Kliiniline küsimus nr 16

Kas enneaegsetel vastsündinutel kindlate saturatsioonipiiride kasutamine võrreldes mittekasutamisega parandab lapse ravitulemit?

- *madalad saturatsioonipiirid võrreldes kõrged saturatsioonipiirid*
- *automaatne FiO2-SpO2 kontroll võrreldes õe poolt juhitud "konventsionaalne"?*

Tulemusnäitajad: lapse peamised tulemusnäitajad, koehüpoksia biokeemilised markerid

Kokkuvõte:

Enneaegsete vastsündinute jaoks on optimaalne hapnikusaturatsioon teadmata.

Lähtudes leitud tõendusmaterjalist (ravijuhend, metaanalüüsid) tuleks eelistada enneaegsetel vastsündinutel kõrgemat saturatsioonipiiri (SpO_2 90-95%). Madalama saturatsioonipiiri (85-89%) kasutamisel esines randomiseeritud kontrolluuringutes vähem rasket ROP—i, kuid võrreldes kõrgema saturatsioonipiiri kasutamisega tõusis oluliselt suremus ning NEK—i esinemissagedus. Neid tulemusi kinnitas ka hiljutine metaanalüüs (Saugstad, O; 2014), mis hõlmas 5 olulisemat RCT-d antud valdkonnas. 2014. a avaldatud metaanalüüsil ei olnud madala või kõrge saturatsioonpiiri vahel erinevusi funktsionaalse BPD, ajukahjustuse ja avatud PDA riski osas.
2015. aasta alguses avaldati uus metaanalüüs, mis haaras eelpoolmainitud 5 suure RCT andmeid (lähi- ja kaugtulem), erinevalt eelnevatest metaanalüüsidest hinnati ka tulemite tõenduspõhisuse kvaliteeti. Selgus, et kõrgema saturatsioonivahemiku grupi suremus oli madalam kojukirjutamise hetkel, kuid tõenduspõhisus vastavalt GRADE süsteemile on madal. Samuti esines kõrgema saturatsioonivahemiku grupis vähem NEK-i. Muude tulemite osas kahe grupi vahel erinevust ei olnud (suremus/puue, BPD, kuulmislangus, psühhomotoorne areng, ROP 24. elukuu vanuses). Seega jääb antud metaanalüüsile põhinedes ebaselgeks, milline oleks optimaalne SpO_2 vahemik hapnikravi saavate enneaegsete jaoks.
Euroopa neonataalse respiratoorse distressi ravijuhendis soovitatakse vältida hüperoksilise piike peale surfaktantravi ning hapniku saturatsiooni kõikumisi, kuna uuringutes on näidatud, et see soodustab ROP—i teket.
Rutiinselt jälgib hapnikravi saavate enneaegsete vastsündinutel saturatsiooniväärtust õenduspersonal ning saturatsiooniväärtuste hoidmiseks etteantud piirides vastvalt vähendatakse või tõstetakse FiO_2-te. Et parandada kinnipidamist etteantud saturatsiooniväärtustest ning vähendada õenduspersonali töökoormus, on loodud algoritmid automaatseks SpO_2-FiO_2 süsteemide loomiseks, sellised süsteemid on rutiinses kasutuses mitmetes USA keskustes.
Automaatse FiO_2-SpO_2 süsteemi efektiivsuse ja ohutuse kohta võrreldes manuaalse FiO_2 regulatsiooniga ei ole avaldatud suuri RCT-sid või metaanalüüse. Väikestes uuringutes on näidatud, et automaatne FiO_2 korrigeerimissüsteem suurendab oluliselt aega, mil saturatsiooniväärtus püsib etteantud piirides ning vähendab hüperoksia aega, samas esines automaatse SpO_2- FiO_2 kontrolli ajal enam hüpoksilisi episoode. Kaugtulemit hindavaid uuringuid ei ole läbi viidud ning on vajalikud pikema-ajalised uuringud neuroloogilise tulemi hindamiseks. Automatiseeritud süsteemid võivad potentsiaalselt langetada haigestumust kõrge-riskiga enneaegsetel ning oluliselt vähendada õenduspersonali koormust.

Ravijuhendid

Lisahapniku kasutamist enneaegsetel vastsündinutel peale esmast stabiliseerimist on käsitletud ühes ravijuhendis (European Consensus Guidelines on the management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update). *Soovitused põhinevad aastatel 2007 – 2012 ilmunud tõendusmaterjalil (Cochrane'i andmebaas), millele on hinnangu andnud Euroopa neonatoloogia ekspertide konsensus.*
Varajane hapnikravi on otseselt seotud enneaegsete retinopaatia (ROP) ja vähemal määral BPD tekkega. Saturatsiooni kõikumised on samuti seotud kõrgenenud retinopaatia riskiga. Hiljuti on läbi viidud suuri randomiseeritud kontrolluuringud, leidmaks madalaimat ohutut saturatsioonivahemikku, milles ühes (SUPPORT) randomiseeriti enneaegsed vastsündinud madala (85-89%) ja kõrge saturatsiooni (91-95%) rühmadesse. Selgus, et madalama saturatsioonivahemiku grupis oli ellujäänud vastsünditutel poole vähem ROP-i, kuid nende suremus oli 4% kõrgem, kui kõrge saturatsiooni grupis olnud lastel.
Interim metaanalüüs BOOST II (Austraalia, UK, UUS-Meremaa) uuringul kinnitas madalama saturatsiooni grupil tõusnud suremust, kuid seda vaid alla 27 GN enneaegsete grupis.

Soovitused:
1) Hapnikravi saavatel lastel peaks olema eesmärk-saturatsioonipiir 90 ja 95 % vahel (B).
2) Peale surfaktantravi peaks vältima kiiret hüperoksilist piiki, vähendades FiO_2-te (C)
3) Postnataalses perioodis peaks vältima saturarsiooni fluktueerumisi (C).

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. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Neonatology. 2013;103(4):353-68.

Table 1. Levels of evidence and grades of recommendation

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High-quality systematic reviews of case control or cohort studies High-quality case control or cohort studies with a very low risk of confounding bias
2+	High quality case control or cohort studies with a low risk of confounding bias
2–	Well-conducted case control or cohort studies with a high risk of confounding bias
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion
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.

Süstemaatilised ülevaated

Saturatsioonipiiride kasutamist enneaegsetel vastsündinutel on käsitletud neljas meta-analüüsis, mis on ilmunud ajavahemikul 2010 – 2015.

I Metaanalüüs: *Chen M.L et al avaldasid 2010. aastal metaanalüüsi, kus analüüsiti raske ROP-i (defineeriti kui ROP III vastavalt ROP-i klassifikatsioonile või pretreshold/treshold ROP (defineeriti nii CryoROP, STOP-ROP ja ET-ROP uuringutes)) esinemissagedust enneaegsetel vastsündinutel (<= 32 GN) seoses madala või kõrge pulssoksümeetrial mõõdetud hapniku saturatsiooniga. Teostati otsing Pubmed ja Embase andmebaasides ning metaanalüüsi selekteeriti 10 publikatsiooni, mis uurisid seost raske ROP-i ja pulssoksümeetrial mõõdetud eesmärk-saturatsioonivahemiku vahel.*
Metaanalüüsil selgus, et madal eesmärk-saturatsioon (79-96%) esimestel postnataalsetel nädalatel seostus madalama raske ROP-i riskiga (RR 0.48, 95% CI 0.31—0.75). Kõrge hapnikusaturatsioon (94—99%) vanuses >= 32 PMA assotsieerus madalama riskiga raske ROP-i tekkeks (RR 0.54, 95% CI 0.35—0.82).
Järeldati*, et enneaegsetel vastsündinutel (<= 32 GN) varane madal ja hilisem kõrge hapniku saturatsioonivahemik seostub madalama riskiga raske ROP-i tekkeks. Autorid rõhutavad, et metaanalüüsi tulemuste kinnitamiseks on vajalik suur randmoseeritud kontrolluuring koos pika—ajalise efekti hindamisega nägemisele, kopsufunktsioonile ning psühhomotoorsele arengule.*

II Metaaanalüüs: *Saugstad, OD ja Aune, D avaldasid 2011. aastal metaanalüüsi, milles uuriti madala ja kõrge saturatsioonipiiri mõju esimestel elunädalatel VLBW ja ELBW vastsündinute ravitulemile (ROP ja BPD). Metaanalüüsi haarati 10 randomiseeritud ja jälgimisuuringut (Pubmed, Embase ja Cochrane Database kuni juuli 2010), kus võrreldi pulssoksümeetrial mõõdetud madala või kõrge saturatsioonigrupi vastsündinute ravitulemit.*
8 uuringul oli tulemusnäitajaks raske ROP-i esinemine (3811 vastsündinut) ning 8 uuringul BPD/kopsuprobleemide esinemine (4612 vastsündinut). RR madala SpO_2 kasuks raske ROP-i ennetamisel oli 0.42 (95% CI 0.34—0.51), BPD ennetamisel 0.73 (95% CI 0.63—0.86) ja suremusele 1.12 (95% CI 0.86—1.45).
Metaanalüüsi kaasati 1 RCT, mille tulemiks oli raske ROP, 3 RCT-d, mille tulemiks oli BPD ja kopsuprobleemid ning 1 RCT, mille tulemiks oli suremus. Kui analüüsiti eraldi vaid RCT—sid, RR raske ROP-i kujunemiseks oli 0.48 (95% CI 0.34—0.68), BPD puhul 0.79 (95%CI 0.64—0.97) ja suremusele 1.27 (95% CI 1.01—1.60).
Järeldused*: Madalamate saturatsioonipiiride kasutamine vähendab raske ROP-i esinemissagedust 50% (20.9% v 9.5%) ja BPD—d 25% (40.8% vs 29.7%). Vajalikud on RCT—d tegemaks lõplikke järeldusi ning hindamaks, kas madalamate saturatsioonipiiride kasutamine mõjutab VLBW ja ELBW laste suremust.*

III metaanalüüs: *Samad autorid avaldasid 2014. aastal järgmise metaanalüüsi, kus võtsid kokku RCT-de tulemused, mis uurisid saturatsioonivahemikke enneaegsetel vastsündinutel. Metaanalüüsi eesmärgiks oli teha kokkuvõte RCT—de tulemustest, mis uurisid madala ja kõrge hapniku saturatsioonipiiri mõju <28 GN vastsündinutel postnataalperioodis ning*

kuulusid NEOPROM (Neonatal Oxygenation Prospective Meta-Analyses) kolloboratiivsesse uuringusse.
SUPPORT (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial), kolme BOOST II (Benefits of Oxygen Saturation Targeting) ja COT (Canadian Oxygen Trial) uuringute andmete põhjal koostati metaanalüüs, mille populatsiooniks oli 4911 vastsündinut, kes randomiseeriti madalasse (85—89%, n=2456) või kõrgesse (91—95%, n=2455) funktsionaalse hapnikusaturatsiooni rühma 24 tunni jooksul peale sündi.
Tulemused: RR (95% CI), mis võrdles madala ja kõrge saturatsiooigrupi tulemit, oli suremuse osas kojukirjutamisel või follow-upil 1.41 (1.14—1.74); raske ROP-i puhul 0.74 (0.59—0.92) ja füsioloogilise BPD korral 0.95 (0.86—1.04); raske NEK-i puhul 1.25 (1.05—1.49); ajukahjustuse tekkeks 1.02 (0.88—1.19) ja PDA jaoks 1.01 (0.95—1.08). RR>1.0 puhul on eelis kõrgemal saturatsioonipiiril.

Järeldused: *Võrreldes madala saturatsioonipiiri imikute gruppi kõrge saturatsiooni grupiga, on RR suremuse ja NEK-i osas oluliselt tõusnud ning raske ROP-i osas oluliselt madalam. Ei olnud statistiliselt olulist erinevust gruppide vahel funktsionaalse BPD, ajukahjustuse või PDA osas. Nende tulemuste põhjal soovitatakse enneaegsetel vastsündinutel <28 GN hoida funktsionaalne SpO_2 90-95% vahel 36. postmenstruaalnädala vanuseni.*

IV metaanalüüs*: 2015. aasta aprillis avaldatud metaanalüüsis hindasid Manja et al restriktiivse (SpO_2 85-89%) ja liberaalse (SpO_2 91-95%) hapnikravi mõju ELBW vastsündinute (<28 GN) haigestumisele ja suremusele. Teostati otsingud andmebaasides Pubmed, CENTRAL ja CINAHL kuni märtsini 2014 ning kaasati abstraktid, mis on esitatud Lastearstide akadeemilistele liitudel vahemikus 2000 – 2014.*
Peamised tulemid: surm enne haiglast väljakirjutamist; surm või raske puue enne 24. elukuud; surm enne 24. elukuud; psühhomotoorse arengu tulemid, kuulmislangus, BPD, NEK ja raske ROP.
Otsingutel alusel kaasati andmetöötlusesse 5 randomiseeritud kontrolluuringut (SUPPORT, COT ja 3 BOOST II uuringut). Need uuringud olid sarnase disainiga, peamiseks tulemiks oli komposiittulem surm/puue korrigeeritud vanuses 18 – 24 elukuud, kuid kahel uuringust viiest ei olnud seda tulemit kirjeldatatud/avaldatud. Enne 24. elukuud ei olnud vahet suremuses/puude esinemises (RR 1.02 [95%CI, 0.92-1.14]). Suremus enne 24. Elukuud ei erinenud (RR 1.13 [95%CI 0,97-1.33]); leiti oluliselt suurem suremus restriktiivse hapnikravi grupis enne haiglast kojukirjutamist (RR 1.18 [95%CI 1.03-1.36]. BPD, kuulmislanguse, ROP-i ja psühhomotoorse arengu mahajäämuse esinemisagedus oli sarnane mõlemas grupis. NEK-i esines enam restriktiivset hapnikravi saanud vastsündinute grupis (RR 1.24 [95% CI 1.05-1.47]). GRADE skaala kriteeriumite alusel on antud tõendusmaterjali kvaliteet keskmine kuni madal.
Järeldused*: Kuigi liberaalse (kõrgema) saturatsiooni rühma vastsündinute suremus oli haiglas kojukirjutamise hetkel oluliselt väiksem võrreldes restriktiivset hapnikravi saanud lastega, on selle tulemi tõenduspõhisuse aste madal. NEK-i esines liberaalse hapnikravi rühmas vähem. Ei leitud olulist erinevus suremuses/raske puude esinemises, BPD, ROP-i psühhomotoorse arengu ja kuulmislanguse osas 24. elukuu vanuses.*

Muud uuringud

Enneaegsetel vastsündinutel esineb sagedasi SpO_2 fluktuatsioone, mis vajavad pidevat FiO_2 tiitrimist õenduspersonali poolt, mistõttu on väljatöötatud automaatsed FiO_2-SpO_2 kontrollsüsteemid, et suurenda aega, mille vältel lapse SpO_2 on ettemääratud piirides ning vähendada hüpokseemiat, hüperokseemiat ning kõrget FiO_2. Automaatse FiO_2—SpO_2 süteemi kasutamise kohta enneaegsetel vastsündinutel ei ole avaldatud antud perioodil (2010-2015) metaanalüüse või suuri RCT-sid. Vastavalt ostsingukriteeriumitele leiti 5 hiljuti avaldatud prospektiivset uuringut, nendest 3 RCT-d.

Claure N et al avaldasid 2011.a prospektiivse mitmekeskuse uuringu, kus hinnati automatiseeritud FiO_2-SpO_2 süsteemi efektiivsust ja ohutust hoidmaks SpO_2-te etteantud piirides (87-93%) 32 enneaegsel mehhaanilisel ventilatsioonil oleval sagedate desaturatsiooniepisoodidega vastsündinul (mediaan 25 (24—27) GN, vanus 27 (IQR 17-36 päeva)). Uuring toimus kahel järjestikkusel 24 tunnisel perioodil, ühe perioodi jooksul reguleeris FiO_2-te meditsiinipersonal ning teisel perioodil automaatne kontrollsüsteem. Leiti, et aeg, mille jooksul oli SpO_2 eesmärkvahemikus, oli oluliselt suurem automatiseeritud kontrollisüsteemi perioodil võrreldes manuaalse FiO_2 regulatsiooniga (40±14% võrreldes 32±13%). Aeg, mille vältel SpO_2 oli >93% või >98% oli oluliselt väiksem automatiseeritud süsteemi puhul (21%±20% vs 37±12%). Automatiseeritud kontrolli perioodil oli SpO_2 <87% oluliselt kauem, kui manuaalse kontrolli puhul (32±12 vs 23±9%).
***Järeldati,** et automatiseeritud FiO_2-SpO_2 süsteemi kasutamise korral oli kinnipidamine etteantud saturatsioonipiirist oluliselt parem ning vähenes aega, mil saturatsioon oli kõrgem etteantud piiridest, samas esines rohkem episoode, mil SpO_2 oli 80-86%.*

Waitz M et al hindasid automatiseeritud FiO_2 korrektsiooni mõju SpO_2-le ja ajukoe oksugenisatsioonile ($SctO_2$) VLBW vastsündinutel, kellel esinesid sagedased SpO_2 kõikumised. Uuringugrupiks oli 15 imikut (mediaan gestatsiooniga 25 GN, IQR 23—28 GN), mediaanvanus 34 päeva, IQR 19—74 päeva), kes juhuslikkuse alusel määrati 24 tunniks automaatsele FiO_2—SpO_2 jälgimisele või manuaalse FiO_2 regulatsioonigruppi. Esmane tulem oli aeg, mille jooksul SpO_2 oli eesmärk-vahemikus ja kurvialune ala ülal- ja allpool defineeritud $SctO_2$ piiri.

***Järeldused**: automatiseeritud FiO_2 kontroll suurendas oluliselt aega, mil SpO_2 oli eesmärgi piires ja vähendas prolongeeritud hüpokseemiliste episoodide arvu võrreldes manuaalse FiO_2 reguleerimisega, kuid ei mõjutanud oluliselt ajukoe oksügenisatsiooni.*

2014. a avaldasid Wilinska et al RCT, kus võrreldi automaatset FiO_2-SpO_2 kontrollsüsteemi hingamistoetust vajavatel enneaegsetel vastsündinutel kitsa SpO_2 (90-93%) piirvahemiku ning standartse SpO_2 (87-93%) piirvahemiku korral. Uuring viidi läbi kahes kolmanda etapi vastsündinute intensiivravi osakonnas, kus kasutatakse rutiinselt automaatset FiO_2-SpO_2 kontrollsüsteemi (Avea-CLiO2, Yorba Linda CA, USA). Tegemist oli 12 tunnise cross-over disainiga uuringuga, kus igale lapsele määrati juhuslikus järjekorras üks SpO_2 uuringueesmärkidest kuni 3 ööpäevaks. Primaarsed tulemid olid: aeg, mil SpO_2 oli vahemikus 87-93%, ekstreemse SpO_2 väärtuse aeg ning SpO_2 eksposiitsiooni jaotuvus.
Uuringu lõpetasid 21 vastsündinut, mediaangestatsioonivanusega 27 GN, mediaankaaluga 1.08 kg ning mediaanvanusega 17 päeva uuringu päeval. Mediaan FiO_2 oli 0.32, 8 vastsündinut olid intubeeritud ning ülejäänud mitteinvasiivsel ventialtsioonil. Kolmes primaarses tulemis ei olnud gruppide vahel vahet. Kitsama/kõrgema eesmärksaturatsiooni puhul oli parem kontroll (IQR 3.0 vs. 4.3 $p < 0.001$) *ning aeg, mil SpO_2 oli madal, 80-86%, väiksem* (6.2% vs. 8.4%, $p = 0.006$).

Hallenberger et al viisid läbi RCT, kus võrreldi automaatse SpO_2-FiO_2 kontrollsüsteemi efektiivsust arteriaalse SpO_2 säilitamisel eesmärkvahemikus võrreldes manuaalse SpO_2 kontrolliga. Tegemist on mitmekeskuse, cross-over disainiga RCT-ga, milles osales 34 enneaegset vastsünditut (invasiivsel või nCPAP ventilatsioonil koos lisaO_2-ga). Võrreldi 24 tunniseid perioode, mil SpO_2-te muudeti manuaalselt ning 24 tunniseid perioode, mil kasutati manuaalset FiO_2 kontrolli koos abistava süsteemi toetusega (suletud-linguga automaatne hapnikukontroll).

Aeg, mil saturatsioon oli eesmärkvahemikus (mediaan) oli 61.4% (31.5-99.5) manuaalse kontrolli korral ning 71.2% (44.0-95.4) automaatse süsteemi korral (p <0.001). Mediaannumber manuaalse FiO_2 reguleerimise vajaduse osas vähenes 77.0 (0.0-224.0) 52.0 (10.0-317.0) vastavalt manuaalse ning automaatse süsteemi puhul (p=0.007).

***Järeldus**: automaatne FiO_2-SpO_2 kontrollsüsteem võib parandada hapniku manustamist enneaegsetele vastsündinutele samas vähendades töökoormust, mis kaasneb manuaalse SpO_2 kontrolliga.*

Zapata et al teostasid RCT spontaanhingamisel hapnikravi saavatel enneaegsetel vastsündinutel, milles võrldesid automaatse FiO_2-SpO_2 süsteemi (Automixer algorütm) efektiivsust võrreldes manuaalse SpO_2 kontrolliga. 20 ELBW enneaegset määrati juhuslikkuse alusel Automixer gruppi või manuaalse sekkumise gruppi 12 tunniks. Eesmärl-SpO_2 oli 85-93%, tulemiteks oli ajaprotsent, mil SpO_2 oli eesmärkvahemikus, SpO_2 variaabelsus, aeg mil SpO_2 oli > 95%, manuaalsete interventsioonide arv ning saadud hapnik?.

Aeg, mil SpO_2 oli eesmärkvahemikus, oli Automixeri grupis 58+- 4% ning manuaalse interventsiooni grupis 33.7+- 4.7%; SpO_2 >95% oli 26.5% vs 54.8%, keskmine SpO_2 ja FiO_2 oli 89.8% vs 92.2% ja 37% vs 44.1%; manuaalsete interventsioonide arv 0 vs 80 (p< 0.05) vastavalt Auto-Mixeri ja manuaalse interventsiooni grupis. Lühikesi episoode, mil SpO_2 < 85%, esines enam Auto-Mixeri rühmas.

Järeldused: automaatne FiO_2-SpO_2 kontrollsüsteem suurendas aega, mil SpO_2 oli eesmärkvahemikus ning vähendas kõrge SpO_2 aega spontaanhingamisel lisaO_2-te saavatel enneaegsetel vastsündinutel.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
BACKGROUND: The optimal oxygen saturation for extremely low birth weight infants in the postnatal period beyond the delivery room is not known. **OBJECTIVES:** To summarize and discuss the results of the randomized trials, constituting the NEOPROM (Neonatal Oxygenation ProspectiveMeta-analysis) collaborative study, examining the effect of low versus high functional oxygen saturation targets in	Saugstad O, D, Aune D, Optimal Oxygenation of Extremely Low Birth Weight Infants: A Meta-Analysis and Systematic Review of the Oxygen Saturation Target Studies. Neonatology 2014;105:55-63

the postnatal period in premature infants with gestational age <28 weeks.

METHODS:

A meta-analysis of SUPPORT (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial), the three BOOST II (Benefits of Oxygen Saturation Targeting) studies and the COT (Canadian Oxygen Trial) was performed including a total of 4,911 infants randomized to either a low (85-89%) or high (91-95%) functional oxygen saturation (SpO2) within the first 24 h after birth.

Table 1. Outcome variables

Outcome variable	SUPPORT	BOOST II	COT
Primary outcome	severe ROP/death before discharge	death or severe disability 18–24 months	death before 18 months or severe neurosensory outcome
Mortality	18–22 months	before discharge	before 18 months
Severe ROP	threshold ROP, eye surgery bevacizumab treatment	treatment (ETROP)	stage 4 or 5, cryotherapy/laser/ bevacizumab
BPD	physiologic	physiologic	physiologic
NEC	stage ≥2	surgery or death	pneumatosis/free air/surgery or death
Brain injury	IVH grade 3 or 4	IVH grade 3 or 4	IVH grade 4, cystic PVL/porencephalic cyst/ventriculomegaly
Patent ductus arteriosus	any therapy	any therapy	any therapy

ETROP = Early Treatment for Retinopathy of Prematurity Cooperative Group [32].

Table 2. Basic characteristics of enrolled infants

	SUPPORT		BOOST II		COT	
	low	high	low	high	low	high
Gestational age, weeks	26 (1)	26 (1)	26.0 (1.2)	26.0 (1.2)	25.6 (1.2)	25.6 (1.2)
Birth weight, g	836 (193)	825 (193)	826 (184)	837 (189)	827 (190)	844 (199)
Antenatal steroids, %	96.8	95.6	89.6	90.7	88.2	90.0
Number	654	662	1,224	1,224	578	569

Gestational ages in BOOST UK were mean (SD) 26.0 (1.3) vs. 26.0 (1.3) in the low and high saturation groups, respectively. For BOOST AU and BOOST NZ, the numbers are 26.0 (1.2) vs. 26.0 (1.2) weeks and 26.1 (1.2) vs. 26.1 (1.2) weeks.

Birth weight in BOOST UK were mean (SD) 818 (182) and 824 (188) g in the low and high saturation groups, respectively. For BOOST AU and BOOST NZ, the numbers are 817 (177) vs. 833 (190) g and 873 (202) vs. 884 (186) g.

RESULTS:

Relative risks (RR; 95% CIs) comparing a low versus a high oxygen saturation target were 1.41 (1.14-1.74) for mortality at discharge or at follow-up, 0.74 (0.59-0.92) for severe retinopathy of prematurity, 0.95 (0.86-1.04) for physiologic bronchopulmonary dysplasia, 1.25 (1.05-1.49) for necrotizing enterocolitis, 1.02 (0.88-1.19) for brain injury, and 1.01 (0.95-1.08) for patent ductus arteriosus. RR >1.0 favors a high oxygen saturation.

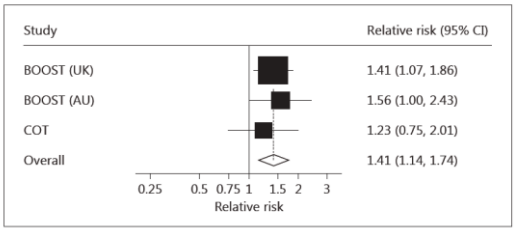


Fig. 1. Summary meta-analysis of mortality in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors a high oxygen saturation target. NEOPROM – revised algorithm. Data from revised software only.

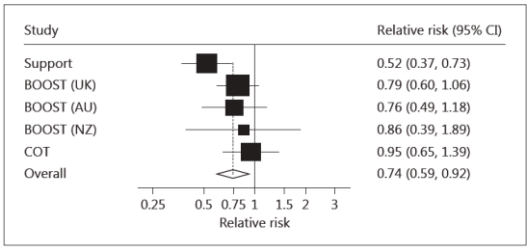


Fig. 2. Summary meta-analysis of severe ROP in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors a high oxygen saturation target.

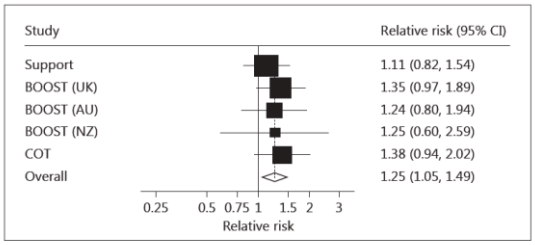


Fig. 3. Summary meta-analysis of NEC in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors a high oxygen saturation target.

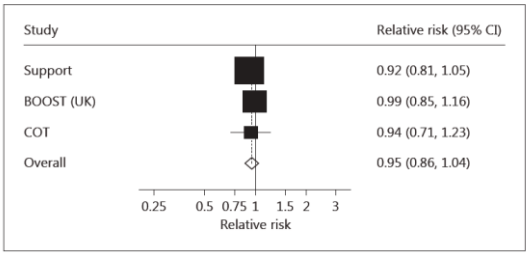


Fig. 4. Summary meta-analysis of BPD in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors high oxygen saturation target.

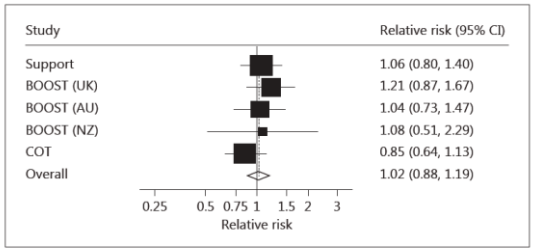


Fig. 5. Summary meta-analysis of IVH grade 2–4 brain injury in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors a high oxygen saturation target.

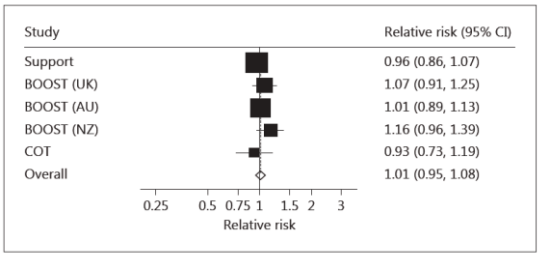


Fig. 6. Summary meta-analysis of patent ductus arteriosus in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors a high oxygen saturation target.

CONCLUSIONS:

RRs for mortality and necrotizing enterocolitis are significantly increased and severe retinopathy of prematurity significantly reduced in low compared to high oxygen saturation target infants. There are no differences regarding physiologic bronchopulmonary dysplasia, brain injury or patent ductus arteriosus between the groups. Based on these results, it is suggested that functional SpO2 should be targeted at 90-95%

ininfants with gestational age <28 weeks until 36 weeks' postmenstrual age. However, there are still several unanswered questions in this field.	
BACKGROUND: The optimal arterial oxygen saturation in the first weeks of life is unknown for immature newborn infants. **OBJECTIVES:** To determine the effect of targeting high versus low oxygen saturation in the first weeks of life on the outcome of very low andextremely low birth weight infants. **METHODS:** Randomized and observational studies were sought that compared the outcomes in babies with high or low oxygen saturation targeting assessed by pulse oximetry. **Table 1.** Characterization of the studies **RESULTS:** Ten studies were identified, of which 8 had severe retinopathy of prematurity (n = 3811) and 8 had bronchopulmonary dysplasia/lung problems (n = 4612) as outcomes. Two studies also provided survival data. The relative risk (RR) in favor of low SpO2 was 0.42 (95% CI 0.34-0.51) for severe retinopathy of prematurity, 0.73 (95% CI 0.63-0.86) for bronchopulmonary dysplasia/lung problems, and 1.12 (95% CI 0.86-1.45) for mortality. There was 1 randomized trial with retinopathy of prematurity, 3 with bronchopulmonary dysplasia/lung problems, and 1 with mortality as the outcome. When analyzing the randomized trial separately, the RR (95% CI) for severe retinopathy of prematurity was 0.48 (0.34-0.68), for bronchopulmonary dyslasia/lung problems it was 0.79 (0.64-0.97), and for mortality it was 1.27 (1.01-1.60).	Saugstad O, D, Aune D, In Search of the Optimal Oxygen Saturation for Extremely Low Birth Weight Infants: A Systematic Review and Meta-Analysis. Neonatology 2011;100:1-8

Study (first author, year)	Gestational age or birth weight	Study design	High SaO_2	Low SaO_2
2000 [22]		Randomized	96–99	89–94
Tin, 2001 [12]	<28 weeks	Observational	88–98	70–90
Sun, 2002 [24]	500–1,000 g	Survey	>95	≤95
Askie, 2003 [23]	<30 weeks	Randomized	95–98	91–94
Chow, 2003 [27]	500–1,500 g	Observational	90–98	85–93
Vanderveen, 2006 [26]	≤28 weeks or ≤1,250 g	Historical control	87–97	85–93
Deulofeut, 2006 [25]	≤1,250 g	Historical control	92–100	85–93
Noori, 2009 [20]	<1,000 g	Historical control	89–94	83–89
Tokuhiro, 2009 [28]	<33 weeks	Historical controls	92–98	88–92
SUPPORT, 2010 [16]	24–28 weeks	Randomized	91–95	85–89

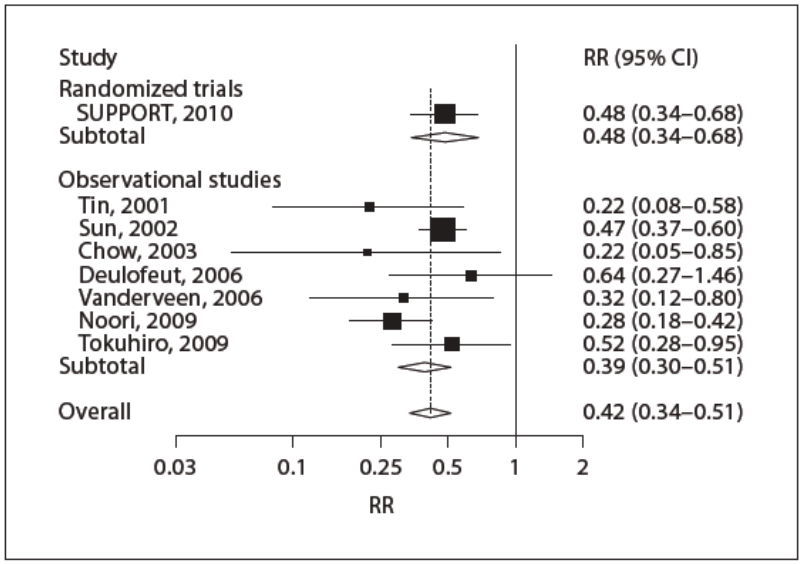


Fig. 1. RR and 95% CI for randomized studies and observational studies as well as overall in 8 studies examining the effect on ROP of high versus low SpO_2 in preterm infants. An RR <1 favors low SpO_2.

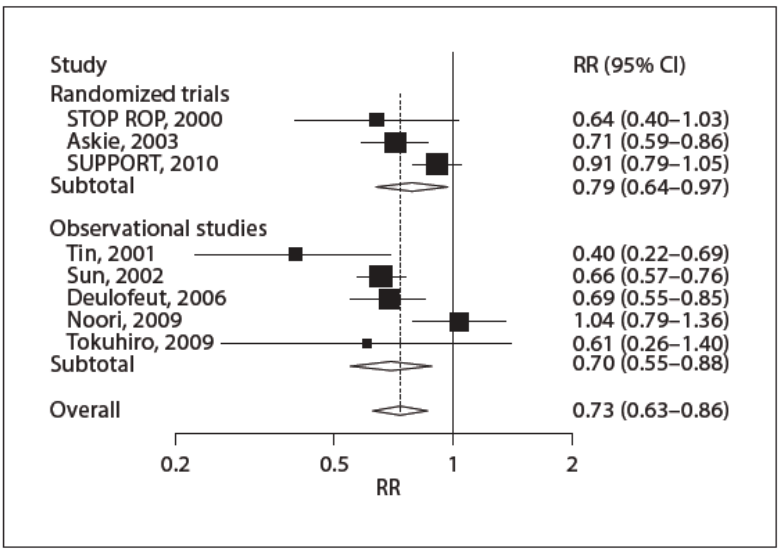


Fig. 2. RR and 95% CI for randomized studies and observational studies as well as overall in 8 studies examining the effect on BPD and/or lung problems of high versus low SpO_2 in preterm infants. An RR <1 favors low SpO_2.

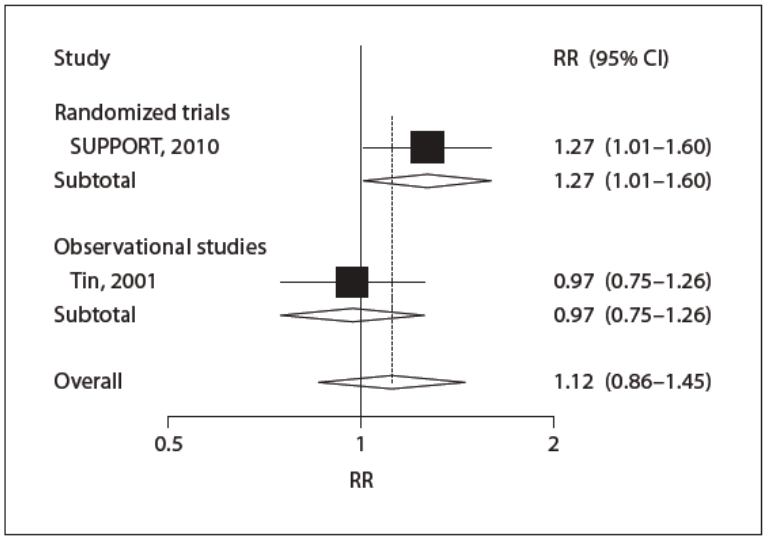


Fig. 3. RR and 95% CI for 2 studies and overall examining the effect on survival of high versus low SpO_2 in preterm infants. An RR<1 favors low SpO_2.

CONCLUSIONS:

A low oxygen saturation approach reduces severe retinopathy of prematurity by 50%, i.e., from 20.9 to 9.5%, and bronchopulmonary dysplasia/lung problems by 25%, i.e., from 40.8 to 29.7%. Further randomized trials are needed to provide definite conclusions and to assess whether reducing oxygen saturation has an impact on mortality among very and extremely low birth weight infants.

Abstract

CONTEXT:

Low oxygen saturation appears to decrease the risk of severe retinopathy of prematurity (ROP) in preterm newborns when administered during the first few weeks after birth. High oxygen saturation seems to reduce the risk at later postmenstrual ages (PMAs). However, previous clinical studies are not conclusive individually.

OBJECTIVE:

To perform a systematic review and meta-analysis to report the association between severe ROP incidence of premature infants withhigh or low target oxygen saturation measured by pulse oximetry.

METHODS:

Studies were identified through PubMed and Embase literature searches through May 2009 by using the terms "retinopathy of prematurity and oxygen" or "retinopathy of prematurity and oxygen therapy." We selected 10 publications addressing the association between severeROP and target oxygen

Chen ML, Guo L, Smith LEH, Dammann CEL, Dammann O. High or Low Oxygen Saturation and Severe Retinopathy of Prematurity: A Meta-analysis.*Pediatrics*. 2010;125(6):e1483-e1492. doi:10.1542/peds.2009-2218.

saturation measured by pulse oximetry. Using a random-effects model we calculated the summary-effect estimate. We visually inspected funnel plots to examine possible publication bias.

TABLE 1 Characteristics of Studies of Preterm Infants in Which the Association Between Low Oxygen Saturation Several Weeks Were Evaluated in the Meta-analysis

Author	Study Type	Recruitment Period	GA, wk	Birth Weight, g	*n*	Oxygen Timing and Duration	Target Saturat
Wright et al[12] (2006)	Prospective cohort	1998–2002	<30	500–1500	350	Immediate postgestation life	Low (85–9 (89–95)
Wallace et al[13] (2007)	Retrospective cohort	2002–2005	≤30	<1250	105	First 6 wk	Low (90–9 (96–10
Vanderveen et al[11] (2006)	Retrospective cohort	2000–2003	≤28	<1250	323	First 4 wk	Low (85–9 (87–97)
Tin et al[10] (2001)	Prospective cohort	1990–1994	<28	810–1074	295	First 8 wk	Low (70–9 (85–96)
Doulofaut et al[14] (2006)	Prospective cohort	2000–2004	26–27 (mean)	<1250	373	Started at birth	Low (85–9 (92–10

GA indicates gestational age; ICROP, international classification of retinopathy of prematurity.

TABLE 2 Characteristics of Studies That Evaluated the Association Between High Oxygen Saturation and Sever Infants Included in the Meta-analysis

Author	Study Type	Recruitment Period	GA, wk	Birth Weight, g	*n*	Oxygen Timing or Duration, wk	T Sa
McGregor et al[17] (2002)	Prospective cohort	1996–1999	26.2 ± 1.8 (mean)	Unknown	365	36.7 ± 2.5 (mean PMA)	High (≥
STOP-ROP group[18] (1999)	RCT	1994–1999	25.4 ± 1.5 (mean)	726 ± 160	649	35.4 ± 2 (mean PMA)	High (9
Gaynon et al[19] (1997)	Retrospective cohort	1985–1993	26–27 (mean)	814–986	153	36 to −38 + 9 to −10 (mean PMA)	High (9
Askie et al[8] (2003)	RCT	1996–2000	<30	917	358	32 + 1 to −10 (PMA)	High (9
Seiberth et al[45] (1998)	Cohort	1994–1996	24–32	Unknown	117	35–42 (PMA; ROP stage 3)	High hi

GA indicates gestational age; ICROP, international classification of retinopathy of prematurity.

RESULTS:

Low oxygen saturation (70%-96%) in the first several postnatal weeks was associated with a reduced risk of severe ROP (risk ratio [RR]: 0.48 [95% confidence interval (CI): 0.31-0.75]). High oxygen saturation (94%-99%) at > or = 32 weeks' PMA was associated with a decreased risk for progression to severe ROP (RR: 0.54 [95% CI: 0.35-0.82]).

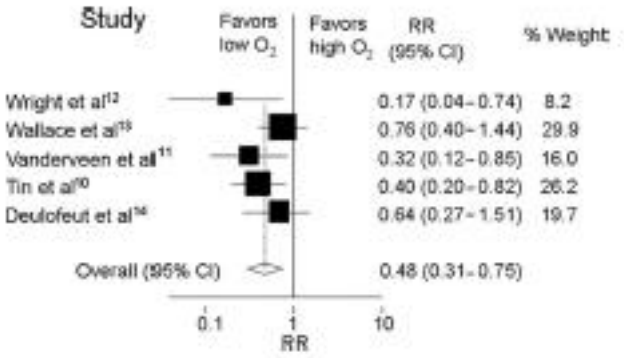


FIGURE 1
Association between low oxygen saturation (70%–99%) and risk of severe ROP during the first weeks of preterm life. The test for heterogeneity was not significant ($\chi^2 = 5.41$ [degrees of freedom = 4]; $P = .248$; $I^2 = 26\%$). The RR significantly favors low O_2 ($z = 4.17$; $P < .001$). The size of the marker corresponds to the weight of that study, and error bars represent 95% CIs.

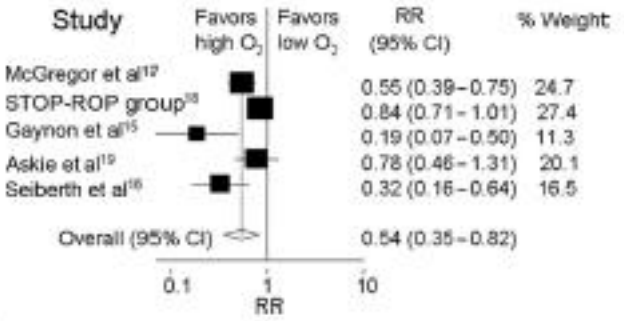
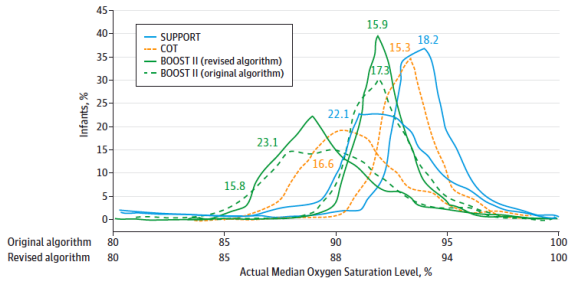


FIGURE 2
Association between high oxygen saturation (94%–99%) and risk of severe ROP at a PMA of ≥32 weeks. The test for heterogeneity was significant ($\chi^2 = 19.49$ [degrees of freedom = 4]; $P = .001$; $I^2 = 79\%$). The RR significantly favors high O_2 ($z = 5.54$; $P < .001$). The size of the marker corresponds to the weight of that study, and error bars represent 95% CIs.

CONCLUSIONS:
Among preterm infants with a gestational age of < or = 32 weeks, early low and late high oxygen saturation were associated with a reduced risk for severe ROP. We feel that a large randomized clinical trial with long-term developmental follow-up is warranted to confirm this meta-analytic result.

Importance The optimal oxygen saturation (SpO_2) target for extremely preterm infants is unknown. **Objective** To systematically review evidence evaluating the effect of restricted vs liberal oxygen exposure on morbidity and mortality in extremely preterm infants. **Data Sources** MEDLINE, PubMed, CENTRAL, and CINAHL databases from their inception to March 31, 2014, and abstracts submitted to Pediatric Academic Societies from 2000 to 2014. **Study Selection** All published randomized trials evaluating the effect of restricted (SpO_2, 85%-89%) vs liberal (SpO_2, 91%-95%) oxygen exposure in preterm infants (<28 weeks' gestation at birth).	Manja V, Lakshminrusimha S, Cook DJ. Oxygen Saturation Target Range for Extremely Preterm Infants: A Systematic Review and Meta-analysis. *JAMA Pediatr*.2015;169(4):332-340. doi:10.1001/jamapediatrics.2014.3307.

Figure 1. Distribution of Actual Median Oxygen Saturation



Distribution in the low oxygen saturation (SpO_2) (85%-89%) and high SpO_2 (91%-95%) arms in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), the Canadian Oxygen Trial (COT), and the Benefits of Oxygen Saturation Targeting II (BOOST II) trials. The mortality numbers currently available are shown as percentages (note that the 18- to 22-month mortality numbers are currently not available for the BOOST II UK and Australia trials). Because the SUPPORT and the original algorithm BOOST II data are reported using the original algorithm, corresponding SpO_2 numbers on the revised algorithm are shown as well. A saturation of 90% in the original algorithm corresponds to a saturation of 88% on the revised algorithm. This figure was adapted from Figure 4 in Lakshminrusimha et al.[19]

Data Extraction and Synthesis All meta-analyses were performed using Review Manager 5.2. The Cochrane risk-of-bias tool was used to assess study quality. The summary of the findings and the level of confidence in the estimate of effect were assessed using GRADEpro. Treatment effect was analyzed using a random-effects model.

Main Outcomes and Measures Death before hospital discharge, death or severe disability before 24 months, death before 24 months, neurodevelopmental outcomes, hearing loss, bronchopulmonary dysplasia, necrotizing enterocolitis, and severe retinopathy of prematurity.

Results Five trials were included in the final synthesis. These studies had a similar design with a prespecified composite outcome of death/disability at 18 to 24 months corrected for prematurity; however, this outcome has not been reported for 2 of the 5 trials. There was no difference in the outcome of death/disability before 24 months (risk ratio [RR], 1.02 [95% CI, 0.92-1.14]). Mortality before 24 months was not different (RR, 1.13 [95% CI, 0.97-1.33]); however, a significant increase in mortality before hospital discharge was found in the restricted oxygen group (RR, 1.18 [95% CI, 1.03-1.36]). The rates of bronchopulmonary dysplasia, neurodevelopmental outcomes, hearing loss, and retinopathy of prematurity were similar between the 2 groups. Necrotizing enterocolitis occurred more frequently in infants on restricted oxygen (RR, 1.24 [95% CI, 1.05-1.47]). Using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria, we found that the quality of evidence for these outcomes was moderate to low.

Figure 2. Mortality Associated With Restrictive or Liberal Use of Oxygen

A Death to hospital discharge

Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II trial,[15] 2013	235	1221	203	1220	65.0	1.16 (0.98-1.37)
SUPPORT II trial,[13] 2010	130	654	107	662	35.0	1.23 (0.98-1.55)
Total (95% CI)		**1875**		**1882**	**100.0**	**1.18 (1.03-1.36)**
Total events	365		310			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.17$, $df = 1$ ($P = .68$); $I^2 = 0\%$
Test for overall effect: $z = 2.39$ ($P = .02$)

B Death or severe disability before 18-24 mo

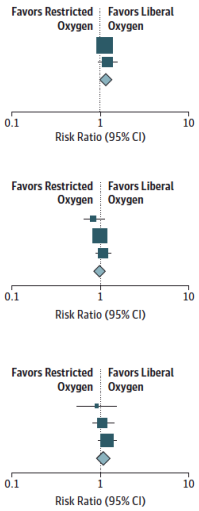
Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II-New Zealand trial,[29] 2014	65	167	76	168	15.7	0.86 (0.67-1.11)
COT,[12] 2013	298	578	283	569	54.9	1.04 (0.92-1.16)
SUPPORT,[28] 2012	185	612	171	622	29.4	1.10 (0.92-1.31)
Total (95% CI)		**1357**		**1359**	**100.0**	**1.02 (0.92-1.14)**
Total events	548		530			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.49$, $df = 2$ ($P = .29$); $I^2 = 20\%$
Test for overall effect: $z = 0.44$ ($P = .66$)

C Death before 18-24 mo

Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II-New Zealand trial,[29] 2014	25	170	27	170	10.2	0.93 (0.56-1.53)
COT,[12] 2013	97	585	88	577	36.5	1.09 (0.83-1.42)
SUPPORT,[28] 2012	140	633	118	648	53.3	1.21 (0.98-1.51)
Total (95% CI)		**1388**		**1395**	**100.0**	**1.13 (0.97-1.33)**
Total events	262		233			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.10$, $df = 2$ ($P = .58$); $I^2 = 0\%$
Test for overall effect: $z = 1.55$ ($P = .12$)



The phrase "favors liberal oxygen" means that the negative outcome is less common in that arm and vice versa. The numbers shown in this plot are raw, unadjusted values and differ from the adjusted risk ratios provided in the references. BOOST indicates Benefits of Oxygen Saturation Targeting; COT, Canadian Oxygen Trial; and SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial.

Figure 3. Morbidity Associated With Restrictive or Liberal Use of Oxygen: Bronchopulmonary Dysplasia, Necrotizing Enterocolitis, and Neurodevelopmental Outcomes

A Bronchopulmonary dysplasia at 36 wk

Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II trial,[15] 2013	160	353	172	376	33.2	0.99 (0.85-1.16)
COT,[12] 2013	164	515	171	517	27.0	0.96 (0.81-1.15)
SUPPORT,[13] 2010	205	540	237	568	39.8	0.91 (0.79-1.05)
Total (95% CI)		**1408**		**1461**	**100.0**	**0.95 (0.87-1.04)**
Total events	529		580			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.63$, $df = 2$ ($P = .73$); $I^2 = 20\%$
Test for overall effect: $z = 1.09$ ($P = .28$)

B Necrotizing enterocolitis

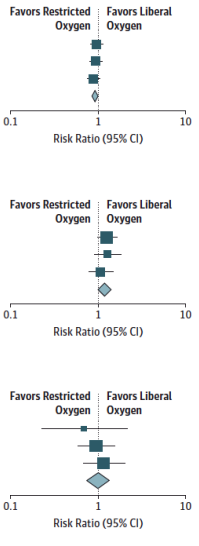
Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II trial,[15] 2013	127	1221	97	1217	44.1	1.30 (1.01-1.68)
COT,[12] 2013	74	602	56	599	26.0	1.31 (0.95-1.83)
SUPPORT,[13] 2010	76	641	70	649	29.9	1.10 (0.81-1.49)
Total (95% CI)		**2464**		**2465**	**100.0**	**1.24 (1.05-1.47)**
Total events	277		223			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.88$, $df = 2$ ($P = .65$); $I^2 = 0\%$
Test for overall effect: $z = 2.54$ ($P = .001$)

C Neurodevelopmental outcomes (GMFCS score ≥2)

Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II-New Zealand trial,[29] 2014	5	144	7	142	9.5	0.70 (0.23-2.17)
COT,[12] 2013	30	488	31	488	50.6	0.97 (0.60-1.57)
SUPPORT,[13] 2012	26	479	23	511	39.9	1.21 (0.70-2.08)
Total (95% CI)		**1111**		**1141**	**100.0**	**1.03 (0.73-1.45)**
Total events	61		61			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.82$, $df = 2$ ($P = .66$); $I^2 = 0\%$
Test for overall effect: $z = 0.14$ ($P = .89$)



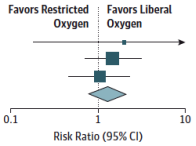
The phrase "favors liberal oxygen" means that the negative outcome is less common in that arm and vice versa. BOOST indicates Benefits of Oxygen Saturation Targeting; COT, Canadian Oxygen Trial; GMFCS, Gross Motor Function Classification System; and SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial.

Figure 4. Morbidity Associated With Restrictive or Liberal Use of Oxygen: Hearing Loss/Impairment and Retinopathy of Prematurity

A Hearing loss/impairment

Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II-New Zealand trial,[29] 2014	2	135	1	136	4.7	2.01 (0.18-21.96)
COT,[12] 2013	18	487	12	489	52.1	1.51 (0.73-3.09)
SUPPORT,[13] 2012	12	479	12	511	43.2	1.07 (0.48-2.35)
Total (95% CI)		**1101**		**1136**	**100.0**	**1.32 (0.78-2.21)**
Total events	32		25			

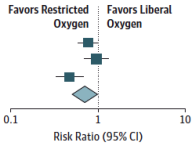
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.53$, $df = 2$ ($P = .77$); $I^2 = 0\%$
Test for overall effect: $z = 1.04$ ($P = .30$)



B Retinopathy of prematurity

Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II trial,[15] 2013	110	1035	141	1044	36.6	0.79 (0.62-0.99)
COT,[12] 2013	64	500	66	503	32.3	0.98 (0.71-1.34)
SUPPORT,[13] 2012	41	475	91	509	31.0	0.48 (0.34-0.68)
Total (95% CI)		**2010**		**2056**	**100.0**	**0.72 (0.50-1.04)**
Total events	215		298			

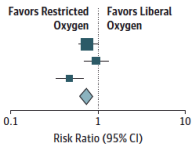
Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 8.93$, $df = 2$ ($P = .01$); $I^2 = 78\%$
Test for overall effect: $z = 1.73$ ($P = .08$)



C Retinopathy of prematurity using a fixed-effects model

Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II trial,[15] 2013	110	1035	141	1044	50.3	0.79 (0.62-0.99)
COT,[12] 2013	64	500	66	503	26.8	0.98 (0.71-1.34)
SUPPORT,[13] 2012	41	475	91	509	22.9	0.48 (0.34-0.68)
Total (95% CI)		**2010**		**2056**	**100.0**	**0.75 (0.63-0.88)**
Total events	215		298			

Heterogeneity: $\chi^2 = 8.93$, $df = 2$ ($P = .01$); $I^2 = 78\%$
Test for overall effect: $z = 3.47$ ($P = .001$)



The phrase "favors liberal oxygen" means that the negative outcome is less common in that arm and vice versa. BOOST indicates Benefits of Oxygen Saturation Targeting; COT, Canadian Oxygen Trial; and SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial.

Table. GRADE Summary of Findings of Restricted vs Liberal Oxygen Exposure for Extremely Premature Infants

Outcomes	No. of Cases per 1000 Infants: Assumed Risk of Liberal Oxygen Exposure[a]	No. of Cases per 1000 Infants: Corresponding Risk of Restricted Oxygen Exposure[a] (95% CI)	RR (95% CI)	Participants, No.	Studies, No.	Quality of Evidence[b]
Death before hospital discharge	165	194 (170-224)	1.18 (1.03-1.36)	3757	4	Low[c,d,e,f]
Death or disability at 24 mo	390	398 (367-445)	1.02 (0.94-1.14)	2716	3	Moderate[c,d]
Death before 24 mo	167	194 (164-229)	1.16 (0.98-1.37)	2783	3	Moderate[c,d]
Bronchopulmonary dysplasia	397	377 (345-413)	0.95 (0.87-1.04)	2869	5	Moderate[c,d]
Neurodevelopmental outcomes at 18-24 mo	53	55 (39-78)	1.03 (0.73-1.45)	2252	3	Moderate[c,d]
Hearing loss	22	29 (17-49)	1.32 (0.78-2.21)	2237	3	Moderate[c,d]
Necrotizing enterocolitis	90	112 (95-133)	1.24 (1.05-1.47)	4929	5	Moderate[c,d]
Retinopathy of prematurity	145	104 (72-151)	0.72 (0.5-1.04)	4066	5	Low[c,d,g]

Abbreviations: GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; RR, risk ratio; SpO_2, oxygen saturation.

[a] The basis for the assumed risk (eg, the median control group risk across studies) is provided. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] The GRADE Working Group grades of evidence are as follows: high quality (further research is very unlikely to change our confidence in the estimate of effect), moderate quality (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), and very low quality (we are very uncertain about the estimate).

[c] The pulse oximeter algorithm was modified midway through the study owing to a calibration correction, and this caused a deviation from SpO_2 values.

[d] The separation of SpO_2 values obtained was not as planned in the study design/protocol. The median SpO_2 value in the restricted arm (planned SpO_2 of 85%-89%) was higher than 90% in some studies (Figure 1).

[e] This was not a prespecified outcome in the Benefits of Oxygen Saturation Targeting II trial, which was prematurely stopped because of this outcome.

[f] Only 4 of the 5 eligible trials reported on the outcome of death before hospital discharge (the Canadian Oxygen Trial group did not).

[g] There was significant unexplained heterogeneity in this outcome, which led to downgrading the quality of evidence by 1.

Conclusions and Relevance Although infants cared for with a liberal oxygen target had significantly lower mortality before hospital discharge than infants cared for with a restricted oxygen target, the quality of evidence for this estimate of effect is low. Necrotizing enterocolitis occurred less frequently in the liberal oxygen group. We found no significant differences in death or disability at 24 months, bronchopulmonary dysplasia, retinopathy of prematurity, neurodevelopmental outcomes, or hearing loss at 24 months.

OBJECTIVE:
To assess the effect of automated adjustment of the inspired oxygen fraction (FiO2) on arterial oxygen saturation (SpO2) and cerebraltissue oxygen saturation (SctO2) in very low

Waitz M, Schmid MB, Fuchs H, Mendler MR, Dreyhaupt J, Hummelr HD. Effects of Automated Adjustment of the Inspired Oxygen on Fluctuations of Arterial and

birth weight infants with frequent fluctuations in oxygenation. **STUDY DESIGN:** Fifteen infants (median gestational age, 25 weeks [range, 23-28 weeks]; median age, 34 days [range, 19-74 days]) were assigned in random sequence to 24 hours of automated adjustment of FiO2 or manual adjustment of FiO2. Primary outcome measurements were time within the SpO2 target range and the area under the curve above and below a defined SctO2 range. **RESULTS:** Percentage of time within the SpO2 target range increased during automated FiO2 control (76.3% ± 9.2% vs 69.1% ± 8.2% for manual; P < .01). Prolonged episodes with SpO2 <88% of >60 seconds duration (median, 115 episodes [range, 67-240] vs 54 episodes [range, 7-184]; P < .01) and of >180 seconds duration (median, 13 episodes [range, 6-39] vs 2 episodes [range, 0-5]; P < .01) decreased significantly during the automatedperiod. Percentage of time with SpO2 >96% decreased during automated control (6.6% ± 4.4% vs 10.4% ± 3.3%; P < .02). There was no significant difference in FiO2 exposure. The area (deviation × time) below and above the defined SctO2 threshold did not differ between the 2 periods (median, 59.7%*seconds [range, 17.2%-208.3%] for manual vs 49.0%*seconds [range, 4.3%-193.7%] for automated; P = .36). **CONCLUSION:** Automated FiO2 control in preterm infants with frequent SpO2 fluctuations significantly increased the time within the SpO2 target range and reduced the incidence of prolonged hypoxemic events compared with manual FiO2 adjustment, but did not significantly affect cerebraltissue oxygenation.	Regional Cerebral Tissue Oxygenation in Preterm Infants with Frequent Desaturations. The Journal of Pediatrics. 2015;166(2): e240 – 244.
OBJECTIVE: To determine the efficacy and safety of automated adjustment of the fraction of inspired oxygen (FIO_2) adjustment in maintaining arterial oxygen saturation (SpO_2) within an intended range for mechanically ventilated preterm infants with frequent episodes of decreased SpO_2. **METHODS:** Thirty-two infants (gestational age [median and interquartile range]: 25 weeks [24–27 weeks]; age: 27 days [17–36 days]) were studied during 2 consecutive 24-hour periods, one with FIO_2 adjusted by clinical staff members (manual) and the other by an automated system (automated), in random sequence. **RESULTS:** Time with SpO_2 within the intended range (87%–93%) increased significantly during the automated period, compared with the manual period (40% ± 14% vs 32% ± 13% [mean ± SD]). Times with SpO_2 of >93% or >98% were significantly reduced during the automated period (21% ± 20%	Claure, N, Banclari E, D'Ugard C, Nelin L, Stein M, Ramanathan R, Hernandez R, Donn SM, Becker M, Bachman T. Multicenter Crossover Study of Automated Control of Inspired Oxygen in Ventilated Preterm Infants. Pediatrics. 2011;127(1):e76-83. doi: 10.1542/peds.2010-0939.

vs 37% ± 12% and 0.7% vs 5.6% [interquartile ranges: 0.1%–7.2% and 2.7%–11.2%], respectively). Time with SpO_2 of <87% increased significantly during the automated period (32% ± 12% vs 23% ± 9%), with more-frequent episodes with SpO_2 between 80% and 86%, whereas times with SpO_2 of <80% or <75% did not differ between periods. Hourly median FIO_2 values throughout the automated period were lower and there were substantially fewer manual FIO_2 changes (10 ± 9 vs 112 ± 59 changes per 24 hours; $P < .001$), compared with the manual period. **CONCLUSIONS:** In infants with fluctuations in SpO_2, automated FIO_2adjustment improved maintenance of the intended SpO_2 range led to reduced time with high SpO_2 and more-frequent episodes with SpO_2 between 80% and 86%.	
BACKGROUND: Managing the oxygen saturation of preterm infants to a target range has been the standard of care for a decade. Changes in target ranges have been shown to significantly impact mortality and morbidity. Selecting and implementing the optimal target range are complicated not only by issues of training, but also the realities of staffing levels and demands. The potential for automatic control is becoming a reality. Results from the evaluation of different systems have been promising and our own experience encouraging. **METHODS:** This study was conducted in two tertiary level newborn nurseries, routinely using an automated FiO2-SpO2 control system (Avea-CLiO2, Yorba Linda CA, USA). The aim of this study was to compare the performance of the system as used routinely (set control range of 87-93% SpO2), to a narrower higher range (90-93%). We employed a 12-hour cross-over design with the order of control ranges randomly assigned for each of up to three days. The primary prospectively identified end points were time in the 87-93% SpO2 target range, time at SpO2 extremes and the distribution of the SpO2 exposure. **RESULTS:** Twenty-one infants completed the study. The infants were born with a median EGA of 27 weeks and studied at a median age of 17 days and weight of 1.08 kg. Their median FiO2 was 0.32; 8 were intubated, and the rest noninvasively supported (7 positive pressure ventilation and 6 CPAP). The control in both arms was excellent, and required less than 2 manual FiO2 adjustments per day. There were no differences in the three primary endpoints. The narrower/higher set control range resulted in tighter control (IQR 3.0 vs. 4.3 $p < 0.001$), and less time with the SpO2 between 80-86 (6.2% vs. 8.4%, $p = 0.006$).	Wilinska M, Bachman T, Swietlinski J, Kostro M, Twardoch-Drozd M. Automated FiO_2-SpO_2 control system in Neonates requiring respiratory support: a comparison of a standard to a narrow SpO_2 control range. *BMC Pediatrics*. 2014;14:130. doi:10.1186/1471-2431-14-130.

CONCLUSIONS: We found that a shift in the median of the set control range of an automated FiO2-SpO2 control system had a proportional effect on the median and distribution of SpO2 exposure. We found that a dramatic narrowing of the set control range had a disproportionally smaller impact. Our study points to the potential to optimize SpO2 targeting with an automated control system.	
Closed-loop automatic oxygen control (CLAC) in preterm infants: a randomized controlled trial. Hallenberger A[1], Poets CF, Horn W, Seyfang A, Urschitz MS; CLAC Study Group. **Collaborators (9)** **Author information** **Abstract** **BACKGROUND AND OBJECTIVE:** In preterm infants receiving supplemental oxygen, routine manual control (RMC) of the fraction of inspired oxygen (FIO2) is often difficult and time consuming. We developed a system for closed-loop automatic control (CLAC) of the FIO2 and demonstrated its short-term safety and efficacy in a single-center study. The objective of this study was to test the hypothesis that this system is more effective than RMC alone in maintaining arterial oxygen saturation within target levels when evaluated over 24 hours under routine conditions and with different target levels. **METHODS:** We performed a multicenter, randomized controlled, crossover clinical trial in 34 preterm infants receiving mechanical ventilation or nasal continuous positive airway pressure and supplemental oxygen. Twenty-four-hour periods with RMC were compared with 24-hour periods of RMC supported by CLAC. **RESULTS:** The median (range) percentage of time with arterial oxygen saturation levels within target range was 61.4 (31.5-99.5) for RMC and 71.2 (44.0-95.4) for CLAC ($P < .001$). The median (range) number of manual FIO2 adjustments was reduced from 77.0 (0.0-224.0) for RMC to 52.0 (10.0-317.0) for CLAC ($P = .007$). **CONCLUSIONS:** CLAC may improve oxygen administration to preterm infants receiving mechanical ventilation or nasal continuous positive airway pressure while reducing workload related to RMC	Hallenberger A[1], Poets CF, Horn W, Seyfang A, Urschitz MS; CLAC Study Group. Closed-Loop Automatic Oxygen Control (CLAC) in Preterm Infants: A Randomized Controlled Trial. Pediatrics 2014; 133:2 e379-e385; published ahead of print January 27, 2014, doi:10.1542/peds.2013-1834
A randomised controlled trial of an automated oxygen delivery algorithm for preterm neonate s receivingsupplemental oxygen without mechanical ventilati	Zapata J, Gómez JJ, Araque Campo R, Matiz Rubio A, Sola A. A randomised controlled trial of an automated oxygen

on. Zapata J[1], Gómez JJ, Araque Campo R, Matiz Rubio A, Sola A. **Author information** **Abstract** **AIM:** Providing consistent levels of oxygen saturation (SpO2) for infants in neonatal intensive care units is not easy. This study explored how effectively the Auto-Mixer(®) algorithm automatically adjusted fraction of inspired oxygen (FiO2) levels to maintain SpO2 within an intended range in extremely low birth weight infants receiving supplemental oxygen without mechanical ventil ation. **METHODS:** Twenty extremely low birth weight infants were randomly assigned to the Auto-Mixer(®) group or the manual intervention group and studied for 12 h. The SpO2 target was 85-93%, and the outcomes were the percentage of time SpO2 was within target, SpO2 variability, SpO2 >95%, oxygen received and manual interventions. **RESULTS:** The percentage of time within intended SpO2 was 58 ± 4% in the Auto-Mixer(®) group and 33.7 ± 4.7% in the manual group, SpO2 >95% was 26.5% vs 54.8%, average SpO2 and FiO2 were 89.8% vs 92.2% and 37% vs 44.1%, and manual interventions were 0 vs 80 ($p < 0.05$). Brief periods of SpO2 < 85% occurred more frequently in the Auto-Mixer(®) group. **CONCLUSION:** The Auto-Mixer(®) effectively increased the percentage of time that SpO2 was within the intended target range and decreased the time with high SpO2 in spontaneously breathing extremely low birth weight infants receiving supplemental oxygen.	delivery algorithm for preterm neonates receiving supplemental oxygen without mechanical ventilation. *Acta Paediatrica (Oslo, Norway : 1992)*. 2014;103(9):928-933. doi:10.1111/apa.12684.

Otsingud	
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Otsingusõnad	Premature infant, premature infants, saturation range, oxymetry, oxygen saturation, supplemental oxygen (delivery room, at birth), oxygen therapy (delivery room, at birth), inspired oxygen fraction, automated FiO2-SpO2 system
Filtrid	5 years, review, systematic review, meta-analyse, randomized controlled trial, english language
Vasteid	262

Sobivaid	1 ravijuhend, 6 metaaanalüüsi, 7 artiklit

Muu leitud tõendusmaterjal:

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. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Neonatology. 2013;103(4):353-68.

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