounded wheezy or whistling?	231 (65.4)	300 (58.3)	1.61 (1.17, 2.21)	<.01
Has your baby's chest sounded wheezy or whistling apart from colds?	129 (36.8)	153 (29.7)	1.57 (1.16, 2.13)	<.01
Illnesses				
Has your child had asthma, reactive airway disease, or BPD flare-up diagnosed by a doctor?	133 (38.0)	165 (32.0)	1.58 (1.17, 2.13)	<.01
Has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?	152 (43.2)	192 (37.4)	1.34 (1.00, 1.80)	.05
Any of asthma, reactive airway disease, BPD flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?	195 (55.4)	250 (48.5)	1.47 (1.08, 2.00)	.01
Has your child had croup diagnosed by a doctor?	29 (8.2)	56 (10.9)	0.78 (0.46, 1.33)	.36
Health services				
Has your child ever had to visit the doctor or emergency room for breathing or wheezing problems?	267 (75.6)	344 (66.8)	1.56 (1.08, 2.25)	.02
Has your child had to stay in a hospital overnight?	186 (52.7)	182 (35.4)	2.22 (1.64, 3.02)	<.0001
Has your child had to stay in a hospital overnight for wheezing/breathing problems?	136 (38.5)	133 (25.9)	1.89 (1.40, 2.57)	<.0001
Medications				
Treated with a diuretic medication?*	47 (12.5)	8 (1.5)	11.86 (5.28, 26.62)	<.0001
Treated with an inhaled steroid medication?	135 (35.8)	106 (19.7)	2.40 (1.75, 3.29)	<.0001
Treated with a nebulized medication?*	35 (9.3)	36 (6.7)	1.53 (0.88, 2.67)	.14
Treated with a systemic steroid medication?	40 (10.6)	46 (8.5)	1.45 (0.93, 2.26)	.10
Treated with oxygen at home?	164 (46.5)	36 (7.0)	9.18 (5.81, 14.52)	<.0001
Family				
Have you had to change your plans because of your child's breathing problems?	143 (40.5)	166 (32.2)	1.34 (1.00, 1.79)	<.05

*Where models did not converge, adjustments are limited to center and gestational age.

Those findings, coupled with the respiratory outcomes reported here, suggest that treatment of extremely preterm infants with CPAP and limited ventilation rather than with intubation and surfactant within 1 hour is safe and may result in less respiratory morbidity during the first
18-22 months CA. findings indicate a high risk of postdischarge respiratory morbidities among preterm infants at 24-27 6/7 weeks gestation (with or without BPD) that not only require close medical monitoring, but also present potential burdens to families as well as to society by increasing health care costs.
Longitudinal assessment of pulmonary morbidity is necessary to fully evaluate the potential benefits of respiratory interventions for neonates.

Early continuous positive airway pressure (CPAP) may reduce lung injury in preterm infants.
Patients and methods: Spontaneously breathing preterm infants were randomised immediately arter birth to nasal CPAP or intubation, surfactant treatment and mechanical ventilation. Pulmonary function tests approximately 8 weeks post-term determined tidal

Positive effects of early continuous positive airway pressure on pulmonary function in

breathing parameters, respiratory mechanics and functional residual capacity (FRC).

Results: 17 infants received CPAP and 22 mechanical ventilation.

Table 1 Patient characteristics

	CPAP group (N=17)	MV group (N=22)	p Value
Birth weight (g)	997 (269)	933 (270)	0.467
Gestational age (weeks)	26.9 (1.3)	26.5 (1.2)	0.302
Male	11 (65%)	15 (68%)	0.819
Prenatal steroids	15 (88%)	18 (82%)	0.679
Surfactant treatment	11 (65%)	22 (100%)	<0.001*
Multiple surfactant doses (>1)	2 (12%)	10 (45%)	0.008*
5 Min Apgar score <8	5 (29%)	12 (55%)	0.117
Time of first intubation (minutes)	45 (8–1920)	6.5 (3–251)	0.599
Duration of MV (0–120 h)	4 (1–119)	72 (1–120)	0.011*
Max PIP 0–120 h (cm H_2O)	18 (0–36)	24 (16–30)	0.027*
Total duration of CPAP (days)	21 (2–48)	31 (4–54)	0.119
Total duration of MV (days)	4 (0–32)	7.5 (1–36)	0.036*
Total duration of any respiratory support (days)	30 (7–56)	47 (4–72)	0.017*
Postnatal steroid treatment	1 (6%)	3 (14%)	0.618
Days in hospital	81 (7–129)	85 (48–114)	0.619

CPAP, continuous positive airway pressure; MV, mechanical ventilation; PIP, peak inspiratory pressure.
Values are mean (SD) or n (%).
*Statistically significant.

Infants with early CPAP had less mechanical ventilation (4 vs 7.5 days; p=0.004) and less total respiratory support (30 vs 47 days; p=0.017). Postterm the CPAP group had lower respiratory rate (41 vs 48/min; p=0.007), lower minute ventilation (223 vs 265 ml/min/kg; p=0.009), better respiratory compliance (0.99 vs 0.82 ml/cm H2O/kg; p=0.008) and improved elastic work of breathing (p=0.004). No differences in FRC were found.

Table 2 Pulmonary function parameters measured at about 2 months

	CPAP group (N=17)	MV group (N=22)	p Value
PCA (weeks) at time of testing	48.4 (5.3)	46.9 (3.4)	0.312
Body weight at time of testing (g)	4293 (815)	4111 (656)	0.447
Tidal volume, V_T (ml/kg)	5.50 (0.94)	5.57 (0.86)	0.823
Respiratory rate, RR (1/min)	41 (5.6)	48 (8.8)	0.007*
Minute ventilation, V'_E (ml/min/kg)	223 (33.5)	265 (55.5)	0.009*
Respiratory compliance, C_{rs} (ml/cm H_2O/kg)	0.99 (0.20)	0.82 (0.15)	0.008*
Respiratory resistance, R_{rs} (cm H_2O/l/s)	66.6 (19.3)	70.3 (25.1)	0.638
Respiratory time constant, T_{rs} (ms)	307 (133.4)	231 (87.0)	0.043*
Elastic work of breathing per minute (mJ/kg/min)	64.3 (18.8)	93.3 (33.7)	0.004*
Functional residual capacity, FRC (ml/kg)	19.3 (5.68)	17.7 (2.77)	0.232

CPAP, continuous positive airway pressure; MV, mechanical ventilation; PCA, post-conceptional age.
Values are mean (SD).
*Statistically significant.

Conclusions Early CPAP is feasible, shortens the total duration of respiratory support and results in improved lung mechanics and decreased work of breathing at about 8 weeks post-term.

extremely premature infants: results of a subgroup analysis of the COIN trial
C C Roehr, H Proquitté, H Hammer, R R Wauer, C J Morley, G Schmalisch
Arch Dis Child Fetal Neonatal Ed 2011;96:F371–F373.

Objective: To determine whether very low birth weight infants (VLBWIs), initially supported with continuous positiive airway pressure (CPAP) and then selectively treated with the INSURE (intubation, surfactant, and extubation to CPAP; CPAP/INSURE) protocol, need less mechanical ventilation than those supported with supplemental oxygen, surfactant, and mechanical ventilation if

Randomized Trial of Early Bubble Continuous Positive Airway Pressure for Very Low Birth

required (Oxygen/mechanical ventilation [MV]).

Table I. Perinatal and demographic characteristics

Characteristic	CPAP/INSURE (n = 131)	Oxygen/MV (n = 125)	*P* value
Body weight, kg, mean ± SD	1196 ± 194.8	1197 ± 189.2	.993
GA, weeks, mean ± SD	29.8 ± 2.4	29.5 ± 2.2	.242
Male sex, %	51.1	51.2	.993
Cesarean birth, %	74.8	73.6	.825
Antenatal steroid use, %	90.8	88.0	.460
Twins, %	21.4	23.2	.726
5-minute Apgar score, median (range)	9 (5-10)	9 (4-10)	.356

Study design: In a multicenter randomized controlled trial, spontaneously breathing VLBWIs weighing 800-1500 g were allocated to receive either therapy.

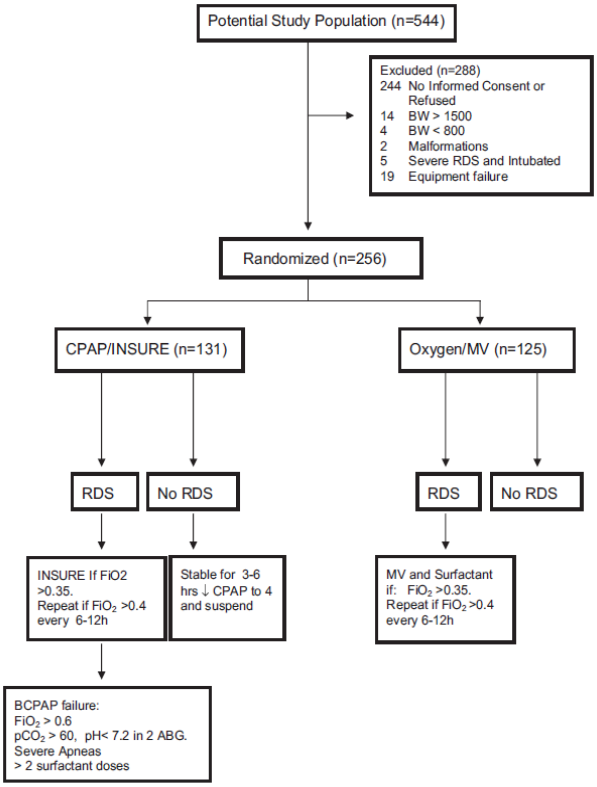

Figure. Patient flow throughout the clinical trial. *BW*, birth weight; *BCPAP*, bubble continuous positive airway pressure; *ABG*, arterial blood gas.

In the CPAP/INSURE group, if respiratory distress syndrome (RDS) did not occur, CPAP was discontinued after 3-6 hours. If RDS developed and the fraction of inspired oxygen (FiO2) was >0.35, the INSURE protocol was indicated. Failure criteria included FiO2 >0.60, severe apnea or respiratory acidosis, and receipt of more than 2 doses of surfactant. In the Oxygen/MV group, in the presence of RDS, supplemental oxygen without CPAP was given, and if FiO2 was >0.35, surfactant and mechanical ventilation were provided.
Results: A total of 256 patients were randomized to either the CPAP/INSURE group (n = 131) or the Oxygen/MV group (n = 125).

Weight Infants J Pediatr 2012; 161:75-80
Jose L. Tapia, MD, Soledad Urzua, MD, Aldo Bancalari, MD, Javier Meritano, MD, Gabriela Torres, MD, Jorge Fabres, MD, MSPH, Claudia A. Toro, MD, Fabiola Rivera, MD, Elizabeth Cespedes, MD,Jaime F. Burgos, MD, Gonzalo Mariani, MD, Liliana Roldan, MD, Fernando Silvera, MD, Agustina Gonzalez, MD, and Angelica Dominguez, BSc, for the South American Neocosur Network

Table II. Respiratory outcomes and mortality

Outcome	CPAP/INSURE (n = 131), %	Oxygen/MV (n = 125), %	RR	95% CI	*P* value
RDS	50.0	56.0	0.89	0.71-1.13	.337
Mechanical ventilation	29.8	50.4	0.59	0.43-0.81	.001
Surfactant requirement	27.5	46.4	0.59	0.42-0.83	.002
Pneumothorax	3.1	5.6	0.55	0.16-1.82	.315
O_2 at 28 days of life	16.0	24.8	0.65	0.39-1.06	.081
BPD	6.9	9.6	0.72	0.31-1.64	.426
Death	8.4	9.6	0.87	0.40-1.91	.737
BPD/death	13.7	19.2	0.72	0.41-1.25	.238

RR, relative risk.

The need for mechanical ventilation was lower in the CPAP/INSURE group (29.8% vs 50.4%; P = .001), as was the use of surfactant (27.5% vs 46.4%; P = .002). There were no differences in death, pneumothorax, bronchopulmonary dysplasia, and other complications of prematurity between the 2 groups.

Table III. Secondary outcomes

Outcome	CPAP/INSURE (n = 131), %	Oxygen/MV (n = 125), %	RR	95% CI	*P* value
PDA	34.4	30.4	1.13	0.79-1.61	.500
IVH total	25.2	20.2	1.25	0.79-1.98	.338
IVH grade III-IV	4.6	6.4	0.72	0.26-2.00	.522
NEC	15.3	13.6	1.12	0.62-2.04	.705
ROP	13.0	16.8	0.77	0.43-1.39	.309
Sepsis	2.3	1.6	1.43	0.24-8.42	.999
Nasal damage	8.4	0.0	-	-	.001

NEC, necrotizing enterocolitis.

Conclusion: CPAP and early selective INSURE reduced the need for mechanical ventilation and surfactant in VLBWIs without increasing morbidity and death. For clinicians managing preterm neonates in the developing world, with few ventilators and a short supply of surfactant, early provision of nasal CPAP administered through an inexpensive system can significantly reduce the need for mechanical ventilation and surfactant without increasing death or morbidity. These results may be particularly relevant for resource-limited regions.

Background: Studies on early surfactant administration during nasal continuous positive airway pressure (NCPAP) [intubateesurfactanteextubate (INSURE)] have used continuous positive airway pressure and INSURE in the first hours after birth, but in many centers patients are transported from far away hospitals, reaching the center at a later time.
The aim of this study was to compare the effect of INSURE with only NCPAP in the management of respiratory distress syndrome (RDS) in an outborn hospital.

Comparison of the Effect of Surfactant Administration During Nasal Continuous Positive Airway Pressure with That of Nasal Continuous

Table 1 Baseline characteristics of the participating infants.

Characteristics	Control group ($N = 30$)	Treatment group ($N = 30$)	p
Birth weight, mean ± SD, g	1709 ± 241.9	1515 ± 433.6	0.03
Gestational age, mean ± SD, wk	31.0 ± 2.1	31.4 ± 1.9	0.2
Male, *n* (%)	14 (46.7)	13 (43.3)	1
C-section, *n* (%)	29 (96.7)	27 (90)	0.6
5-min Apgar score, median	8	8	1
Prenatal steroids, *n* (%)	26 (90)	28 (96)	0.6
RDS score, mean ± SD	6.2 ± 0.9	6.5 ± 1.0	0.14

Control group: NCPAP only; treatment group: INSURE method. INSURE = intubation, surfactant, extubation; NCPAP = nasal continuous positive airway pressure; RDS = respiratory distress syndrome; SD = standard deviation.

Methods: This study was a controlled randomized clinical trial on 60 neonates who were transported to the neonatal intensive care unit of Boo-Ali Sina Hospital.

Treatment failure in the treatment group was determined when the infant could not be extubated within 1 hour of INSURE, and in both groups when there was a need for mechanical ventilation within 5 days. Indications for mechanical ventilation were as follows: (1) the presence of prolonged (>20 seconds) or recurrent apnea accompanied by bradycardia or desaturation below 85%; (2) pH < 7.20, PCO2 > 60, and PaO2 < 50 on arterial blood gas, with a maximum FiO2 of 0.7 and CPAP of 5e6 cmH2O; and (3) progressive respiratory distress. In case of treatment failure, in both groups, the infant was intubated for mechanical ventilation. Then in the control group, if an FiO2 of more than 0.3 was necessary to maintain the SpO2 above 88%, the rescue dose of Survanta was administered. In the INSURE group, if the FiO2 requirement remained above 0.3 after 6 hours of INSURE procedure, the rescue dose of surfactant was given.

In both groups, if FiO2 was >0.3 after the first dose of rescue surfactant, subsequent doses of surfactant were administered every 6 hours up to a maximum of four doses.

Positive Airway Pressure Alone on Complications of Respiratory Distress Syndrome: A Randomized Controlled Study

Maryam Nakhshab , Mehdi Tajbakhsh , Soghra Khani , Roya Farhadi. Iran , Pediatrics and Neonatology 2014

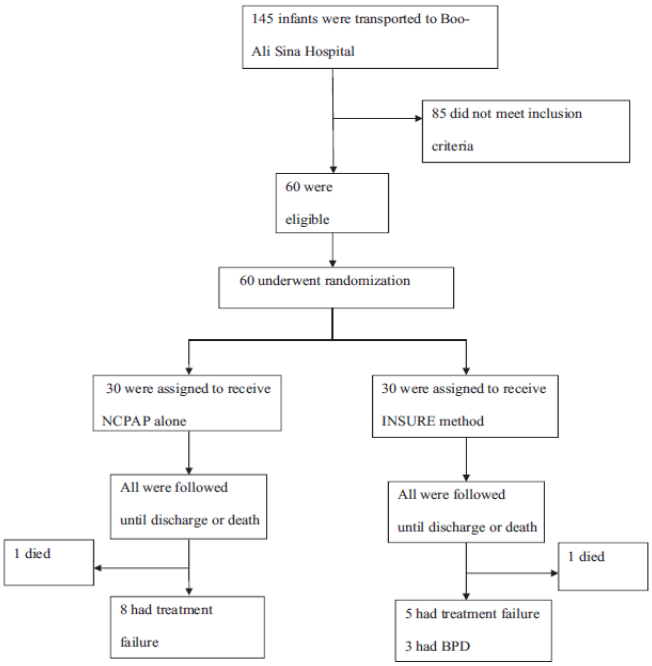

Figure 1 Flow diagram of study participants. BPD = Bronchopulmonary Dysplasia; INSURE = intubation, surfactant, extubation; NCPAP = nasal continuous positive airway pressure.

Neonates born at 27+0/7 to 34+6/7 weeks of gestation, aged <12 hours, and diagnosed with RDS were placed on NCPAP and then randomly assigned to INSURE or NCPAP alone. The primary outcome was the need for intubation and mechanical ventilation on the basis of the criteria defined by us, and the secondary outcomes were neonatal mortality and other complications of RDS.

Results: In 13 months, 60 eligible neonates were enrolled. Our participants in INSURE group received surfactant at the mean age of 5.1 hours. The relative risk of need for mechanical ventilation was 0.55 (95% confidence interval: 0.15e1.9, p = 0.53), and the rate of mortality or other complications of RDS was statistically similar between the two groups.

Table 2 Primary and major secondary outcomes.

Outcome	Control group ($N = 30$) n (%)	Treatment group ($N = 30$) n (%)	RR (95% CI)	p
Treatment failure (MV)	8 (26.7)	5 (16.7)	0.55 (0.15–1.9)	0.53
Death	1 (3.3)	1 (3.3)	1 (0.6–16.7)	1
CLD	3 (10)	3 (10)	1 (0.18–5.4)	1
Pneumothorax	2 (6.7)	0 (0)		0.49
IVH, Grade III or IV	1 (3.3)	3 (10)	3.2 (0.31–32.8)	0.6
PVL	1 (3.3)	1 (3.3)	1 (0.6–16.7)	1
ROP	3 (10)	2 (6.1)	0.6 (0.1–4.1)	1

Control group: NCPAP only; treatment group: INSURE method. CI = confidence interval; CLD = chronic lung disease; INSURE = intubation, surfactant, extubation; IVH = intraventricular hemorrhage; MV = mechanical ventilation; NCPAP = nasal continuous positive airway pressure; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity; RR = relative risk; SD = standard deviation.

Table 3 Other secondary outcomes.

Outcome	Control group ($N = 30$)	Treatment group ($N = 30$)	p
Rescue surfactant, n (%)	7* (23.3)	0 (0)	0.01
Length of hospitalization, mean ± SD, d	15.1 ± 5.5	14.2 ± 6.3	0.57
Days of MV, mean ± SD	1.9 ± 3.7	1.4 ± 2.7	0.5
Days on oxygen, mean ± SD	7.8 ± 3.4	5.9 ± 3.0	0.03
Days on NCPAP, mean ± SD	4.4 ± 2.3	3.2 ± 1.1	0.35

Control group: NCPAP only; treatment group: INSURE method. INSURE = intubation, surfactant, extubation; MV = mechanical ventilation; NCPAP = nasal continuous positive airway pressure; SD = standard deviation.

* Each of them received only one dose of surfactant.

Conclusions: After the first few hours of life (mean age of 5.1 hours), the rate of mortality and chronic lung disease and the need for mechanical ventilation were not statistically different between patients receiving INSURE and those in receipt of NCPAP alone.

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