Kliiniline küsimus nr 26

Kas enneaegsetel vastsündinutel tuleb ravitulemi parandamiseks ennetada hemodünaamiliselt oluliselt avatud arterioosjuha erinevate ravivõtetega (vedeliku piiramine, diureetikumravi, varane enteraalne toitmine, mitteinvasiivne ventilatsioon, profülaktiline NSAID) võrreldes mittesekkumisega?
NB! Millal oleks optimaalne aeg teha esimene EhhoKG uuring?

Tulemusnäitajad: lapse peamised tulemusnäitajad, avatud arterioosjuha medikamentoosse ja kirurgilise ravi vajadus, hingamistoetuse kestus.

Kokkuvõte:

Ajalistel vastsündinutel arterioosjuha konstrikteerub sünnijärgselt ning sulgub funktsionaalselt 72 tunni vanuseks. Enneaegsetel vastsündinutel sulgumine hilistub, arerioosjuha jääb avatuks 10% 30-37 GN sündinud imikutest, 80% 25-28 GN sündinud imikutest ning 90% 24 GN sündinud vastsündinutest. 7. elupäevaks need protsendid langevad vastavalt 2%, 65% ja 87%.
Avatud PDA puhul tekib "vargusfenomen" – suurem osa verest suunatakse kopsuringesse, mis võib viia kopsuturse ja hingamispuudulikkuse süvenemiseni, samas ammendub süsteemse vereringe kompensatsioonivõime ning tekib kardiaalne puudulikku ning elutähtsate organite perfusioonihäire (sool, neer, aju). Pikaajaliselt püsivat PDA-d seostatakse mitmete ebasoodsate kaugtulemitega nagu prolongeeritud mehhaanilise ventilatsiooni vajadus ja kõrgem suremus, BPD, kopsuverejooks, NEK, neerufunktsiooni häire, IVH ja periventrikulaarne leukomalaatsia, PCI. Nendest seostest tulenevalt postuleeriti, et PDA sulgemisega on võimalik vältida enneaegsusest tulenevaid komplikatsioone ning hakati laiaulatuslikult kasutama interventsioone saavutamaks PDA varajast sulgumist.
Arterioosjuha sulgub suure tõenäosusega ilma ravita >28 GN (73%) vastsündinutel sünnikaaluga > 1000 g (94%) ning 26-29 GN sündninud imikutel, kel ei ole RDS-i (93%). PDA spontaanse sulgumise protsent väiksema gestatsioonivanuse ja RDS-iga imikutel on teadmata laiaulatusliku ravimeetmete kasutamise tõttu saavutamaks PDA sulgumist. Platseebogruppide andmed randomiseeritud kontrolluuringutest näitavad, et spontaanne PDA sulgumine on sage. TIPP uuringus (Trial of Indomethacin Prophylaxis in Preterms, 2001), mis hõlmas vastsündinuid sünnikaaluga 500-999 g, 50% platseeborühmast ei kujunenud kunagi kliiniliselt PDA sümptomeid. Uuringus, kus hinnati enneaegsetel vastsündinutel 26-31 GN varajase indometatsiinravi mõju võrreldes hilise indometatsiinraviga, leiti, et lastel, kellel esines EhhoKG uuringul PDA 3. elupäeval, sulgus see hilisem interventsiooni grupis spontaanselt 9.elupäevaks 78%. (Ameerika Pediaatrite Akadeemia).
Ravi võimalused on järgnevad: profülaktiline ravi – ravitakse kõiki enneaegseid vastsündinuid, tavaliselt esimese 24 tunni jooksul peale sündi. Varajane eesmärgistatud ravi vastavalt EhhhoKG leiule (hemodünaamiliselt oluline PDA, kuid asümptomaatiline). Sümptomaatiline ravi (tavaliselt peale 72 h), aluseks hemodünaamiliselt oluline PDA EhhoKG-l ning kliinilise sümptomaatika esinemine.
Ameerika Pediaatrite Akadeemia järedab oma konsesusdokumendis, et praeguseks on olemas piisav tõenduspõhisus, mis näitab, et varajane, rutiine PDA ravi enneaegsetel vastsündinutel (medikamentoosne või kirurgiline) esimesel 2. elunädalal ei paranda pikaajalist kaugtulemit (1A).

Lähtudes leitud tõendusmaterjalist (3 ravijuhendit, 1 konsesusdokument, 5 meta-analüüsi, 5 artiklit) enneaegsetel vastsündinutel hemodünaamiliselt olulise PDA ennetamiseks:

1) Profülaktiline NSAID ravi (ibuprofeen, indometatsiin) vähendab oluliselt PDA esinemissagedust ning indometatsiini puhul ka IVH ja kopsuverejooksu esinemissagedust, kuid sellel puudub mõju kaugtulemile (suremus, BPD, psühhomotoorne areng) ning oluliste kõrvaltoimete riski (NEK, gastrointestinaalne verejooks, SIP, neerupuudulikkus) tõttu ei ole see rutiinselt näidustatud kõikidele enneaegsetele vastsündinutele. Alla 28 GN enneaegsetel võib kaaluda varajast eesmärgistatud ravi vastavalt ehhoKG leiule.
2) Diureetikumide manustamine (furosemiid, teofülliin) ei ole PDA ennetamise eesmärgil näidustatud. Furosemiidi manustamise vajadusel peaks tõsiselt kaaluma kahju ja kasu suhet, arvestades hüpovoleemia ja sümptomaatilise PDA kujunemisriski.
3) Vedelikupiiramine (eriti parenteraalse) vähendas metaanalüüsis oluliselt PDA ja NEK-i esinemissagedust ja suurendas oluliselt postnataalset kaalukadu. Vedelikupakkumine peaks siiski jääma füsioloogilistesse piiridesse, et vältida dehüdratatsiooni ja oligouuriat. 2012. a uuringus leiti, et 24 tundi peale vedelikurestriktsiooni langes oluliselt verevool alumises õõnesveenis ja ülemises mesenteriaalarteris ning diurees vähenes 60%. Puudus efekt respiratoorsetele näitajatele ja PDA olemasolule.
4) Mitteinvasiivse ventilatsiooni rolli kohta PDA ennetamiseks leiti tõendusmaterjali vähe. 2014. a avaldatud uuringus INSURE meetodi puhul (intubatsioon, surfaktant, kiire ekstubatsioon < 1 t möödumist ja nCPAP) vähenes mehhaanilise ventilatsiooni ja hapnikravi vajadus ning esines vähem PDA-d ja IVH võrreldes konventsionaalse mehhaanilise ventilatsiooni grupiga. 2007. a avaldatud meta-analüüsis, mis võrdles varajast surfaktandi manustamist ja lühiajalist ventilatsiooni selektiivse surfaktandi manustamise ja konventsionaalse ventilatsiooniga leiti, et varjane surfaktandi manustamine, ekstubatsioon ning nCPAP ravi võrrelduna hilisema selektiivse surfaktandi asenduse ning jätkuva mehhaanilise ventilatsiooniga seostub väiksema mehhaanilise ventilatsiooni vajadusega ning madalama BPD ja õhulekke sündroomide esinemissagedusega. Madalam ravi tinginud FiO2 (<0.45) annab kõige enam kasu õhulekete ja BPD vähendamise seiuskohast ning kõrge ravi alustamise tinginud FiO2 (>0.45) assotseerub kõrgenenud PDA riskiga. Need andmed viitavad, et varane surfaktantravi lühiaegse intubatsiooniga madala FIO2 (<0.45) piirväärtuse juures on eelistatum võrreldes hilisema, selektiivse surfaktantravi ja lühiaegse intubatsiooniga kõrgema FiO2 (<0.45) juures või hingamispuudulikkuse ja mehhaanilise ventilatsiooni vajaduse tekkel.
5) Varajase enteraalse toitmise kohta PDA ennetamiseks uuringuid ei leitud.

EhhoKG optimaalne ajastamine: tõendusmaterjali põhjal ei olnud ühtset seisukohta, millal peaks tegema esimese ehhoKG uuringu. Austraalias 2014. a koostatud ravijuhend soovitab teha vastsündinutel <28 GN esimese ehhoKG uuringu 3-6 tunni, kuid mitte hiljem kui 12 tunni vanuses. >28 GN vastsündinutel soovitatakse teha ehhoKG uuring vastavalt kliinilisele sümptomaatikale. Rootsi enneaegsete vastsündinute ravijuhendis soovitatakse ehhoKG teha 1-3. elupäeval.
Artiklites on soovitatud esmane ehhoKG teha 24 – 72 tunni vanuses. Kuna viimastel aastatel on metanalüüside ja randomiseeritud kontrolluuringutega näidatud, et varajane PDA ravi võrreldes hilise PDA raviga ei too kaasa olulisi tüsistusi ning ei paranda enneaegsete laste kaugtulemit, on ka seisukohti, et ehhoKG peaks teostama ainult PDA kliinilise sümptomaatika ilmnedes, et vältida PDA üleravimist.

Ravijuhendid

Avtud arterioosjuha ennetamise kohta erinevate meetmete abil leiti ajavahemikul 2010-2015 kolm ravijuhendit. I Avatud arterioosjuha teemat oli põgusalt käsitletud Euroopa RDS-i juhendis, *European Guidelines on the Management of neonatal respiratory distress syndrome in preterm infants – 2013 update, lõigus Managing Blood Pressure, Perfusion and Patent Ductus Arteriosus. Soovitused põhinevad aastatel 2007 – 2012 ilmunud tõendusmaterjalil (Cochrane'i andmebaas), millele on hinnangu andnud Euroopa neonatoloogia ekspertide konsensus*.
Antud juhend järeldab, et hetkel ei ole veenvat tõendust, et soovitada, millal ravida PDA-d, kuid tsüklooksügenaasi inhibiitorieid (indometatsiin, ibuprofeen) tuleks kaaluda, kui lapsel, keda ei õnnestu võõrutada hingamistoetusest, esineb halb perfusioon ja suur vasakult paremale šunt. Profülaktiline indometatsiini manustamine vähendab PDA ja IVH esinemissagedust, kuid kaugtulemis erisusi ei ole. Indometatsiiini ja ibuprofeeni efektiivsus on ekvivalentne, kuid ibuprofeenil võib olla vähem kõrvaltoimeid. Ka suukaudne ibuprofeen on efektiivne PDA sulgemiseks. Esineb seos kirurgilise PDA ligeerimise ning halva kaugtulemi vahel, siiski pole selge, kas see on tingitud otseselt kirurgiast või komplikatsioonidest, mis on tekkinud oodates lõikust. SOOVITUS: kui on tehtud otsus sulgemaks PDA terapeutiliselt, on indometatsiin ja ibuprofeen mõlemad võrdselt efektiivsed, kuigi ibuprofeeni puhul on vähem tõendusmaterjali NEK-i või transientse neerupuudulikkuse esinemiseks (A). If a decision is made to attempt therapeutic closure of the PDA then indomethacin or ibuprofen have been shown to be equally efficacious, although there is less evidence of transient renal failure or NEC with ibuprofen (A).
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.

II ravijuhend Austraalia Sydney ravijuhend: Management of Patent Ductus Arteriosus in Preterm Infants, M
arch 2014
PDA kõige olulisem riskifaktor on madal gestatsioonivanus. Kaasuvate riskifaktoritena tulevad arvesse antenataalse steroidikuuri puudulikkus ja mehhaanilise ventilatsiooni vajadus.

Diagnoosimine:

- **Kliiniliselt oluline PDA:** esinevad füüsilised sümptomid, mis viitavad PDA-le – kahin, aktiivne precordium, täitunud pulss. Soovitav on korrelatsioon EhhoKG-ga.
- **Sümptomaatiline PDA:** PDA olemasolu mõjutab beebi seisundit. Raskesti defineeritav, kuna kliinilised PDA-le viitavad sümptomid on mitte-septsiifilised ja ei pruugi tegelikult olla seotud PDA olemasoluga. Siia kuuluvad respiratoorsed ja vereringega seotud sümptomid nagu halvenev hingamisfunktsioon, süvenevad või korduvad apnoed, kopsuverejooks, ja hüpotensioon. Kõige spetsiifilisem sümptom on kopsuverejooks, eriti esimesel elunädalal ning juhul, kui see on seotud halveneva hingamisfunktsiooniga.
- **Hemodünaamiliselt oluline PDA:** viitab EhhoKG leiule, mis on kooskõlas suure šundivooluga. Baseerub tavaliselt PDA läbimõõdul ning indirektsetel šundivoolu mahu markeritel.

Kliinilistele sümptomitele põhinedes on võimalik diagnoosida olulist PDA-d ainult juhtudel, mis oluline vasakult paremale šunt on püsinud mitme päeva vältel. Pimendatud uuringutes, kus võrreldi PDA kliiniliste sümtomite ja UH markerite esinemist, on näidatud, et on tavapärane, et hemodünaamiliselt oluline PDA on kliiniliselt vaikne esimesed 2-3 elupäeva. Alates 4. elupäevast on kliinilised sümptomid, eriti kahina esinemine täpsemad, kuid ei pruugi olla piisavad kuni 7. elupäevani. Suur pulsirõhk ei ole samuti täpne marker olulise PDA diagnoosimiseks esimesel elunädalal.
Seega hemodünaamiliselt olulise PDA täpne ja varajane diagnoosimine sõltub varajasest EhhoKG-st.
EhhoKG PDA sümptomid:

- turbulentne diastoolne vool kopsuarteris Doppler uuringul
- šundi voolu suund pulsilaine ja värvi-Doppleriga – vasakult paremale, paremalt vasakule või bidirektsionaalne peamiselt vasakult paremale
- hemodünaamiline olulisus – värvi-Doppleril PDA kitsaim läbimõõt ning puuduv või retrograadne vool post-duktaalses aordis
    - **Suur PDA** – minimaalne PDA läbimõõt värvi-Doppleril > 2 mm, predominantselt vasakult paremale šundiga, esineb retrograadne vool alanevas aordis ning kopsuarteri verevoolukiirused on tõusnud
    - **Keskmine PDA** – minimaalne PDA läbimõõt värvi-Doppleril 1.5-2 mm, ligikaudne Q_p:Q_s> 5:1.
    - **Väike PDA** – minimaalne PDA läbimõõt alla 1.5 mm, alaneva aordi verevool on antegraadne ning vasaku kopsuarteri voolukiirused normi piires
    - Sulgunud PDA – värvi-Doppleril ei ole šundivool registreeritav
- voolukiirus vasakus pulmonaalarteris (LPA), mis peegeldab suurenenud verevoolu kopsuringesse. Keskmine LPA voolukiirus >0.42 m/s ja/või lõpp-diastoolne vool >0.2 m/s ennustab hemodünaamiliselt olulise PDA olemasolu (ligikaudne Q_p:Q_s> 2:1)

Varajane konstriktsiooni puudumine tihti püsib ning ennustab hea täpsusega hemodünaamiliselt olulise PDA kujunemist hiljem. **PDA läbimõõt 5 tunni vanuses > 1.6 mm ennustab sümptomaatilise PDA kujunemist 67% spetsiifilisuse ja 89% sensitiivsusega.**

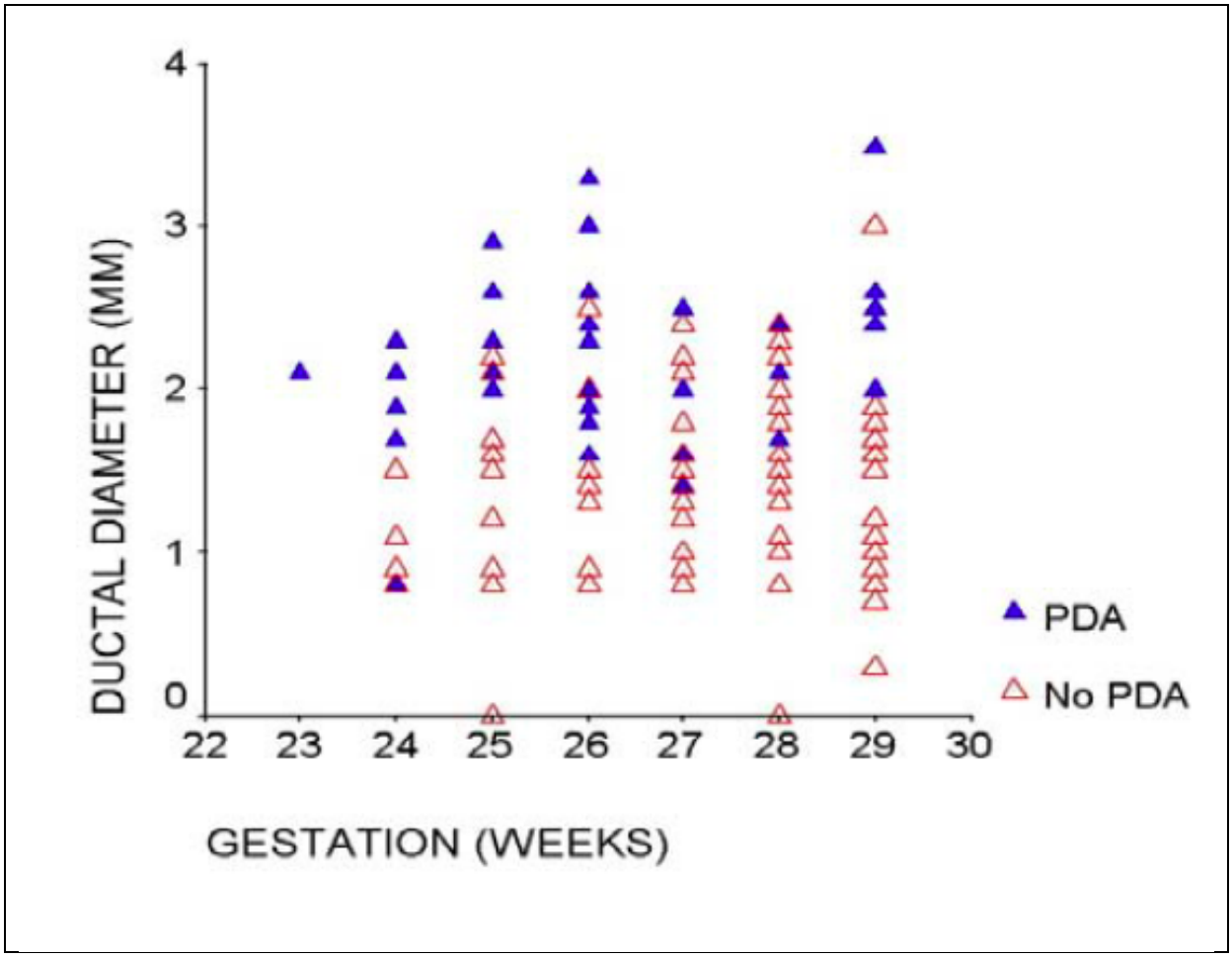
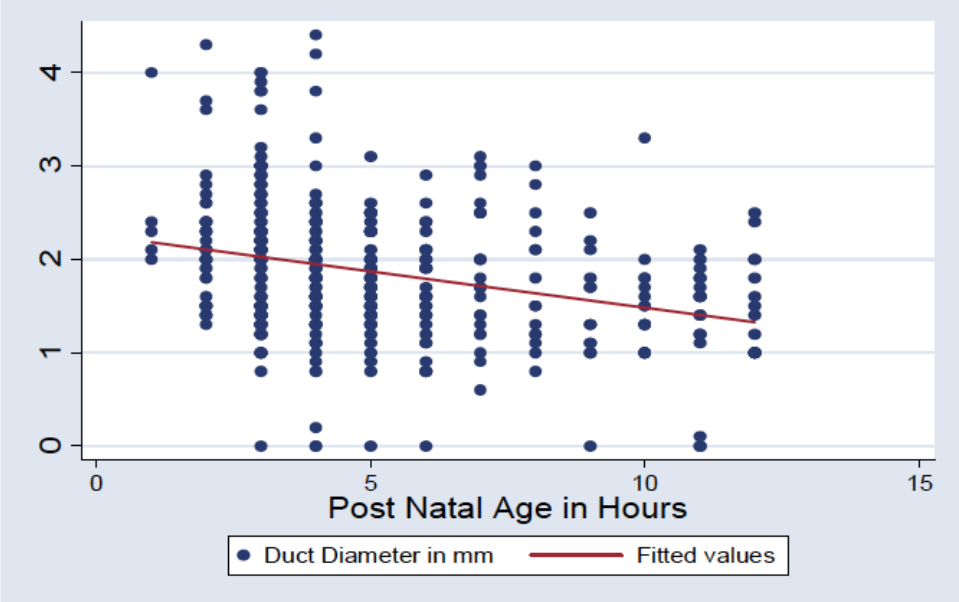

DUCTAL DIAMETER (MM)
4
3
2
1
0
22
23
24
25
26
27
28
29
30
GESTATION (WEEKS)
PDA
No PDA

Figure: Plots ductal diameter against gestation at 5 hours of age in 124 babies born befo weeks. The closed triangles label babies who later needed treatment for a clinically appa PDA.

The median diameter of the duct does vary with postnatal age. In the graph below, ductal diame plotted against postnatal age in hours in 417 babies with an average gestational age of 26 week regression line shows the impact of postnatal age on diameter.



PDA voolukõver – võib anda lisainformatsiooni lisana PDA läbimõõdule. Esineb 4 voolumustrid – pulmonaalne hüpertensioon, kasvav, pulsatiivne ja sulguv. Kliiniliselt oluline PDA progresseerus üle pulsatiivse ja kasvava voolukõvera, sulguva PDA puhul jäid need faasid vahele ning esines kohselt sulguv voolukõver.

Soovitused:

I. Vastsündinutel alla 28 GN kasutada varast EhhoKG-st lähtuvat ravi. Patofüsioloogiliselt on näidatud, et enneaegse halvasti kontrakteeruval PDA-l on varajane mõju hemodünaamikale ning suureneb IVH ja kopsuverejooksude esinemissagedus; selles grupis võib olla kasu profülaktilisest või varajasest ravist. On piisav tõenduspõhisus, et profülaktiline/varajane ravi on ohtutu ning empiiriliselt tuleks eesmärgistada varjane ravi just nendele lastele, kellel võiks olla suurim kasu varajasest PDA sulgumisest.

- Nendel lastel peaks neonatoloog teostama südame ultraheli, ideaalis 3-6 elutunni vahel, kuid enne 12 elutundi.
- Last tuleb ravida ibuprofeniga 10 mg/kg i.v või indometatsiiniga 0.2 mg/kg iv, kui on täidetud järgnevad EhhoKG kriteeriumid:
  - tegemist on strukturaalselt normaalse südamega, eriti pöörata tähelepanu aordikaarele
  - PDA läbimõõt on >/= 2 mm kitsaimast kohast (tavaliselt kopsuarteri poolt mõõdetuna)
  - On välistatud oluline pulmonaalne hüpertensioon (igasugune paremalt vasakule šunteerumine moodustab <30% südame tsüklist)
  - Kui esineb oluline pulmonaalne hüpertensioon ja PDA läbimõõduga =/> 2 mm, kaalu kordusEhhoKG uuringut 6 tunni möödudes ja ravi juhul, kui PDA läbimõõt

on endiselt suur ja šunt on enam suunaga vasakult paremale.

II Vastsündinud > 28 GN kasutada sümptomaatilist ravi.
Nendel vastsündinutel peaks jälgima olulise PDA olemasolu rutiinse kliinilise läbivaatusega ning EhhoKG tuleks teostada, kui esineb kliiniline vajadus.
Ravi on näidustatud juhul kui on täidetud 3 kriteeriumi:

- Lapsel esineb oluline PDA vastavalt kliinilistele sümptomitele
- EhhoKG kinnitab olulise šundiga suure PDA olemasolu järgmiste kriteeriumide alusel:
  - PDA läbimõõt kitsaimas kohas =/> 2 mm koos järgnevate leidudega:
    - ❖ Pöördunud diastoolne vool postduktaalses alanevas aordis
    - ❖ Kiirenenud voolukõverad vasakus pulmonaalarteris (diastoolne vool >0.2 m/sek, keskmine vool <0.45 m/sek)
    - ❖ Vasaku koja või vasaku vatsakese dilatatsioon
- Sümtomid on tõenäoliselt seotud vere šunteerumisest PDA kaudu:
  - Inotroobile resitentne hüpotensioon
  - Kopsuverejooks
  - Hingamisaparaadist võõrutamine ei õnnestu
  - Resipratoorne ebastabiilsus – süvenevad apnoed ja tõusev lisaO_2 vajadus
  - Hilised sümptomid – mittespetsiifilised, mida võiks positiivse EhhoKG leiu alusel omistada PDA-le:
    - ❖ Peristeeruv hapniksõltuvus
    - ❖ Toidutalumatus
    - ❖ Vedeliku retentsioon või teised neerupuudulikkuse sümptomid

.

Key Point	Level of Evidence
Risk of PDA increases with lower gestation, lack of antenatal steroids and hyaline membrane disease.	Level of Evidence III[3,4]
Early diagnosis requires cardiac ultrasound	Level of Evidence II[5,6]
Larger ductal diameter is associated with lower systemic blood flow in the first 12 hours after birth.	Level of Evidence II[15]
Indomethacin or Ibuprofen are the first line treatment. Consider surgery only if medical treatment has failed or is contraindicated and there are persisting cardiopulmonary symptoms that are probably due to ductal shunting.	Level of Evidence I[33] Grade of Recommendation A
Prophylactic indomethacin reduces incidence of IVH but does not improve neurodevelopmental outcomes.	Level of Evidence I[39]
Early prophylactic or targeted treatment of ducts may reduce the risk of early pulmonary haemorrhage.	Level of Evidence II[27,28] Grade of Recommendation B
If the duct has significantly constricted 24 hrs after the first dose, consideration should be given to not giving further doses.	Level of Evidence II[30] Grade of Recommendation B
Oral ibuprofen appears to be as effective. and may be more effective, as intravenous ibuprofen in babies treated after 48 hrs of age.	Level of Evidence II[42,43] Grade of Recommendation B
Oral paracetamol may be as effective as oral ibuprofen in the	Level of Evidence II[58,59]

Evans, N. **Guideline. Management of Patent Ductus Arterisosus in Preterm infants**. Health Sydney Local Health District. March 2014.
http://www.slhd.nsw.gov.au/rpa/neonatal/content/pdf/guidelines/PDA_2014_guideline.pdf

III ravijuhend – Rootsi enneaegsete ravijuhend, 2014.
Kuigi PDA on enneaegsete vastsündinute jaoks sage probleem ning võib omada lapse jaoks tõsiseid tagajärgi, on tõenduspõhisus PDA parima diagnostika ja ravi osas ebaselge. Reeglina baseerub diagnoos ehhokardiograafilisel leiul, kuid puuduvad ühtsed kriteeriumid, millal PDA muutub oluliseks ning millal seda peaks ravima. PDA ravi võib olla farmakoloogiline või kirurgiline, kuid ravi vajadus on küsitav, kuna spontaanne hiline sulgumine on suhteliselt sage.
Soovitused:
1) PDA ennetamiseks soovitatakse ravida kortikosteroididega rasedaid naisi, keda ähvardab enneaegne sünnitus, kuna lisaks kopsude ettevalmistamisele vähendab see protseduur ka olulise PDA esinemissagedust.
Kortikosteroidid vähendavad tundlikkust prostaglandiinidele, mis muidu hoiavad PDA avatuna.

2) Profülaktilist PDA sulgemist (farmakoloogilist või kirurgilist) ei soovitata.
Profülaktiline farmakoloogiline PDA sulgemine küll vähendab hemodünaamiliselt olulise PDA esinemissagedust ja vajadust kirurgilise ravi järele, kuid kõrvaltoimete risk on liiga suur, et seda rutiinselt soovitada. Uuringutes ei ole näidatud, et profülaktiline ravi omaks pikaajalist efekti suremusele või psühhomotoorsele arengule.
Nabaväädi hiline läbilõikamine (30-120 sekundit peale sündi) ning varajane CPAP ravi hõlbustavad vereringe adapteerumist sünnil ning vähendavad PDA-ga seotud haigestumist.

3) EhhoKG: Rootsi ravijuhendis soovitatakse esmane EhhoKG uuring teostada kõikidele enneaegsetele vastsündinutele 1-3 elupäeva jooksul. Tegemist on konsesusliku soovitusega.
Kliiniline leid ning röntgenpildid võivad olla olulised PDA diagnoosimises ning hindamises, näiteks kahinad südamel, nõrgad perifeersed pulsid, madal diastoolne vererõhk.
Ehhokardiograafiline hindamine nõuab hästi kvalitfitseeritud ning kogenud uuringuteostajat. Šundi suurus sõltub arterioosjuha laiusest, samuti rõhu ja resistentsuste näitajatest pulmonaalses ja süsteemses ringes. Uuringu teostamise tingimused on sageli halvad, kuna ehhoKG aken on väga limiteeritud. Alati tuleb enne PDA sulgemist välistada ductus-sõltuvad kongenitaalsed südamerikked.
Kuigi on avaldatud palju selleteemalisi uuringuid, tugev teaduslik põhjendus või konsensus diagnoosikriteeriumite osas puudub.
Hemodünaamiliselt olulisele PDA-le viitavad järgmised märgid:

- PDA läbimõõt > 1.5 mm
- Vasema koja laienemine, selle hindamiseks tuleb mõõta vasaku koja diameeter (LA) ja aordijuur (Ao). LA/Ao suhe üle 1.5 on iseloomulik olulisele šundile, väärtus üle 2 viitab väga suurele šundile.
- Lapsel esinen madal või retrograadme diastoolne verevool alanevas aordis, mesenteriaalarterites või tserebraalarteris (tugev märk)
- Kopsuarteri harudes esineb diastoolne edasivool. Lõppdiastoolne voolukiirus >0.2 m/s viitab olulisele PDA-le, voolukiirus >0.5 m/s viitab väga suurele šundile.

PDA varajast ravi tuleks kaaluda ühe või mitme ehhokardiograafilise kriteeriumi ja kliiniliste PDA sümptomite koosesinemisel. Hemodünaamiliselt olulise PDA esmavaliku raviks on farmakoloogiline ravi ibuprofeeniga. Kirurgilist ravi tuleks kasutada säästlikult ning see tuleb kõne alla, kui farmakoloogiline ravi ebaõnnestub või on vastunäidustatud. (Teadusallikad ning konsensus)

CPAP ravi efekt hemodünaamiliselt olulise PDA ennetamiseks/raviks on madala teaduspõhisusega. Mõnes vaatlusuuringus on olnud vedeliku restriktsioonil efekt PDA ennetamises ning seda võib kaaluda, kui õnnestub tagada adekvaatne toitmine. Lingudiureetikumid võivad häirida PDA sulgumist ning neid ravimeid tuleks kasutada vaid lastel, kel esineb hüpervoleemia kopsuvereringes ja teised ägeda südamepuudulikkuse tunnused. Vereülekanne ei kergenda PDA sulgumist ning sellel eesmärgil ei ole see näidustatud.

The Swedish National Board of Health and Wlefare. Care of extremely premature infants
A guideline for the care of children born before 28 full weeks of pregnancy have passed.
Published www.socialstyrelsen.se, September 2014

Süstemaatilised ülevaated

Avatud arterioosjuha ennetamise kohta erinevate ravivõtete abil (vedeliku restriktsioon, diureetikumravi, profülaktiline indometatsiin, profülaktiline ibuprofeen, mitte-invasiivne ventilatsioon) leiti ajavahemikul 2010 – 2015 5 meta-analüüsi.

I Sütemaatiline ülevaade: Bell EF ja Acarregui MJ avaldasid 2014.a süstemaatilise ülevaate, kus analüüsiti piiratud vedelikupakkumise mõju võrreldes liberaalse vedelikupakkumisega suremusele ja haigestumisele enneaegsetel vastsündinutel <37 GN. Teostati otsingud andmebaasides MEDLINE (Pubmed), CINAHL, EMBASE ja CENTRAL (Cochrane Library) kuni aastani 2014. Uuringutesse kaasati 5 randomiseeritud kontrolluuringut (Bell 1980, Kavvadia 2000, Lorenz 1982, Tammela 1992, von Stockhausen 1980), kus osalesid 582 enneaegset vastsündinut, kõik uuringud võrdlesid kahte uuringugruppi, kellest üks sai liberaalse vedelikupakkumise (standart ehk kontrollgrupp) ning teine piiratud vedelikupakkumise. Peamine erisus uuringute vahel oli ajastus ning periood, mille vältel vedelikupakkumine oli määratud uuringuprotokolli poolt. Tulemiteks oli kaalulangus, dehüdratatsioon, avatud PDA, NEK, BPD, IVH, surm. Analüüsi tulemusena leiti, et piiratud vedelikupakkumine suurendas oluliselt postnataalselt kaalukadu ning vähendas olulilselt PDA ja NEK-i riski. Piiratud vedelikupakkumise puhul oli trend dehüdratatsiooni tekkeks ning esines vähem BPD-d, IVH-d ja surma, kuid need muutused ei olnud statistiliselt olulised. Kuna uuringupopulatsioonis oli ELBW vastsündnite osakaal madal, tuleks olla ettevaatlik nende tulemuste ekstrapoleerimisel sellele populatsioonile. Vajalikud on edaspidised uuringud, mis defineeriksid kriitilise perioodi, mille vältel vedelikupakkumine peaks olema kontrollitud, et vältida enneaegsusest tulenevaid komplikatsioone. Väärtuslikud oleksid mudelid, mis võtaksid arvesse vedelikuvajaduse olulisi determinante nagu sünnikaal, gestatsioonivanus, postnataalne vanus ja õhuniiskus, määramaks liberaalset või piiratud vedelikupakkumist suremuse ja haigestumise vähendamiseks enneaegsetel vastsündinutel. Uued uuringud peaksid hõlmama kõige rohkem mõjutatud ELBW vastsündinute populatsiooni.

II Sütemaatiline ülevaade: 2011 a, Stewart A et al. Ülevaate eesmärgiks oli hinnata diureetikumide manustamisega seotud riske ja kasutegureid respiratoorse distressiga

enneaegsetel vastsündinutel. Analüüsi kaasati uuringud, kus RDS-iga enneaegsed vastsündinud randomiseeriti enne 5. elupäeva diureetikumide manustamise rühma või kontrollgruppi, kokku 250 vastsündinut. Kaasati ainult uuringud, milles hinnati vähemalt ühte järgnevaist tulemitest: suremus, PDA, hüpovoleemiline šokk, IVH, neerupuudulikkus, hapnikravi kestvus, mehhanilise ventilatsiooni kestvus, lisaO2 vajadus 28 elupäeval, lisaO2 vajadus postmenstruaalvanuses 36 nädalat, hospitaliseerimise kestvus, rehospitaliseerimiste arv esimesel eluaastal, psühhomotoorne areng. Kriteeriumitele vastas 7 uuringut (Belik 1987, Cattarelli 2006, Green 1983, Green 1988, Marks 1978, Savage 1975, Yeh 1984), 6 neist viidi läbi enne prenataalsete steroidide, surfaktandi ja vedelikurestriktsiooni ajastut.

Leiti, et furosemiidi manustamisel ei olnud pikaajalisi kasulikke mõjusid. Furosemiidi manustamisest tingitud lühiajaline kopsufunktsiooni paranemine ei kaalunud üles kõrgenenud PDA ja ebastabiilse hemodünaamika riski. Teofülliinil ei leitud ühes hiljutises uuringus pikaajalist kasulikku efekti. Teofülliin vähendas oluliselt oligoanuuria riski ja parandas lühiajaliselt ebapüsivalt neerufunktsiooni, kuid ei mõjutanud oluliselt neerufunktsiooni kojukirjutamisel või teisi hinnatud tulemeid.

Järeldused: ei ole andmeid, mis toetaksid rutiinset furosemiidi manustamist enneaegsetele RDS-iga vastsündinutele. Elektiivset furosemiidi manustamist RDS-iga patsiendile tuleks väga hoolikalt kaaluda, võttes arvesse hüpovoleemia tekkeriski ning võimalust sümptomaatilise PDA tekkeks. Ei ole piisavalt andmeid, et toetada rutiinset madalas doosis teofülliiini manustamist RDS-iga enneaegsetele vastsündinutele.

III süstemaatiline ülevaade: 2011. a Ohlsson A, Shah SS – ibuprofeen PDA ennetamiseks võrreldes platseebo/mitte-sekkumisega enneaegsetel ja/või madala sünnikaaluga vastsündinutel. Uuringu primaarseks eesmärgiks oli hinnata profülaktilise ibuprofeeni efektiivsust ja ohutust võrreldes platseebo/mittesekkumisega või teiste tsüklooksügenaasi inhibiitoritega (COX) PDA ennetamiseks enneaegsetel vastsündinutel. Sekundaarseks eesmärgiks oli teostada subgrupi analüüsid seoses ibuprofeeni doosiga, manustamisviisiga (i.v või p.o), gestatsioonivanusega (<28 GN, 28-32 GN, 33-37 GN), sünnikaaluga (<100g, 1000-1500, >1500 - <2500g), PDA diagnoosimise meetod (kliinilised kriteerimuid või ehhoKG). Ülevaatesse kaasati randmomiseeritud või kvasirandomiseeritud kontrolluuringud, mis võrdlesid ibuprofeeni platseebo/mitte-sekkumisega või teiste tsüklooksügenaasi inhibeerivate ravimitega seisuga detsember 2010. Tulemiteks olid PDA olemasolu 3.elupäeval, vajadus kirurgilise ligeerimise järele või hädaabi ravi tsüklooksügenaasi inhibiitoritega, suremus, IVH, renaalsed, pulmonaalsed ja gastrointestinaalsed komplikatsioonid.

Ülevaatesse kaasati 7 uuringut (Van Overmeire 2004; Dani 2000; DeCarolis 2000; Gournay 2004; Dani 2005; Sangtawesin 2006; Sangtawesin 2008), milles kokku osales 931 enneaegset vastsündinut. Ibuprofeeni doos ja profülaktika kestvus olid sarnased kõigis uuringutes, vanus alustamise hetkel varieerus 2 tunnist 24 tunnini.

Ibuprofeen vähendas PDA esinemissagedus 3.elupäeval (RR 0.36, (95% CI 0.29-0.46); RD -0.27 (95%CI -0.32- -0.21); NNT 4 (95% CI 3-5)), vähendas vajadust hädaabieaviks COX inhibiitoritega ning vähendas kirurgilise ligatsiooni vajadust. Tulemused kahes oraalset ibuprofeeni kasutanud uuringus oli sarnased, kuid näitasid kõrgenenud riski gastrointestinaalse verejooksu tekkeks (NNH 4, 95% CI 2 – 17). Kontrollgrupis oli sopntaanne PDA sulgumise sagedus 58% kolmandaks elupäevaks. Ibuprofeen mõjutab negatiivselt neerufunktsiooni. Ei olnud olulisi erinevusi suremuses, IVH ja kroonilise kopsuhaiguse esinemissageduse osas.

Järeldused: Profülaktiline ibuprofeeni manustamine vähedas PDA esinemissagedust, vähendas vajadust hädaabi ravi järele COX-inhibiitoritega ja vähendas kirurgilise sekkumise vajadust. Kontrollgrupis sulgus PDA spontaanselt 3.elupäevaks 58% vastsündinutest. Profülaktiline ibuprofeeni manustamine eksponeerib paljusid imikuid ravimile, millele on muret tekitavad renaalsed ja grastointestinaalsed kõrvaltoimed, toomata kaasa olulisi lühiajalisi kasutegureid, mistõttu antud ülevaate autorid seda kasutada ei soovita. Ibuprofeeni rühmas oli tõusnud risk kreatiniini tõusuks ning kõrgenenud oligouuria risk. Suukaudse ibuprofeeni manustamisega kaasnes oluline gastrointesinaalse verejooksu tekkerisk. Rühmade vahel ei olnud olulisi erisusi suremuses, NEK-i, kroonilise kopsuhaiguse, III või IV astme IVH esinemissageduses ning ajas, mil saavutati täisenteraalne toitmine. Ühes ülevaatesse kaasatud uuringus seostati profülaktilist ibuprofeeni raske pulmonaalhüpertensiooni tekkega kolmel vastsündinul.

Käesolev tõenudsmaterjal ei toeta profülaktilise ibuprofeeni manustamist PDA ennetamiseks. Kuni ei ole avaldatud ülevaatesse kaasatud uuringute pikaajalise follow-up-i tulemusi, ei soovitata läbi viia uusi uuringuid profülaktilise ibuprofeeniga.

IV Süstemaatiline ülevaade: Fowlie PW et al, 2010.a: Profülaktiline indometatsiin vähendamaks suremust ja haigestumist enneaegsetel vastsündinutel. Ülevaate eesmärgiks oli määrata kindlaks indometatsiini efekt enneaegsete vastsündinute (<37GN) suremusele ja haigestumisele. Uuringud teostati andmebaasides vastavalt Cochrane Neonatal Review Group otsingute strateegiale kuni aprillini 2010, ülevaatesse kaasati randomisseritud või kvasirandomiseeritud kontrolluuringud, mis võrdlesid profülaktilist indometatsiini platseebo või mitte-sekkumisega enneaegsetel vastsündinutel.

Primaarsed tulemid: suremus enne kojukirjutamist ja enne viimast arstivisiiti; psühhomotoorne areng. Sekundaarsed tulemid: PDA esinemine ja vajadus kirurgilise sulgemise järgi; IVH, kopsu-, neeru- ja gastrointestinaalsete komplikatsioonide ning hemostaasihäirete ja ROP-i esinemissaegdus.

Leiti 19 kriteeriumitele vastavat uuringut, millesse oli kaasatud 2872 imikut, neist enamus olid VLBW vastsündinud, suurimas kaasatud uuringus osalesid vaid ELBW vastsündinud (TIPP 2001, n=1202). Uuringud olid üldiselt hea kvaliteediga. Sümptomaatilise PDA esinemissagedus (RR 0.44, 95%CI 0.38-0.50) ja kirurgiline PDA ligatsiooni esinemissagedus (RR 0.51, 95%CI 0.37-0.71) oli statistiliselt oluliselt madalam ravi saanud imikutel. Profülaktilise indometatsiin vähendas oluliselt tõsise (III ja IV aste) IVH esinemissagedust (RR 0.66, 95% CI 0.53-0.82). Metaanalüüsil ei leitud erinevust suremuses (RR 0.96, 95% VI 0.81-1.12) või komposiittulemis surm või tõsine psühhomotoorse arengu puue 18-36 kuu vanuses (RR 1.02, 95%CI 0.90-1.15).

Järeldused: profülaktilisel indometatsiini manustamisel enneaegsetele vastsündinutele on lühiaegsed kasutegurid nagu sümptomaatilise PDA esinemisageduse, PDA kirurgilise ravi vajaduse ning tõsise IVH esinemissageduse vähenemine. Siiski, ei ole tõendust, et sel oleks efekti suremusele või psühhomotoorsele arengule.

Praktiline väärtus: arvestades, et tõendus on puudulik pikaajalise efektiivuse osas kaugtulemile, sõltub otsus kasutada profülaktilist indometatsiini sellest, kui suure väärtuse omistavad raviarst ja lapsevanemad lühiaegsele kasulikule efektile. Profülaktilise indometatsiin võib osutada kasulikumaks vastsündinute osakondades, kus EhhoKG ja kirurgiline ravi ei ole hea kättesaadavusega.

Edasised randomiseeritud kontrolluuringud antud teemal ei ole prioriteet. Uuringutes osalenud laste kaugtulemi hindamise jätkamine on õigustatud, kuna psühhomotoorse arengu erisused võivad ilmneda koolieas või varases täiskasvanueas.

V metaanalüüs, 2007. a, Stevens TP et al – varajane surfaktandi manustamine lühiaegse ventilatsiooniga versus selektiivne surfaktandi manustamine ning jätkuv kopsude mehhaaniline ventilatsioon RDS-i riskiga enneaegsetel vastsündinutel. Antud ülevaates võrreldei profülaktilise/varajase surfaktandi manustamist ja kiiret ekstubatsiooni (mehhaaniline ventilatsioon < 1 tunni) hilisema surfaktandi manustamise ning jätkuva mehhaanilise ventilatsiooniga. Varajase surfaktandi manustamise gruppi määrati vastsündinud, kes said surfaktanti enne, kui vajasid intubatsiooni hingamispuudulikkuse tõttu ning kõrge RDS-i riskiga vastsündinud (surfaktanti manustatakse prodülaktiliselt 15 min jooksul peale sündi). Otsingud teostati andmebaasides vastavalt Cochrane'i kriteeriumitele seisuga detember 2006, ülevaatesse kaasati randomiseeritud või kvasirandomiseeritud kontrolluuringud mis võrdlesid kahte eelpoolmainutud strateegiat. Tulemid: mehhaanilise ventilatsiooni esinemissagedus (>1h), BPD, kroonilise kopsuhaiguse esinemissagedus, suremus, mehhaanilise ventilatsiooni, hopitaliseerimise, hapnikravi ja hingamistoetuse (k.a CPAP ja ninakanüül) kestvus, surfaktanti saanud patsientide arv, surfaktandi dooside arv ühe patsiendi kohta, õhulekke sündroomide, ravi vajava PDA, kopsuverejooksude ja teiste enneaegsuse komplikatsioonide arv. Stratifitseeritud analüüs teostati vastavalt FiO_2 väärtusele, mis tingis varase intubatsiooni ja surfaktandi manustamise ravigrupis: madalam FiO2 <0.45 või kõrge FiO2 >0.45 uuringusse värbamise hetkel.

Kriteeriumitele vastas 6 randomiseeritud kontrolluuringut (Verder 1994, NICHD 2002, Vermont Oxford 2003, Dani 2004, Texas Research Group 2004, Reininger 2005), uuringutes osales 663 enneaegset vastsündinut <37 GN. RDS-i sümptomitega imikutel, kelle puhul intubatsioonile ja surfaktandi manustamisele järgnes ekstubatsioon ja nCPAP ravi esines väiksem mehhaanilise ventilatsiooni vajadus (RR 0.67, 95% CI 0.57,0.79), vähem õhulekke sündroome (RR 0.52, 95%CI 0.28, 0.96) ja BPD-d (RR 0.51, 95%CI 0.26,0.99) võrreldes hilisema selektiivse surfaktandi manustamisega. Varase surfaktandi grupis sai suurem proportsioon lapsi surfaktanti võrreldes selektiivse surfaktandi manustamisega (RR 1.62, 95%CI 1.41,1.86). Surfaktandi dooside arv oli oluliselt suurem varajase surfaktandi grupis (WMD 0.57 doosi patsiendi kohta, 95%CI 0.44, 0.69). FiO_2 järgi stratifiseeritud analüüsis madalama FiO_2 (<0.45) grupis ravi alustamise hetkel esines väiksem õhulekete (RR 0.46, 95%CI 0.23,0.93) ja BPD (RR 0.43, 95%CI 0.20, 0,92) esinemissagedus. **Kõrge FiO_2 (>0.45) grupis ravi alustamise hetkel esines enam ravi vajavat PDA-d (RR 2.15, 95%CI 1.09,4.13).**

Järeldused: varjane surfaktandi manustamine, ekstubatsioon ning nCPAP ravi võrrelduna hilisema selektiivse surfaktandi asenduse ning jätkuva mehhaanilise ventilatsiooniga seostub väiksema mehhaanilise ventilatsiooni vajadusega, madalama BPD ja õhulekke sündroomide esinemissagedusega. Madalam ravi tinginud FiO_2 (<0.45) annab kõige enam kasu õhulekete ja BPD vähendamise seiuskohast ning kõrge ravi alustamise tinginud FiO_2 (>0.45) assotseerub kõrgenenud PDA riskiga. Need andmed viitavad, et varajane surfaktantravi lühiaegse intubatsiooniga madala FIO_2 (<0.45) piirväärtusega on eelistatum selektiivse surfaktantravi ning mehhaanilise ventilatsiooni alustamise ees kõrgema FiO_2 (<0.45) läviväärtuse saavutamisel või hingamispuudulikkuse tekkel.

Muud uuringud

Mitteinvasiivne ventilatsioon – ajavahemikul 2010-2015 leiti 1 randomiseeritud uuring mitteinvasiivse ventilatsiooni mõju kohta avatud PDA-le enneaegsetel vastsündinutel. Nayeri EA et al. avaldasid 2014. a artikli, kus võrdlesid konvetsionaalse ventilatsiooni ja INSURE (intubatsioon, surfaktandi manustamine ja ekstubatsioon) meetodi mõju RDS-iga enneaegsetele vastsündinutele (<35 GN). Uuringusse kaasati kõik RDS-i sümptomaatikaga enneaegsed vastsündinu (n=42) <=35 GN, kes hopitaliseeriti Valiasr haigla NICU-sse. Patsiendid jagati juhuslikkuse alusel konventsionaalse mehhaanilise ventilatsiooni ja INSURE rühma. Esimese rühma lastele manustati surfaktanti ning jätkati pikaajalise konventsionaalse mehhaanilise ventilatsiooniga. Teise rühma imikutele (INSURE) manustati surfaktanti, neid ventileeriti lühiajaliselt mehhaaniliselt ning seejärel ekstubeeriti ning jätkati nCPAP-iga. Hinnati mehaanilise ventilatsiooni ja hapnikravi kestvust, IVH, PDA, õhulekke sündroomide ja BPD esinemissagedust ning suremust. Vajadus mehhaanilise ventilatsiooni järele 5. hospitaliseerimise päeval langes INSURE rühmas 43 % (p=0.005) võrreldes konventsionaalse mehhaanilise ventilatsiooni grupiga. Samuti saavutati vähenes oluliselt IVH ja PDA esinemissagedus (p=0.01). Pneumotooraksi (p=0.25), kroonilise kopsuhaiguse (p=0.14) esinemissageduses ja suremuses (p=0.25) olulisi erisusi kahe grupi vahel ei leitud.
Järeldati, et INSURE meetod RDS-i ravis vähendab enneaegsetel vastsündinutel mehhaanilise ventilatsiooni ja hapnikravi vajadust, samuti oli vähenenud oluliste tüsitsuste, IVH ja PDA esinemissagedus. Seega tundub ratsionaalne kasutada INSURE meetodit esmase ravivõttena kerge kuni mõõduka RDS-i ravis.

Vedeliku restriktsioon PDA ennetamiseks: leiti 1 prospektiivne mitmekeskuse jälgimisuuring (De Buyst et al, 2012), mille eesmärgiks oli hinnata olulise PDA-ga enneaegsetel vastsündinutel vedelikurestriktsiooni mõju hemodünaamikale. Uuringusse kaasati 18 enneaegset vastsündinut >= 24 GN ja < 32 GN (kesmine 24.8 +/- 1.1 nädalat, sünnikaal 850 +/- 180 g, postnataalne vanus esmasel EhhoKG-l 26.5 +/- 1.3 GN), kellel oli eelnevalt diagnoositud oluline PDA. 8 vastsündinut oli kopsude mehhanilisel ventilatsioonil, ülejäänud said hingamistoetust nCPAP-iga. Vasopressoreid või inotroope ei kasutatud. Salvestati hemodünaamilised ja Doppler ehhokardiograafilised muutujad enne ja 24 tundi peale vedelikurestriktsiooni. Vedelikupakkumist vähendati 145 +/- 15 ml/kg/die 108 +/- 10 ml/kg/die. Respiratoorsed muutujad, FiO_2, veregaasi väärtused, PDA diameeter, verevoolu kiirused PDA-s, vasakus pulmonaalarteris ja ülanevas aordis ja vasaku koja/aordijuure suhe ei muutunud peale vedeliku restriktsiooni. Kuigi süsteemne vererõhk ei muutunud, vähenes verevool ülemises õõnesveenis 105 +/- 40 ml/kg/min 61 +/- 25 ml/kg/min (p<0.001). Diurees vähenes 60% peale vedelikurestriktsiooni (p<0.05). Keskmine verevoolukiirus ülemises mesenteriaalarteris oli 24 tundi peale vedelikurestriktsiooni algust madalam. Järeldati, et uuringutulemused ei kinnita hüpoteesi, et enneaegsetel vastsündinutel on vedelikurestriktsiooni puhul positiivne efekt pulmonaalsele või süsteemsele hemodünaamikale.

<u>EhhoKG, optimaalne ajastus</u> – optimaalne aeg esmase ehhoKG teostamiseks on teadamata. Lisasin 3 RCT-d, mis on avaldatud ajavahemikul 2010-2015.
DeMauro et al viisid läbi 2 keskuse RCT </1250 g vastsündinutel < 30 GN, mille eesmärgiks oli hinnata, kas rutiinne ehhoKG teostamine tõstab PDA diagnoosimist ning suurendab PDA ravimist. Viidi läbi ehhoKG uuringud 3-5. ja 7-10. elupäeval. 88 vastsündinut randomiseeriti kahte gruppi – esimeses oli raviarst teadlik ehhoKG tulemustest, teises grupis raviarst ehhoKG tulemusi ei teadnud ning need avaldati vaid juhul, kui oli alust kliiniliste sümptomite alusel kahtlustada PDA olemasolu. Primaarseks tulemiks oli sünnikaalu saavutamine. I grupis oli raviarst 100% teadlik ehhoKG tulemustest, II grupis 16% juhtudes I ehhoKG ning 29% II

ehhoKG puhul. Leiti statistliselt ebaoluline farmakoloogilise PDA sulgemise vähenemine II vastsündinute grupis. Sünnikaalu saavutamises või teistes olulistes neonataalsetes tulemites erisusi ei olnud. II grupi vastsündinutel esines suurema tõenäosusega füsioloogiline kaalulangus ja nad saavutasid suurema tõenäosusega sünnikaalu 7-14 elupäeva jooksul. Järeldati, et rutiinse EhhoKg mitte-teostamine võib vähenda farmakoloogilist PDA sulgemist ilma oluliste tüsistusteta.

Thankhavel et al näitasid 2013. a avaldatud RCT-s, et 72 tunni vanuses ehhoKG-l mõõdetud PDA:LPA suhte alusel on võimalik ennustada PDA sulgusmist <30GN enneaegsetel vastsündinutel.

EPIPAGE-2 uuringugrupp uuris skriining-ehhoKG müju haiglasisest suremust 1513 enneaegsel (>29GN) vastsündinul, kes olid hospitaliseeritud 68 Prantsusmaa NICU-sse aprill-detsember 2011. Skriinitud vastsündinutel raviti PDA-d sagedamini, kui kontrollgrupil (55.1% vs 43.1%, OR 1.62, 95%CI 1.31,2.00), nende haiglasisene suremus oli madalam (14.2% vs 18.5%, OR 0.73, 95%CI 0.54,0.98) ning neil esines vähem kopsuverejooksu (5.6% vs 8.9%, OR 0.60, 95%CI 0.38, 0.95). NEK-i, raske BPD ja tõsiste ajulesioonide osas olulisi erinevusi ei leitud.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
BACKGROUND: Most premature infants are physiologically not sufficiently mature to orally ingest all of their required water and nutrients. Therefore,premature infants rely on their caregivers to regulate their volume of water intake. Thus, the caregiver must determine the amount of water to be given each day to such infants. **OBJECTIVES:** To determine the effect of water intake on postnatal weight loss and the risks of dehydration, patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, intracranial hemorrhage, and death in premature infants. **SEARCH METHODS:** Randomized clinical trials (RCTs) identified in previous versions of this review were re-examined and, in each case, retained. Additional trials were sought that compared the outcomes of interest in groups of premature infants who were given different levels of water intake according to an experimental protocol. Such trials were sought in a list of trials provided by the Cochrane Neonatal Review Group, with a PubMed search and in the authors' personal files.This search was updated in 2014. **SELECTION CRITERIA:** Only RCTs of varying water intake in premature infants were included. The review was limited to trials that included infantswhose water intake was provided mainly or	Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD000503. DOI: 10.1002/14651858.CD000503.pub3.

entirely by intravascular infusion.

DATA COLLECTION AND ANALYSIS:

The standard methods of The Cochrane Collaboration were used. Study selection and data abstraction were performed independently by each review author. The adverse event rates were calculated for the restricted and liberal water intake groups for each dichotomous outcome, and the relative risk and risk difference were computed. In addition, the maximal weight loss results were recorded and the weighted mean difference was computed.

MAIN RESULTS:

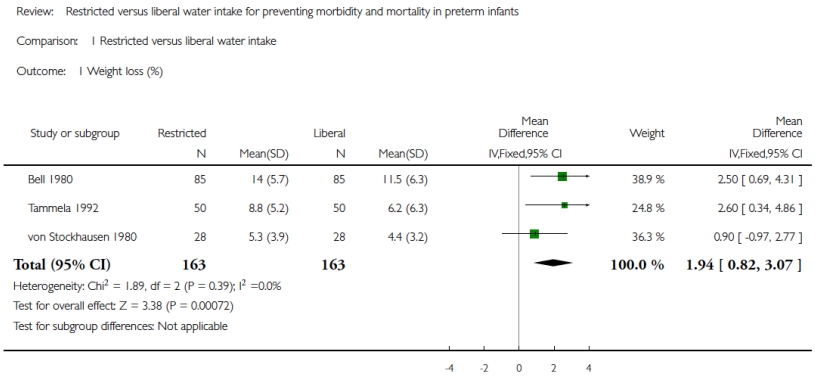
The analysis of the five studies taken together indicated that restricted water intake significantly increased postnatal weight loss and significantly reduced the risks of patent ductus arteriosus and necrotizing enterocolitis. With restricted water intake, there were trends toward increased risk of dehydration and reduced risks of bronchopulmonary dysplasia, intracranial hemorrhage, and death but these trends were not statistically significant.

AUTHORS' CONCLUSIONS:

Based on this analysis, the most prudent prescription for water intake to premature infants would seem to be careful restriction of water intake so that physiological needs are met without allowing significant dehydration. This practice could be expected to decrease the risks of patent ductus arteriosus and necrotizing enterocolitis without significantly increasing the risk of adverse consequences.

Comparison 1. Restricted versus liberal water intake

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight loss (%)	3	326	Mean Difference (IV, Fixed, 95% CI)	1.94 [0.82, 3.07]
2 Dehydration	2	258	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [0.71, 8.28]
3 Patent ductus arteriosus	4	526	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.37, 0.73]
4 Necrotizing enterocolitis	4	526	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.21, 0.87]
5 Bronchopulmonary dysplasia	4	526	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.63, 1.14]
6 Intraventricular hemorrhage (all grades)	3	356	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.48, 1.14]
7 Death	5	582	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.23]

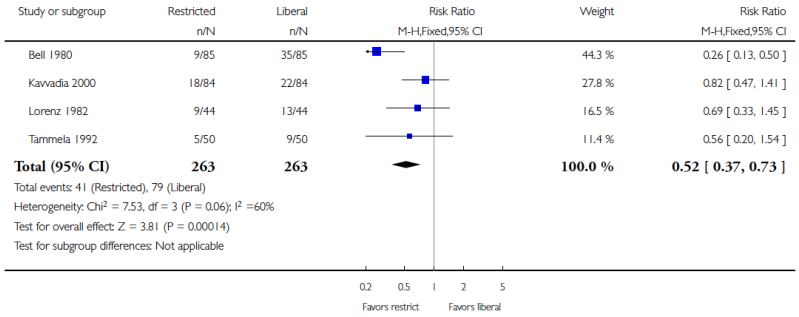


Analysis 1.3. Comparison 1 Restricted versus liberal water intake, Outcome 3 Patent ductus arteriosus.

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 3 Patent ductus arteriosus

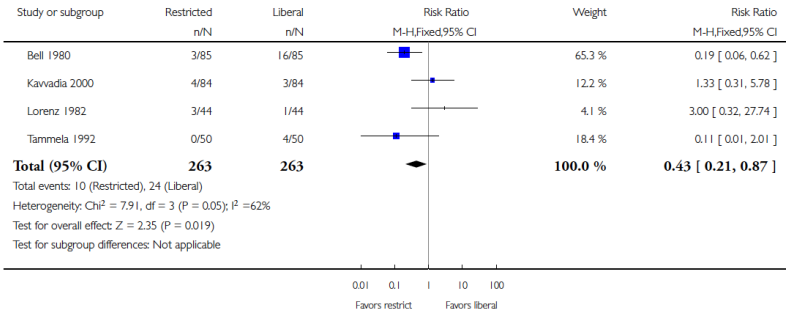


Analysis 1.4. Comparison 1 Restricted versus liberal water intake, Outcome 4 Necrotizing enterocolitis.

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 4 Necrotizing enterocolitis

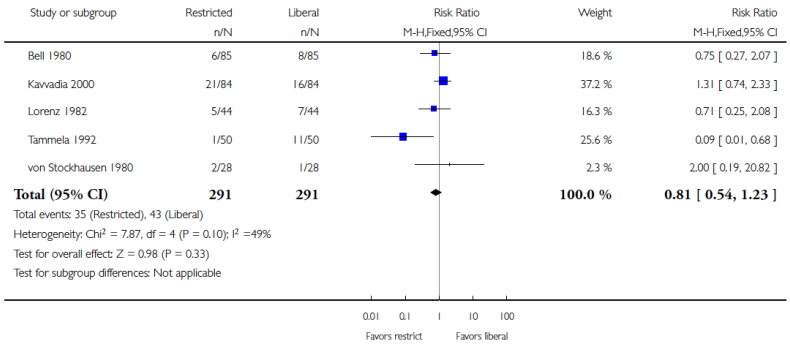


Analysis 1.7. Comparison 1 Restricted versus liberal water intake, Outcome 7 Death.

Review: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants

Comparison: 1 Restricted versus liberal water intake

Outcome: 7 Death



BACKGROUND:
Lung edema may complicate respiratory distress syndrome (RDS) in preterm infants.

OBJECTIVES:
The aim of this review was to assess the risks and benefits of diuretic administration in preterm infants with RDS.

SEARCH METHODS:
The standard search method of the Cochrane Neonatal Review Group was used. The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), MEDLINE and

Stewart A, Brion LP, Soll R. Diuretics for respiratory distress syndrome in preterm infants. Cochrane Database of Systematic
Reviews 2011, Issue 12. Art. No.: CD001454. DOI: 10.1002/14651858.CD001454.pub3.

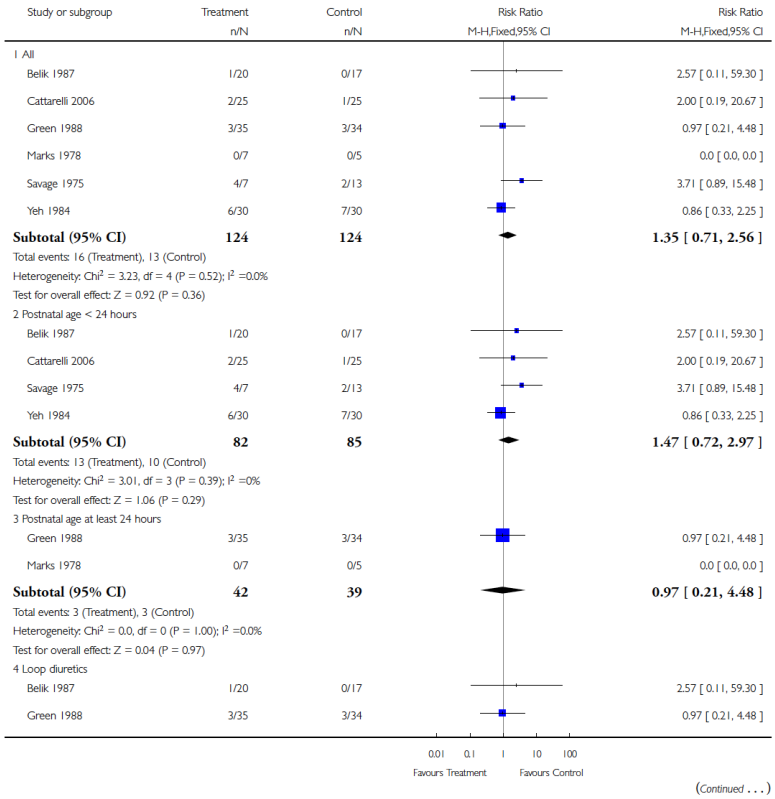
EMBASE were searched. These searches were updated in April 2003, March 2007, January 2011. In addition, the abstract books of the American Thoracic Society and Society for Pediatric Research were searched. MEDLINE and CENTRAL search was conducted using the keyword "Respiratory Distress Syndrome" alone, to find studies of medications recently classified as diuretics, such as theophylline. In addition, EMBASE, controlled-trials.com and clinicaltrials.gov searches were completed in January 2011. MEDLINE search updated to August 2011. **SELECTION CRITERIA:** Trials were included in which preterm infants with RDS and less than five days of age were randomly allocated to diuretic administration. Of those trials, studies were only included in which at least one of the following outcomes measures was evaluated: mortality, patent ductus arteriosus, hypovolemic shock, intraventricular hemorrhage, renal failure, duration of oxygen supplementation, duration of mechanical ventilation, need for oxygen supplementation at 28 days of life, oxygen supplementation at 36 weeks of postmenstrual age (gestational age + postnatal age), length of stay, number of rehospitalizations during the first year of life, and neurodevelopmental outcome. **DATA COLLECTION AND ANALYSIS:** The standard method for the Cochrane Collaboration, which is described in the Cochrane Collaboration Handbook, was used. Two investigators extracted, assessed and coded separately all data for each study. Any disagreement was resolved by discussion. **MAIN RESULTS:** Seven studies met inclusion criteria. Six studies using furosemide were done before the current era of prenatal steroids, surfactant and fluid restriction. Furosemide administration had no long-term benefits. Furosemide-induced transient improvement in pulmonary function did not outweigh an increased risk for patent ductus arteriosus and for hemodynamic instability. In one recent study, theophylline had no long-term benefits. Theophylline significantly decreased the risk of oligoanuria and transiently increased renal function, but did not significantly affect renal function at discharge or other outcomes.	

Analysis 1.1. Comparison 1 Routine diuretic administration versus placebo, no treatment or PRN diuretic administration, Outcome 1 Death.

Review: Diuretics for respiratory distress syndrome in preterm infants

Comparison: 1 Routine diuretic administration versus placebo, no treatment or PRN diuretic administration

Outcome: 1 Death



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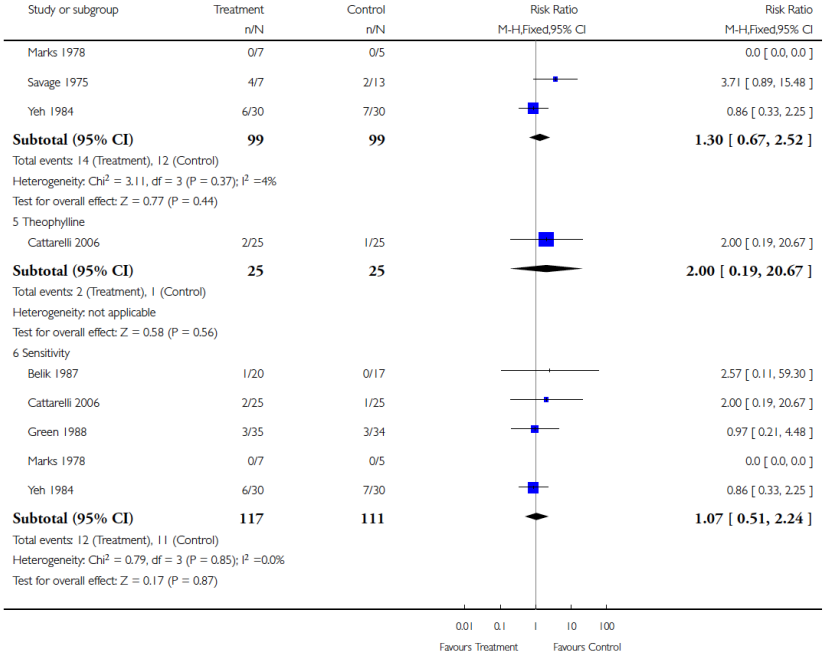


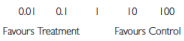
Analysis 1.2. Comparison 1 Routine diuretic administration versus placebo, no treatment or PRN diuretic administration, Outcome 2 Clinically significant PDA.

Review: Diuretics for respiratory distress syndrome in preterm infants

Comparison: 1 Routine diuretic administration versus placebo, no treatment or PRN diuretic administration

Outcome: 2 Clinically significant PDA

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All					
Belik 1987	0/19	1/17		5.8 %	0.30 [0.01, 6.91]
Cattarelli 2006	6/23	5/24		18.1 %	1.25 [0.44, 3.54]
Green 1988	14/35	8/34		30.0 %	1.70 [0.82, 3.53]
Yeh 1984	10/29	12/27		46.0 %	0.78 [0.40, 1.49]
Subtotal (95% CI)	**106**	**102**		**100.0 %**	**1.11 [0.72, 1.71]**
Total events: 30 (Treatment), 26 (Control)					
Heterogeneity: Chi^2 = 3.18, df = 3 (P = 0.36); I^2 =6%					
Test for overall effect: Z = 0.48 (P = 0.63)					
2 Postnatal age < 24 hours					
Belik 1987	0/19	1/17		8.4 %	0.30 [0.01, 6.91]
Cattarelli 2006	6/23	5/24		25.9 %	1.25 [0.44, 3.54]
Yeh 1984	10/29	12/27		65.8 %	0.78 [0.40, 1.49]
Subtotal (95% CI)	**71**	**68**		**100.0 %**	**0.86 [0.50, 1.48]**
Total events: 16 (Treatment), 18 (Control)					
Heterogeneity: Chi^2 = 1.03, df = 2 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.54 (P = 0.59)					
3 Postnatal age at least 24 hours					
Green 1988	14/35	8/34		100.0 %	1.70 [0.82, 3.53]
Subtotal (95% CI)	**35**	**34**		**100.0 %**	**1.70 [0.82, 3.53]**
Total events: 14 (Treatment), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.43 (P = 0.15)					
4 Loop diuretics					
Belik 1987	0/19	1/17		7.1 %	0.30 [0.01, 6.91]
Green 1988	14/35	8/34		36.7 %	1.70 [0.82, 3.53]
Yeh 1984	10/29	12/27		56.2 %	0.78 [0.40, 1.49]
Subtotal (95% CI)	**83**	**78**		**100.0 %**	**1.08 [0.67, 1.73]**
Total events: 24 (Treatment), 21 (Control)					
Heterogeneity: Chi^2 = 3.11, df = 2 (P = 0.21); I^2 =36%					



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Analysis 2.2. Comparison 2 Routine diuretic administration versus placebo or no treatment, Outcome 2 Clinically significant PDA.

Review: Diuretics for respiratory distress syndrome in preterm infants

Comparison: 2 Routine diuretic administration versus placebo or no treatment

Outcome: 2 Clinically significant PDA

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 All					
Belik 1987	0/19	1/17		8.4 %	0.30 [0.01, 6.91]
Cattarelli 2006	6/23	5/24		25.9 %	1.25 [0.44, 3.54]
Yeh 1984	10/29	12/27		65.8 %	0.78 [0.40, 1.49]
Subtotal (95% CI)	**71**	**68**		**100.0 %**	**0.86 [0.50, 1.48]**
Total events: 16 (Treatment), 18 (Control)					
Heterogeneity: Chi^2 = 1.03, df = 2 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.54 (P = 0.59)					
2 Postnatal age < 24 hours					
Belik 1987	0/19	1/17		8.4 %	0.30 [0.01, 6.91]
Cattarelli 2006	6/23	5/24		25.9 %	1.25 [0.44, 3.54]

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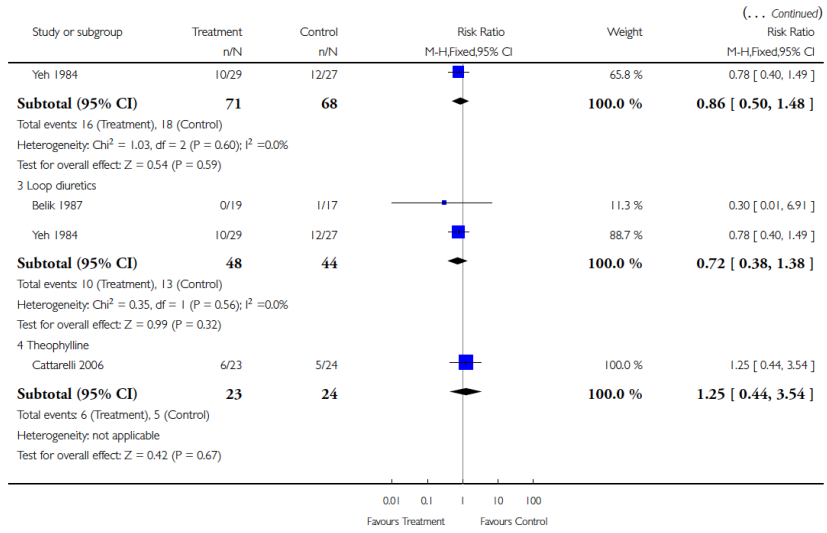
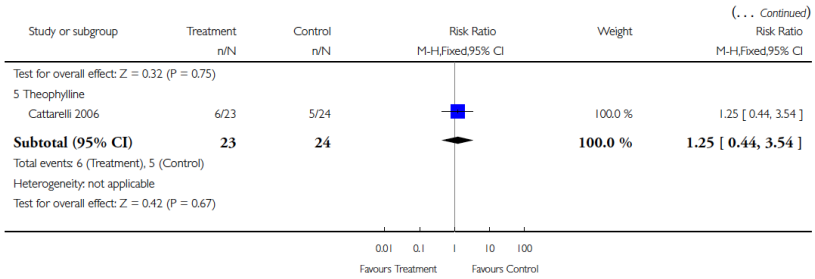


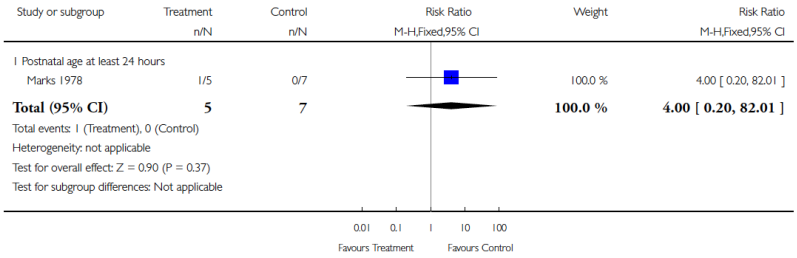


Analysis 1.3. Comparison 1 Routine diuretic administration versus placebo, no treatment or PRN diuretic administration, Outcome 3 Hypovolemic shock.

Review: Diuretics for respiratory distress syndrome in preterm infants

Comparison: 1 Routine diuretic administration versus placebo, no treatment or PRN diuretic administration

Outcome: 3 Hypovolemic shock

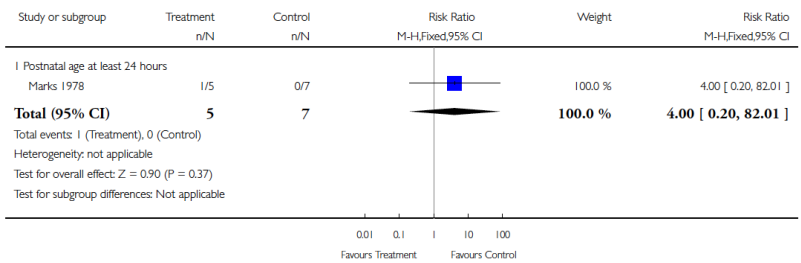


Analysis 2.3. Comparison 2 Routine diuretic administration versus placebo or no treatment, Outcome 3 Hypovolemic shock.

Review: Diuretics for respiratory distress syndrome in preterm infants

Comparison: 2 Routine diuretic administration versus placebo or no treatment

Outcome: 3 Hypovolemic shock

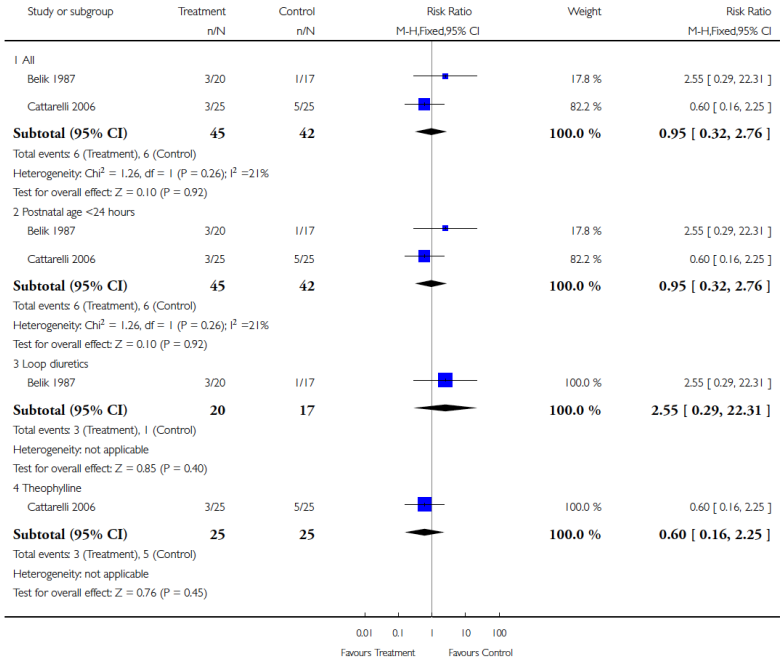


Analysis 1.16. Comparison 1 Routine diuretic administration versus placebo, no treatment or PRN diuretic administration, Outcome 16 Death or BPD.

Review: Diuretics for respiratory distress syndrome in preterm infants

Comparison: 1 Routine diuretic administration versus placebo, no treatment or PRN diuretic administration

Outcome: 16 Death or BPD

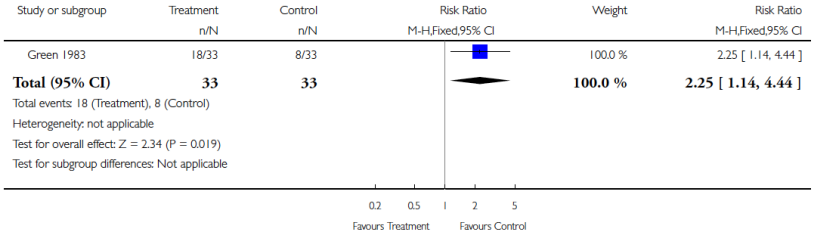


Analysis 3.2. Comparison 3 PRN furosemide versus PRN chlorothiazide, Outcome 2 Clinical diagnosis of PDA during the study.

Review: Diuretics for respiratory distress syndrome in preterm infants

Comparison: 3 PRN furosemide versus PRN chlorothiazide

Outcome: 2 Clinical diagnosis of PDA during the study

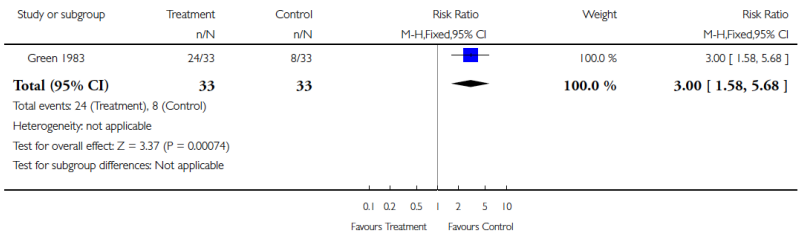


Analysis 3.3. Comparison 3 PRN furosemide versus PRN chlorothiazide, Outcome 3 Clinical diagnosis of PDA (during the study or later).

Review: Diuretics for respiratory distress syndrome in preterm infants

Comparison: 3 PRN furosemide versus PRN chlorothiazide

Outcome: 3 Clinical diagnosis of PDA (during the study or later)



AUTHORS' CONCLUSIONS:

There are no data to support routine administration of furosemide in preterm infants with RDS. Elective administration of furosemide to any patient with RDS should be carefully weighed against the risk of precipitating hypovolemia or developing a symptomatic patent ductus arteriosus. There are not enough data

to support routine administration of low-dose theophylline in preterm infants with RDS.	
BACKGROUND: Patent ductus arteriosus (PDA) complicates the clinical course of preterm infants and increases the risk of adverse outcomes. Indomethacin has been the standard treatment to close a PDA but is associated with renal, gastrointestinal and cerebral side-effects. Ibuprofen has less effect on blood flow velocity to important organs. **OBJECTIVES:** To determine the effectiveness and safety of prophylactic ibuprofen compared to placebo/no intervention in the prevention of PDA in preterm infants. **SEARCH STRATEGY:** Randomized controlled trials of prophylactic ibuprofen were identified by searching in The Cochrane Library, MEDLINE, CINAHL, EMBASE and trials registries in December 2010. **SELECTION CRITERIA:** Randomized or quasi-randomised controlled trials comparing ibuprofen with placebo/no intervention or other cyclo-oxygenase inhibitor drugs to prevent PDA in preterm and/or low birth weight infants. **DATA COLLECTION AND ANALYSIS:** Outcomes data including presence of PDA on day three, need for surgical ligation or rescue treatment with cyclo-oxygenase inhibitors, mortality, intraventricular haemorrhage (IVH), renal, pulmonary and gastrointestinal complications were extracted. Meta-analyses were performed and treatment estimates are reported as typical weighted mean difference, relative risk (RR), risk difference (RD) and, if statistically significant, number needed to treat to benefit (NNT) or number needed to treat to harm (NNH) along with their 95% confidence intervals (CI). **MAIN RESULTS:** In this update, seven studies (n = 931) comparing prophylactic ibuprofen with placebo/no intervention are included. Ibuprofen decreased the incidence of PDA on day three [typical RR 0.36 (95% CI 0.29 to 0.46); typical RD -0.27 (95% CI -0.32 to -0.21); NNT 4 (95% CI 3 to 5)], decreased the need for rescue treatment with cyclo-oxygenase inhibitors and decreased the need for surgical ligation. Results from two studies administering oral ibuprofen had similar results, but showed an increased risk of gastrointestinal bleeding (NNH 4, 95% CI 2 to 17). In the controlgroup the spontaneous closure rate was 58% by day three. Ibuprofen negatively affects renal function. No significant differences in mortality, IVH, chronic lung disease were found.	Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD004213. DOI: 10.1002/14651858.CD004213.pub3.

Comparison 1. Ibuprofen (iv or oral) vs placebo or none

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Presence of PDA on 3rd day of life (72 hours of treatment)	7	931	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.29, 0.46]
2 Neonatal mortality (at < 28 days of life)	4	234	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.47, 2.48]
3 All cause mortality during hospital stay	4	700	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.62, 1.30]
4 Mortality before 36 weeks PMA	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.56, 1.66]
5 Need for rescue medical treatment with cyclo-oxygenase inhibitors	6	776	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.11, 0.26]
6 Need for surgical closure of PDA	6	889	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.18, 0.88]
7 Duration of mechanical ventilation (days)	5	470	Mean Difference (IV, Fixed, 95% CI)	1.02 [-1.99, 4.03]
8 Days requiring supplemental oxygen	3	259	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-4.98, 4.61]
9 CLD at 28 days of life among survivors	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.32, 2.42]
10 CLD at 36 weeks corrected GA	4	781	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.87, 1.25]
11 CLD (age at diagnosis not stated)	2	99	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.51, 1.72]
12 Pulmonary hypertension	4	390	Risk Ratio (M-H, Fixed, 95% CI)	7.11 [0.37, 134.91]
13 IVH all grades	5	839	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.82, 1.23]
14 IVH (grades not stated)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.09, 2.20]
15 IVH grade III - IV	5	827	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.54, 1.26]
16 PVL	4	747	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.64, 2.18]
17 NEC	7	930	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.63, 1.70]
18 Gastrointestinal haemorrhage	3	184	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.16, 3.55]
19 Gastro-intestinal perforation	1	131	Risk Ratio (M-H, Fixed, 95% CI)	5.08 [0.61, 42.28]
20 Time to full enteral feeds (days)	3	184	Mean Difference (IV, Fixed, 95% CI)	0.47 [-2.99, 3.94]
21 Length of hospital stay (days)	4	339	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-7.08, 3.58]
22 Urine output after treatment (mL/kg/hr)	3	650	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.26, 0.15]
23 Oliguria	3	701	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.02, 1.98]
23.1 Oliguria < 0.5 ml/kg/hour	1	415	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.01, 2.34]
23.2 Oliguria < 1.0 ml/kg/hour	2	286	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.71, 2.12]
24 Serum creatinine levels after treatment (mg/dL)	5	754	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.05, 0.13]
25 At least one episode of serum creatinine > 140 micromol/L (>1.5 mg/dl)	2	285	Risk Ratio (M-H, Fixed, 95% CI)	3.70 [1.05, 12.98]
26 At least one episode of severe hypoxaemia	1	131	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.80, 3.59]
27 Nitric oxide during first week of life	1	131	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.80, 4.42]
28 ROP	4	333	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.73, 1.41]
29 Sepsis	2	201	Risk Ratio (M-H, Fixed, 95% CI)	2.70 [1.10, 6.59]
30 Presence of PDA on 3rd day of life in infants </= 28 weeks gestation at birth	2	420	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.29, 0.58]
31 Presence of PDA on 3rd day of life in infants 29-30 weeks gestation at birth	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.13, 0.64]
32 Presence of PDA on 3rd day of life in infants </= 1000 g	1	196	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.23, 0.61]
33 Presence of a PDA on 3rd day of life in infants 1001 - 1500 g	1	185	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.27, 0.81]

Analysis 1.1. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 1 Presence of PDA on 3rd day of life (72 hours of treatment).

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 1 Presence of PDA on 3rd day of life (72 hours of treatment)

Study or subgroup	Ibuprofen n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dani 2000	3/40	21/40		10.7 %	0.14 [0.05, 0.44]
Dani 2005	7/77	23/78		11.6 %	0.31 [0.14, 0.68]
De Carolis 2000	3/23	14/23		7.1 %	0.21 [0.07, 0.65]
Gournay 2004	18/65	36/66		18.1 %	0.51 [0.32, 0.80]
Sangtawesin 2006	1/22	7/20		3.7 %	0.13 [0.02, 0.97]
Sangtawesin 2008	6/31	13/31		6.6 %	0.46 [0.20, 1.06]
Van Overmeire 2004	33/205	84/210		42.1 %	0.40 [0.28, 0.57]
Total (95% CI)	**463**	**468**		**100.0 %**	**0.36 [0.29, 0.46]**

Total events: 71 (Ibuprofen), 198 (Control)

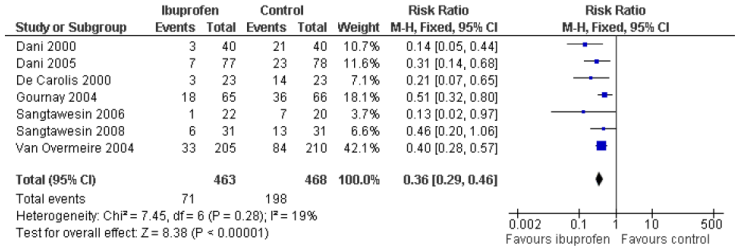
Heterogeneity: $Chi^2 = 7.45$, df = 6 (P = 0.28); $I^2 = 19\%$

Test for overall effect: Z = 8.38 (P < 0.00001)

0.002 0.1 1 10 500

Favours ibuprofen Favours control

Figure 3. Forest plot of comparison: 1 Ibuprofen vs placebo or none, outcome: 1.1 Presence of PDA on 3rd day of life (72 hours of age).



Analysis 1.2. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 2 Neonatal mortality (at < 28 days of life).

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 2 Neonatal mortality (at < 28 days of life)

Study or subgroup	Ibuprofen n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dani 2000	0/40	1/40		15.7 %	0.33 [0.01, 7.95]
De Carolis 2000	5/25	4/25		41.9 %	1.25 [0.38, 4.12]
Sangtawesin 2006	3/22	1/20		11.0 %	2.73 [0.31, 24.14]
Sangtawesin 2008	2/31	3/31		31.4 %	0.67 [0.12, 3.72]
Total (95% CI)	**118**	**116**		**100.0 %**	**1.08 [0.47, 2.48]**

Total events: 10 (Ibuprofen), 9 (Control)

Heterogeneity: $Chi^2 = 1.58$, df = 3 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 0.19 (P = 0.85)

0.002 0.1 1 10 500

Favours ibuprofen Favours control

Analysis 1.3. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 3 All cause mortality during hospital stay.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 3 All cause mortality during hospital stay

Study or subgroup	Ibuprofen n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dani 2000	0/40	1/40		3.0 %	0.33 [0.01, 7.95]
Dani 2005	15/77	20/78		39.7 %	0.76 [0.42, 1.37]
De Carolis 2000	6/25	4/25		8.0 %	1.50 [0.48, 4.68]
Van Overmeire 2004	23/205	25/210		49.3 %	0.94 [0.55, 1.61]
Total (95% CI)	**347**	**353**		**100.0 %**	**0.90 [0.62, 1.30]**

Total events: 44 (Ibuprofen), 50 (Control)
Heterogeneity: Chi^2 = 1.50, df = 3 (P = 0.68); I^2 =0.0%
Test for overall effect: Z = 0.58 (P = 0.56)

Analysis 1.5. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 5 Need for rescue medical treatment with cyclo-oxygenase inhibitors.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 5 Need for rescue medical treatment with cyclo-oxygenase inhibitors

Study or subgroup	Ibuprofen n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dani 2000	0/40	19/40		15.2 %	0.03 [0.00, 0.41]
De Carolis 2000	3/23	16/23		12.4 %	0.19 [0.06, 0.56]
Gournay 2004	2/65	34/66		26.3 %	0.06 [0.01, 0.24]
Sangtawesin 2006	0/22	6/20		5.3 %	0.07 [0.00, 1.17]
Sangtawesin 2008	3/31	11/31		8.6 %	0.27 [0.08, 0.88]
Van Overmeire 2004	13/205	42/210		32.3 %	0.32 [0.18, 0.57]
Total (95% CI)	**386**	**390**		**100.0 %**	**0.17 [0.11, 0.26]**

Total events: 21 (Ibuprofen), 128 (Control)
Heterogeneity: Chi^2 = 9.14, df = 5 (P = 0.10); I^2 =45%
Test for overall effect: Z = 8.03 (P < 0.00001)

Analysis 1.6. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 6 Need for surgical closure of PDA.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 6 Need for surgical closure of PDA

Study or subgroup	Ibuprofen n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dani 2000	0/40	0/40		0.0 [0.0, 0.0]
Dani 2005	0/77	1/78		0.34 [0.01, 8.16]
De Carolis 2000	1/23	3/23		0.33 [0.04, 2.97]
Gournay 2004	0/65	6/66		0.08 [0.00, 1.36]
Sangtawesin 2008	1/31	0/31		3.00 [0.13, 70.92]
Van Overmeire 2004	5/205	10/210		0.51 [0.18, 1.47]
Total (95% CI)	**441**	**448**		**0.40 [0.18, 0.88]**

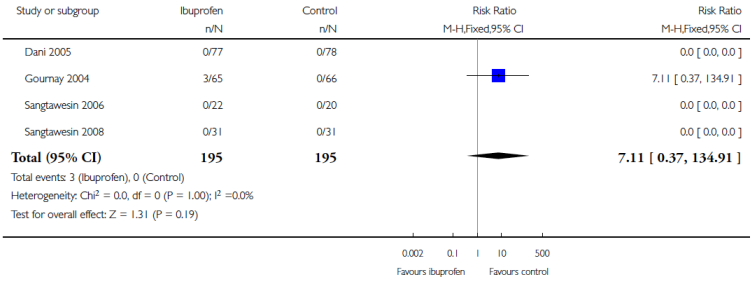
Total events: 7 (Ibuprofen), 20 (Control)
Heterogeneity: Chi^2 = 3.06, df = 4 (P = 0.55); I^2 =0.0%
Test for overall effect: Z = 2.28 (P = 0.022)

Analysis 1.12. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 12 Pulmonary hypertension.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 12 Pulmonary hypertension

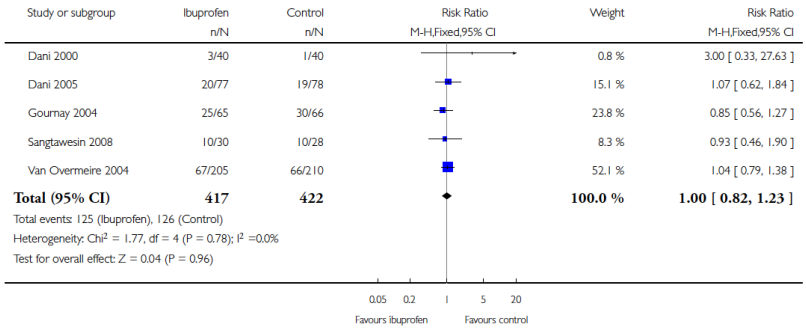


Analysis 1.13. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 13 IVH all grades.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 13 IVH all grades

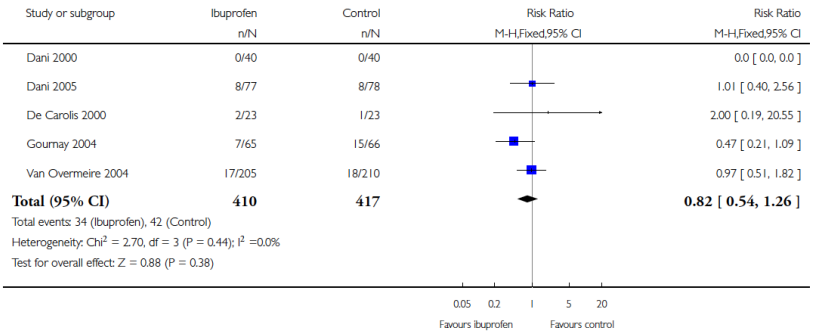


Analysis 1.15. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 15 IVH grade III - IV.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 15 IVH grade III - IV

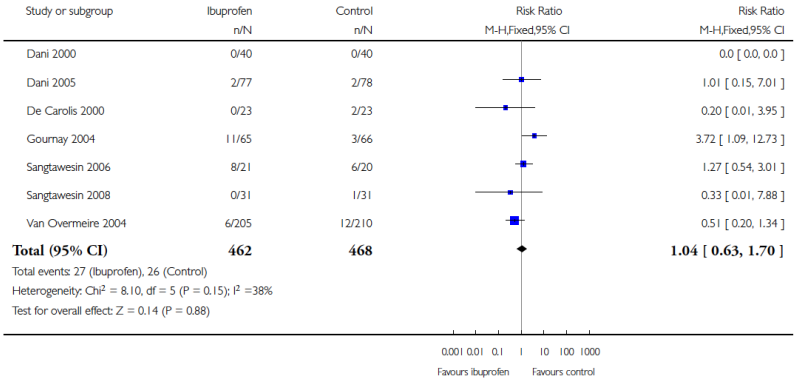


Analysis 1.17. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 17 NEC.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 17 NEC

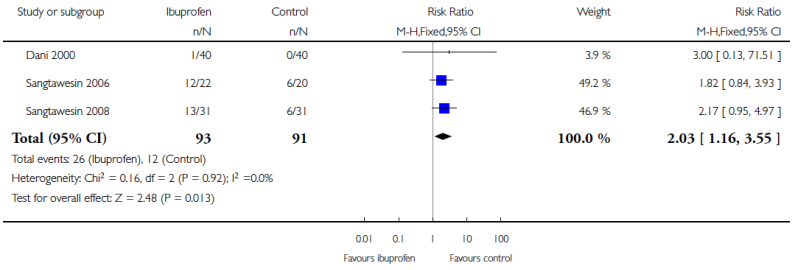


Analysis 1.18. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 18 Gastrointestinal haemorrhage.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 18 Gastrointestinal haemorrhage

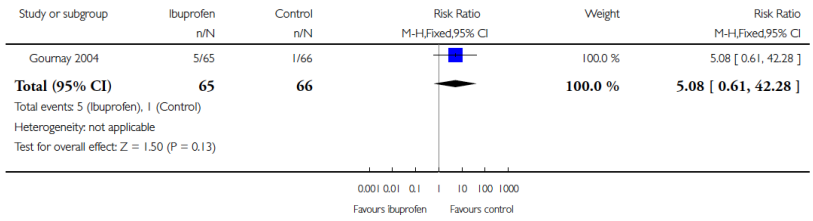


Analysis 1.19. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 19 Gastro-intestinal perforation.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 19 Gastro-intestinal perforation

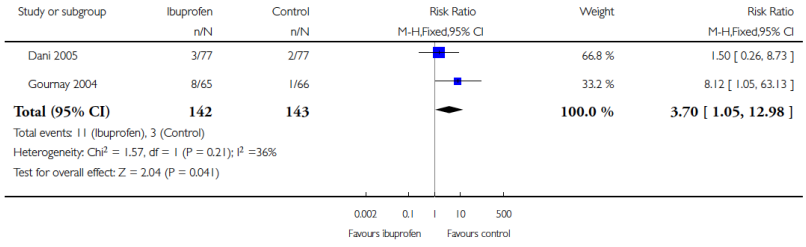


Analysis 1.25. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 25 At least one episode of serum creatinine > 140 micromol/L (>1.5 mg/dl).

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 25 At least one episode of serum creatinine > 140 micromol/L (>1.5 mg/dl)

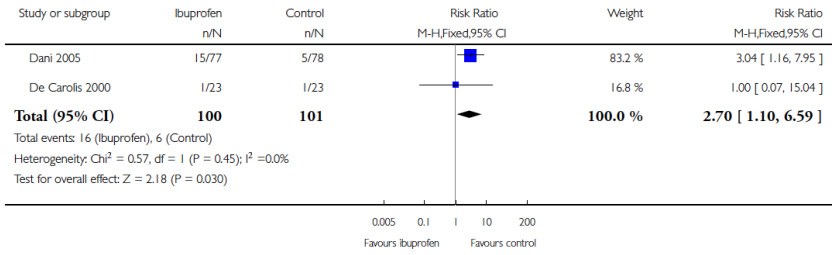


Analysis 1.29. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 29 Sepsis.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 29 Sepsis

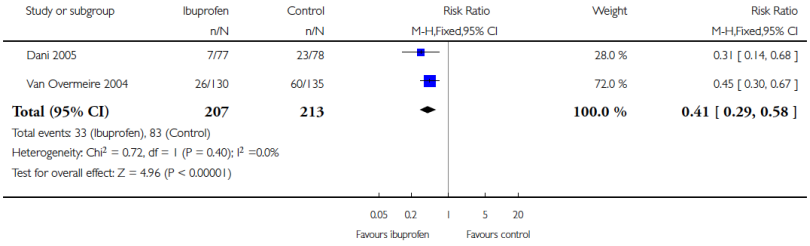


Analysis 1.30. Comparison 1 Ibuprofen (iv or oral) vs placebo or none, Outcome 30 Presence of PDA on 3rd day of life in infants </= 28 weeks gestation at birth.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 1 Ibuprofen (iv or oral) vs placebo or none

Outcome: 30 Presence of PDA on 3rd day of life in infants </= 28 weeks gestation at birth

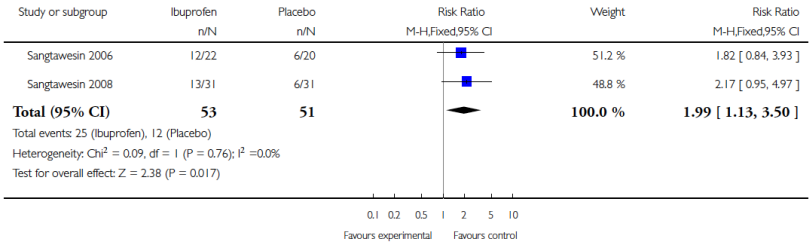


Analysis 2.2. Comparison 2 Ibuprofen (oral) vs placebo or none, Outcome 2 Gastrointestinal haemorrhage.

Review: Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants

Comparison: 2 Ibuprofen (oral) vs placebo or none

Outcome: 2 Gastrointestinal haemorrhage



AUTHORS' CONCLUSIONS:

Prophylactic use of ibuprofen decreased the incidence of PDA, decreased the need for rescue treatment with cyclo-oxygenase inhibitors and decreased the need for surgical closure. In the control group, the PDA closed spontaneously by day three in 58% of the neonates. Prophylactic treatment exposes many infants to a drug that has concerning renal and gastrointestinal side effects without conferring any important short-term benefits and is not recommended. Until long-term follow-up results are published from the trials included in this updated review, no further trials of prophylactic ibuprofen are recommended.

BACKGROUND:

Persistent patent ductus arteriosus (PDA) is associated with mortality and morbidity in preterm infants. Prostaglandin synthetase inhibitors such as indomethacin promote PDA closure

Fowlie PW,Davis PG,McGuireW. Prophylactic intravenous indomethacin for preventingmortality andmorbidity in preterm

but also have potential side effects. The effect of the prophylactic use of indomethacin, whereinfants who may not have gone on to develop a symptomatic PDA would be exposed to indomethacin, warrants particular scrutiny. **OBJECTIVES:** To determine the effect of prophylactic indomethacin on mortality and morbidity in preterm infants. **SEARCH STRATEGY:** The standard search strategy of the Cochrane Neonatal Review Group was used. This included searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 5, 2010), MEDLINE, EMBASE and CINAHL (until April 2010), conference proceedings, and previous reviews. **SELECTION CRITERIA:** Randomised or quasi-randomised controlled trials that compared prophylactic indomethacin versus placebo or no drug in preterm infants. **DATA COLLECTION AND ANALYSIS:** The standard methods of the Cochrane Neonatal Review Group were used, with separate evaluation of trial quality and data extraction by two review authors. **MAIN RESULTS:** Nineteen eligible trials in which 2872 infants participated were identified. Most participants were very low birth weight, but the largest single trial restricted participation to extremely low birth weight infants (N = 1202). The trials were generally of good quality.The incidence of symptomatic PDA [typical relative risk (RR) 0.44, 95% confidence interval (CI) 0.38 to 0.50] and PDA surgical ligation (typical RR 0.51, 95% CI 0.37,0.71) was significantly lower in treated infants. Prophylactic indomethacin also significantly reduced the incidence of severe intraventricular haemorrhage (typical RR 0.66, 95% CI 0.53 to 0.82). Meta-analyses found no evidence of an effect on mortality (typical RR 0.96, 95% CI 0.81 to 1.12) or on a composite of death or severe neurodevelopmental disability assessed at 18 to 36 months old (typical RR 1.02, 95% CI 0.90, 1.15).	**infants. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD000174. DOI: 10.1002/14651858.CD000174.pub2.**

Figure 1. Forest plot of comparison: 1 Prophylactic indomethacin vs. control, outcome: 1.1 Death to hospital discharge.

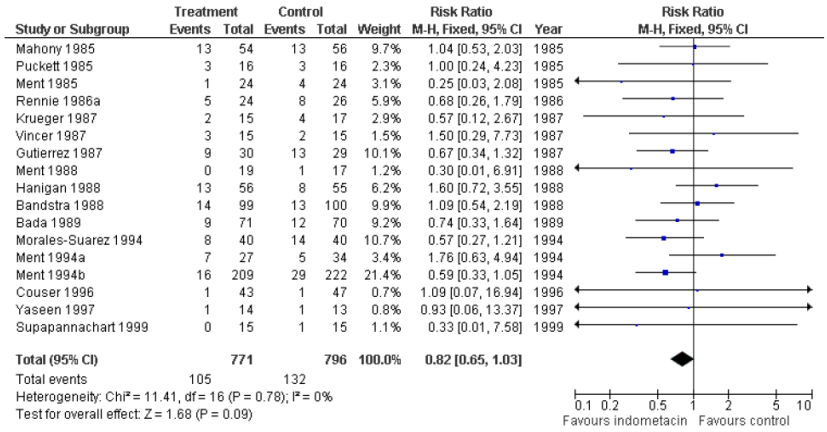


Figure 3. Forest plot of comparison: 1 Prophylactic indomethacin vs. control, outcome: 1.3 Death or severe neurosensory impairment.

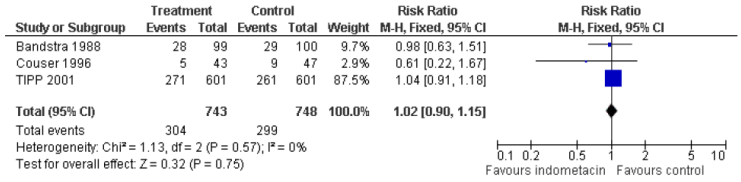


Figure 4. Forest plot of comparison: 1 Prophylactic indomethacin vs. control, outcome: 1.4 Cerebral palsy, visual impairment, hearing impairment and severe neurodevelopmental impairment.

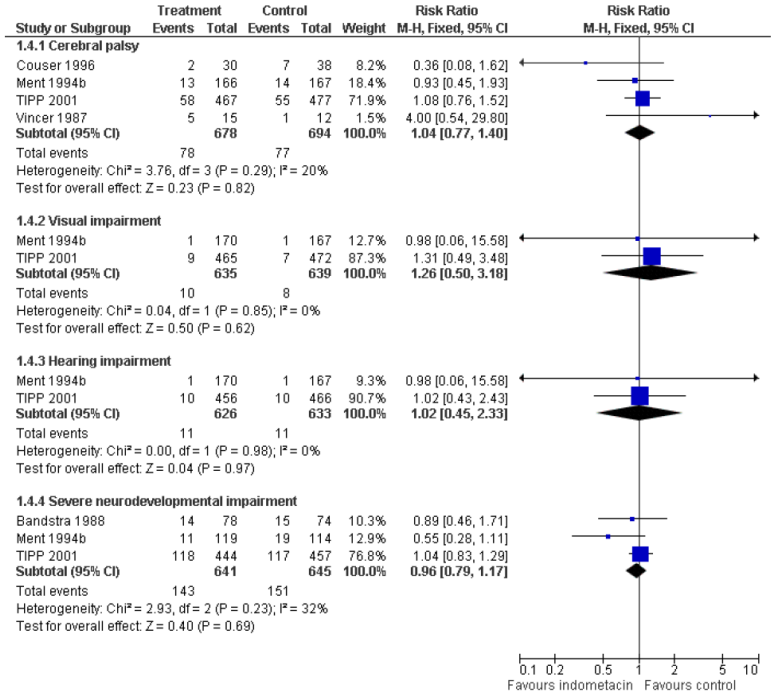


Figure 8. Forest plot of comparison: 1 Prophylactic indomethacin vs. control, outcome: 1.12 All PDA (echo-diagnosed, symptomatic or not).

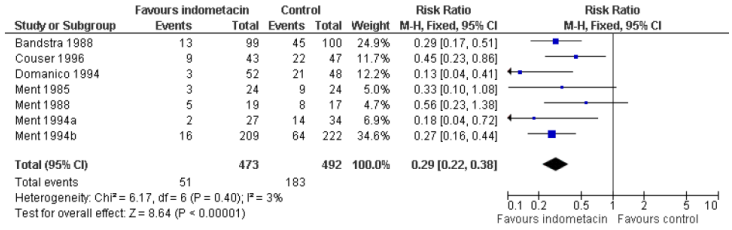


Figure 9. Forest plot of comparison: 1 Prophylactic indomethacin vs. control, outcome: 1.11 Symptomatic PDA.

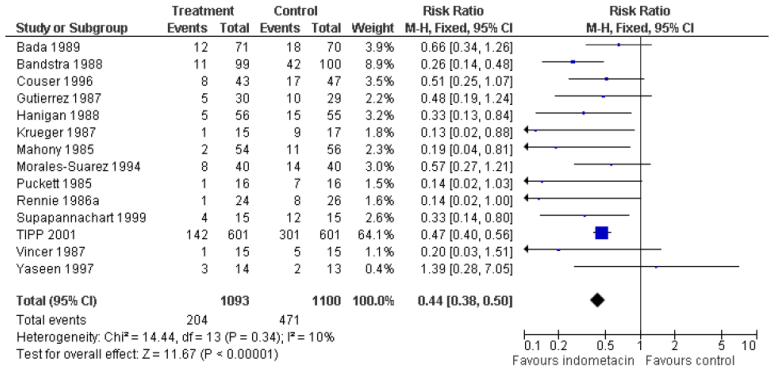


Figure 10. Forest plot of comparison: 1 Prophylactic indomethacin vs. control, outcome: 1.13 PDA ligation.

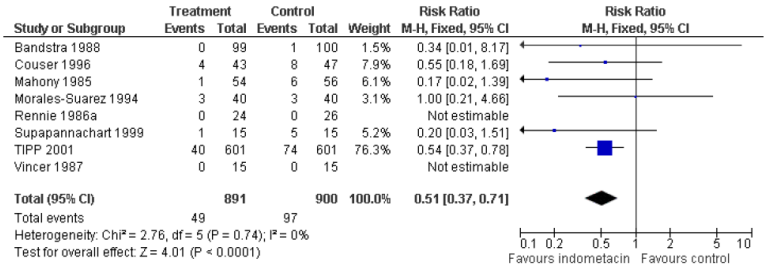


Figure 12. Forest plot of comparison: 1 Prophylactic indomethacin vs. control, outcome: 1.15 Severe IVH: grades III - IV.

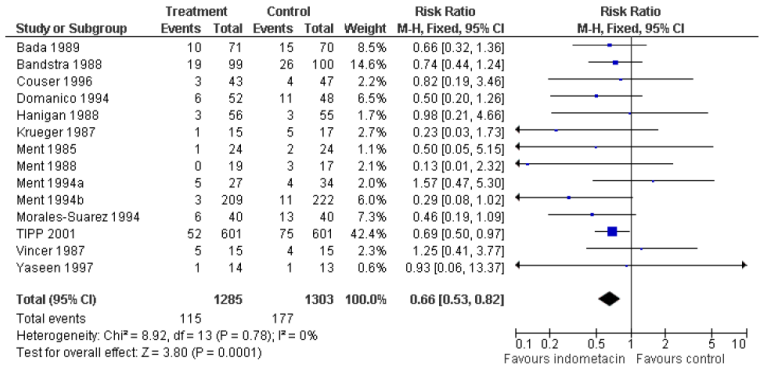


Figure 21. Forest plot of comparison: 1 Prophylactic indomethacin vs. control, outcome: 1.23 Oliguria/anuria.

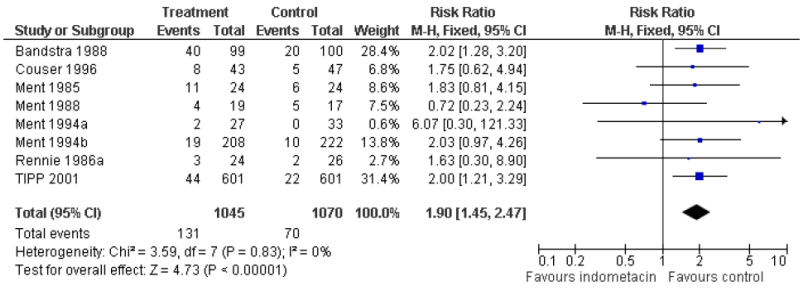
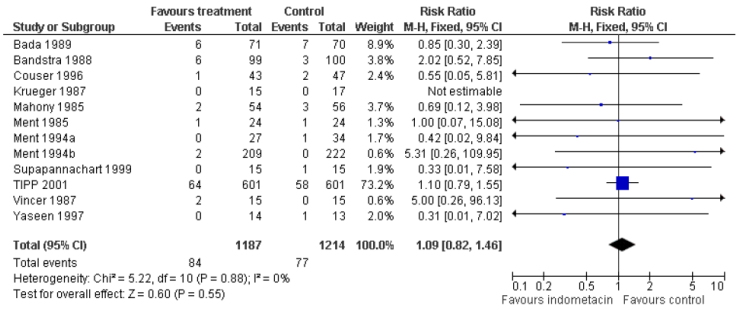


Figure 23. Forest plot of comparison: 1 Prophylactic indomethacin vs. control, outcome: 1.26 Necrotizing enterocolitis.



AUTHORS' CONCLUSIONS:

Prophylactic indomethacin has short-term benefits for preterm infants including a reduction in the incidence of symptomatic PDA, PDA surgical ligation, and severe intraventricular haemorrhage. However, there is no evidence of effect on mortality or neurodevelopment.

BACKGROUND:

Both prophylactic and early surfactant replacement therapy reduce mortality and pulmonary complications in ventilated infants withrespiratory distress syndrome (RDS) compared with later selective surfactant administration. However, continued post-surfactant intubation andventilation are risk factors for bronchopulmonary dysplasia (BPD). The purpose of this review was to compare outcomes between two strategies ofsurfactant administration in infants with RDS; prophylactic or early surfactant administration followed by prompt extubation, compared with later,selective use of surfactant followed by continued mechanical ventilation.

OBJECTIVES:

To compare two treatment strategies in preterm infants with or at risk for RDS: early surfactant administration with brief mechanical ventilation (less than one hour) followed by extubation vs. later selective surfactant administration, continued mechanical ventilation, and extubation from low respiratory support. Two populations of infants receiving early surfactant were considered:

Stevens TP, Blennow M,Myers EH, Soll R. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003063. DOI: 10.1002/14651858.CD003063.pub3.

spontaneously breathing infants with signs of RDS (who receive surfactant administration during evolution of RDS prior to requiring intubation for respiratory failure) and infants at high risk for RDS (who receive prophylactic surfactant administration within 15 minutes after birth).

SEARCH STRATEGY:
Searches were made of the Oxford Database of Perinatal Trials, MEDLINE (1966 - December 2006), CINAHL (1982 to December Week 2, 2006), EMBASE (1980 - December 2006), Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2006), Pediatric Research (1990 - 2006), abstracts, expert informants and hand searching. No language restrictions were applied.

SELECTION CRITERIA:
Randomized or quasi-randomized controlled clinical trials comparing early surfactant administration with planned briefmechanical ventilation (less than one hour) followed by extubation vs. selective surfactant administration continued mechanical ventilation, and extubation from low respiratory support.

DATA COLLECTION AND ANALYSIS:
Data were sought regarding effects on the incidence of mechanical ventilation (ventilation continued or initiated beyond one hour after surfactant administration), incidence of bronchopulmonary dysplasia (BPD), chronic lung disease (CLD), mortality, duration of mechanical ventilation, duration of hospitalization, duration of oxygen therapy, duration of respiratory support (including CPAP and nasal cannula), number of patients receiving surfactant, number of surfactant doses administered per patient, incidence of air leak syndromes (pulmonaryinterstitial emphysema, pneumothorax), patent ductus arteriosus requiring treatment, pulmonary hemorrhage, and other complications of prematurity. Stratified analysis was performed according to inspired oxygen threshold for early intubation and surfactant administration in the treatment group: inspired oxygen within lower ($FiO2 < 0.45$) or higher ($FiO2 > 0.45$) range at study entry. Treatment effect was expressed as relative risk (RR) and riskdifference (RD) for categorical variables, and weighted mean difference (WMD) for continuous variables.

MAIN RESULTS:
Six randomized controlled clinical trials met selection criteria and were included in this review. In these studies of infants with signs and symptoms of RDS, intubation and early surfactant therapy followed by extubation to nasal CPAP (NCPAP) compared with

later selectivesurfactant administration was associated with a lower incidence of mechanical ventilation [typical RR 0.67, 95% CI 0.57, 0.79], air leak syndromes [typical RR 0.52, 95% CI 0.28, 0.96] and BPD [typical RR 0.51, 95% CI 0.26, 0.99]. A larger proportion of infants in the early surfactant group receivedsurfactant than in the selective surfactant group [typical RR 1.62, 95% CI 1.41, 1.86]. The number of surfactant doses per patient was significantly greater among patients randomized to the early surfactant group [WMD 0.57 doses per patient, 95% CI 0.44, 0.69]. In stratified analysis by FIO2 at study entry, a lower threshold for treatment (FIO2< 0.45) resulted in lower incidence of airleak [typical RR 0.46 and 95% CI 0.23, 0.93] and BPD [typical RR 0.43, 95% CI 0.20, 0.92]. A higher treatment threshold (FIO2 > 0.45) at study entry was associated with a higher incidence of patent ductus arteriosus requiring treatment [typical RR 2.15, 95% CI 1.09, 4.13].

Comparison 1. Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Need for mechanical ventilation.	6	664	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.57, 0.79]
1.1 FIO2 at Study Entry <=0.45	4	464	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.59, 0.87]
1.2 FIO2 at Study Entry > 0.45	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.40, 0.77]
2 Bronchopulmonary dysplasia: need for oxygen at 28 days chronologic age.	4	262	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.26, 0.99]
2.1 FIO2 at Study Entry <=0.45	3	194	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.20, 0.92]
2.2 FIO2 at Study Entry > 0.45	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.20, 4.35]
3 Neonatal mortality: death prior to 28 days of age.	6	396	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.17, 1.56]
3.1 FIO2 at study entry <=0.45	4	196	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.15, 3.55]
3.2 FIO2 at study entry > 0.45	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.08, 1.81]
4 Intraventricular hemorrhage	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 IVH, any severity	5	517	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.41, 1.39]
4.2 Serious IVH, Grades III-IV	3	358	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.15, 2.18]
5 Retinopathy of prematurity, any severity	3	109	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.63]
6 Periventricular leukomalacia	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.47]
7 Pulmonary hemorrhage	4	532	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.35, 4.07]
7.1 FIO2 at study entry < = 0.45	2	332	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.30, 27.24]
7.2 FIO2 at study entry > 0.45	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.14, 3.46]
8 Use of surfactant	4	262	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.41, 1.86]
9 Number of surfactant doses per patient	3	470	Mean Difference (IV, Fixed, 95% CI)	0.57 [0.44, 0.69]
10 Air leak syndromes, pulmonary interstitial emphysema, pneumothorax	6	664	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.28, 0.96]
10.1 FIO2 at Study Entry <= 0.45	4	464	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.23, 0.93]
10.2 FIO2 at Study Entry > 0.45	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.22, 2.89]

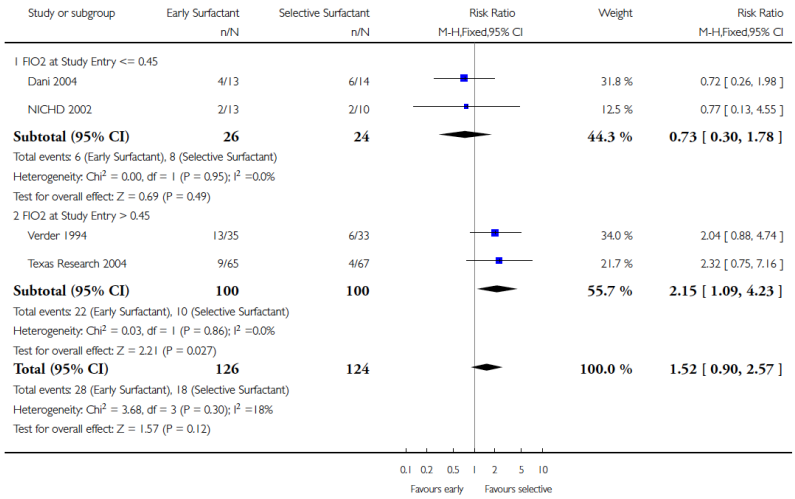
11 Patent ductus arteriosus requiring treatment	4	250	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.90, 2.57]
11.1 FIO2 at Study Entry <= 0.45	2	50	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.30, 1.78]
11.2 FIO2 at Study Entry > 0.45	2	200	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.09, 4.23]
12 Necrotizing enterocolitis (NEC)	4	388	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.12, 3.25]
13 Duration of mechanical ventilation (d)	3	278	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.81, 0.10]
14 Duration in oxygen	1	27	Mean Difference (IV, Fixed, 95% CI)	-4.30 [-7.63, -0.97]

Analysis 1.11. Comparison 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS., Outcome 11 Patent ductus arteriosus requiring treatment.

Review: Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome

Comparison: 1 Early surfactant, rapid extubation to NCPAP vs. selective surfactant, ventilation in babies with RDS.

Outcome: 11 Patent ductus arteriosus requiring treatment



AUTHORS' CONCLUSIONS:

Early surfactant replacement therapy with extubation to NCPAP compared with later selective surfactant replacement and continued mechanical ventilation with extubation from low ventilator support is associated with less need mechanical ventilation, lower incidence of BPD and fewer air leak syndromes. A lower treatment threshold (FIO2< 0.45) confers greater advantage in reducing the incidences of airleak syndromes and BPD; moreover a higher treatment threshold (FIO2 at study > 0.45) was associated with increased risk of PDA. These data suggest that treatment with surfactant by transient intubation using a low treatment threshold (FIO2< 0.45) is preferable to later, selective surfactant therapy by transient intubation using a higher threshold for study entry (FIO2 > 0.45) or at the time of respiratory failure and initiation of mechanical ventilation.

Abstract

Despite a large body of basic science and clinical research and clinical experience with thousands of infants over nearly 6 decades,[1] there is still uncertainty and controversy about the significance, evaluation, and management of patent ductus

William E. Benitz and COMMITTEE ON FETUS AND NEWBORN Patent Ductus Arteriosus in Preterm Infants. Pediatrics; originally published online December 15, 2015; DOI:

arteriosus in preterm infants, resulting in substantial heterogeneity in clinical practice. The purpose of this clinical report is to summarize the evidence available to guide evaluation and treatment ofpreterm infants with prolonged ductal patency in the first few weeks after birth. *Clinical Epidemiology and Natural History of Patent Ductus Arteriosus* In term infants, the ductus arteriosus normally constricts after birth and becomes functionally closed by 72 hours of age.[2] In preterm infants, however, closure is delayed, remaining open at 4 days of age in approximately 10% of infants born at 30 through 37 weeks' gestation, 80% of those born at 25 through 28 weeks' gestation, and 90% of those born at 24 weeks' gestation.[3] By day 7 after birth, those rates decline to approximately 2%, 65%, and 87%, respectively. The ductus is likely to close without treatment in infants born at >28 weeks' gestation (73%),[4] in those with birth weight >1000 g (94%),[5] and in infants born at 26 through 29 weeks' gestation who do not have respiratory distress syndrome (93%).[6] Rates of later spontaneous ductal closure among smaller, less mature infants with respiratory distress syndrome are not known because of widespread use of treatments to achieve closure of the patent ductus arteriosus (PDA) in such infants. Data from placebo arms of controlled trials demonstrate that spontaneous ductal closure in these infants is frequent, however. In the Trial of Indomethacin Prophylaxis in Preterms, for example, which included infants with birth weight from 500 to 999 g, 50% of placebo recipients never developed clinical signs of a PDA.[7] In a trial of early versus late indomethacin treatment of infants born at 26 through 31 weeks' gestation in whom PDA was confirmed by echocardiography on day 3, the ductus closed spontaneously by 9 days of age in 78% of those randomized to late intervention.[8] *Evidence for Benefits of Treatment* Since the early reports of feasibility of surgical closure[22] and efficacy of nonsteroidal antiinflammatory drugs for medical treatment[23,24] of PDA, results have been reported for 50 randomized controlled trials enrolling 4878 preterm infants.[9,25] Although medical and surgical treatments are efficacious in closing the PDA in a large proportion of infants, neither individual clinical trials nor meta-analyses have demonstrated that closing the ductus results in improved long-term outcomes. Odds ratios for the most important outcomes (BPD, necrotizing enterocolitis, neurosensory impairment, death, the combined outcomes of death or BPD and death or neurosensory impairment) indicate that early, routine treatment has no effect, with narrow confidence intervals, so it is unlikely	10.1542/peds.2015-3730 http://pediatrics.aappublications.org/content/early/2015/12/13/peds.2015-3730.long

that substantial differences have gone undetected.[9] When given as prophylaxis for IVH beginning within 12 hours of birth, treatment with indomethacin reduces rates of IVH, IVH greater than grade II, and early, severe pulmonary hemorrhage but does not improve long-term neurodevelopmental or respiratory outcomes.[7,26–28] The early neuroprotective effects of indomethacin may not depend on effects on ductal patency and are not replicated with similar use of ibuprofen.[29] In all published trials of prophylaxis or treatment, interventions were initiated within 2 weeks after birth for almost all subjects in the treatment arms, and later backup treatment to achieve ductal closure was common among control subjects.[30,31]The available evidence is therefore insufficient to permit assessment of potential benefits of treatments initiated after 2 weeks of age. The cumulative evidence supports the conclusion that early (in the first 2 weeks after birth), routine (as prophylaxis or for infants with echocardiographic confirmation of ductal patency with or without clinical signs) treatment to close the ductus arteriosus does not improve long-term outcomes for preterm infants. There is insufficient evidence to determine whether there are preterm infants who might benefit from early treatment or that later treatment has no potential benefit. These data also cannot be extrapolated to novel treatments (such as acetaminophen, recently reported to promote ductal closure[32,33]) because the balance between beneficial and adverse effects of new treatments may differ substantially from that for previously studied treatments.

Clinical experience with less aggressive strategies for PDA management suggests that a more permissive approach does not result in worse outcomes. Strategies avoiding use of indomethacin or ibuprofen yield outcomes comparable to contemporaneous external benchmarks.[51,52] Less frequent use of surgical ligation in infants with PDA after failure of indomethacin prophylaxis was associated with a lower rate of necrotizing enterocolitis and no increase in rates of other adverse outcomes.[53] Reduced use of indomethacin and ligation at 1 center was associated with an increased rate of the combined outcome of death or chronic lung disease but no increase in rates of individual morbidities or mortality.[54] These experiences indicate that longer periods of exposure to left-to-right ductal shunting may not result in significantly compromised outcomes, supporting equipoise regarding enrollment of preterm infants into randomized trials designed to assess treatment strategies for preterm infants with PDA.

Conclusions

A large body of evidence now exists demonstrating that early, routine treatment to induce closure of the ductus in preterm infants, either medically or surgically, in the first 2 weeks after

birth does not improve long-term outcomes (level of evidence: 1A[60]). The role of more selective use of medical methods for induction of ductal closure, either for defined high-risk infants in the first 2 postnatal weeks, or more generally, for older infants in whom the ductus remains patent, remains uncertain and requires further study. Prophylactic use of indomethacin may be appropriate in settings where rates of IVH are high or if early, severe pulmonary hemorrhage is common, but may not be justified by expected effects on PDA or by an expectation of better long-term outcomes. There is a lack of evidence to guide management of PDA, necessitating equipoise regarding treatment options and support for parents to permit enrollment of their infants in trials that can expand the available body of evidence.	
Administration of endotracheal surfactant is potentially the main treatment for neonates suffering from RDS (Respiratory Distress Syndrome), which is followed by mechanical ventilation. Late and severe complications may develop as a consequence of using mechanical ventilation. In this study, conventional methods for treatment of RDS are compared with surfactant administration, use of mechanical ventilation for a brief period and NCPAP (Nasal Continuous Positive Airway Pressure), (INSURE method ((Intubation, Surfactant administration and extubation)). A randomized clinical trial study was performed, including all newborn infants with diagnosed RDS and a gestational age of 35 weeks or less, who were admitted in NICU of Valiasr hospital. The patients were then divided randomly into two CMV (Conventional Mechanical Ventilation) and INSURE groups. Surfactant administration and consequent long-term mechanical ventilation were done in the first group (CMV group). In the second group (INSURE group), surfactant was administered followed by a short-term period of mechanical ventilation. The infants were then extubated, and NCPAP was embedded. The comparison included crucial duration of mechanical ventilation and oxygen therapy, IVH (Intraventricular Hemorrhage), PDA (Patent Ductus Arteriosus), air-leak syndromes, BPD (Broncho-Pulmonary Dysplasia) and mortality rate. The need for mechanical ventilation in 5th day of admission was 43% decreased (P=0.005) in INSURE group in comparison to CMV group. A decline (P=0.01) in the incidence of IVH and PDA was also achieved. Pneumothorax, chronic pulmonary disease and mortality rates, were not significantly different among two groups. (P=0.25, P=0.14, P=0.25, respectively). This study indicated that INSURE method in the treatment of RDS decreases the need for mechanical ventilation and oxygen-therapy in preterm neonates. Moreover, relevant complications as IVH and PDA were observed to be reduced. Thus, it seems	Nayeri FS, Esmaeilnia Shirvani T, Aminnezhad M, Amini E, Dalili H, Moghimpour BF. Comparison of INSURE method with conventional mechanical ventilation after surfactant administration in preterm infants with respiratory distress syndrome: therapeuti challenge. Acta Med Iran. 2014;52(8):596-600.

rationale to perform this method as the initial treatment for neonates with mild to moderate RDS.

Table 2. Demographic characteristics of cases

Variable		M.V group (Control), n=21	INSURE group (Intervention), n=21	Significance
Weight(g)		1484.7(SD ± 572)	1532.4(SD ± 539)	0.783
Gestational age(week)		30.3(SD ± 2.87)	31(SD ± 2.6)	0.404
Sex	Male	13	12	0.75
	Female	8	9	

Table 3. Frequency of outcomes

Variable	M.V group (Control), n=21	INSURE group (Intervention), n=21	p-value
Need for mechanical ventilation on the 5th day	(14)66.7%	(5)23.8%	0.005
Pneumothorax	(6)28.6%	(3)14.3%	0.259
PDA	(12)57.1%	(1)4.8%	0.001
IVH	(9)42.9%	(2)9.5%	0.014
BPD	(2)9.5%	(0)0%	0.147
Mortality rate	(6)28.6%	(3)14.3%	0.259

OBJECTIVE:
To determine the hemodynamic impact of fluid restriction in preterm newborns with significant patent ductus arteriosus.

STUDY DESIGN:
Newborns ≥24 and <32 weeks' gestational age with significant patent ductus arteriosus were eligible for this prospective multicenter observational study. We recorded hemodynamic and Doppler echocardiographic variables before and 24 hours after fluid restriction.

RESULTS:
Eighteen newborns were included (gestational age 24.8 ± 1.1 weeks, birth weight 850 ± 180 g). Fluid intake was decreased from 145 ± 15 to 108 ± 10 mL/kg/d. Respiratory variables, fraction of inspired oxygen, blood gas values, ductus arteriosus diameter, blood flow-velocities in ductusarteriosus, in the left pulmonary artery and in the ascending aorta, and the left atrial/aortic root ratio were unchanged after fluid restriction. Although systemic blood pressure did not change, blood flow in the superior vena cava decreased from 105 ± 40 to 61 ± 25 mL/kg/min (P < .001). The mean blood flow-velocity in the superior mesenteric artery was lower 24 hours after starting fluid restriction.

De Buyst J, Rakza T, Pennafort T, Johansson AB, Storme I Hemodynamic effects of fluid restrictio in preterm infants with significant pater ductus arteriosus.

J Pediatr. 2012 Sep;161(3):404-8. doi: 10.1016/j.jpeds.2012.03.012. Epub 2012 Apr 24.

Table I. Change in hemodynamic and respiratory variables for ECHO 1 and ECHO 2 (N = 18)

	ECHO 1	ECHO 2
F_{IO_2}, (%)	26 ± 4	24 ± 3
pH	7.29 ± 0.1	7.28 ± 0.09
P_{aCO_2} (mm Hg)	51 ± 5	53 ± 6
Heart rate (beats/min)	156 ± 12	160 ± 10
Systolic blood pressure (mm Hg)	53 ± 10	54 ± 7
Diastolic blood pressure (mm Hg)	32 ± 9	32 ± 4
Mean blood pressure (mm Hg)	41 ± 7	40 ± 4
Urine output (mL/kg/h)	2.5 ± 1.1	1.0 ± 0.6*

FI02, fraction of inspired oxygen.
Data are expressed as mean ± SD.
*$P < .05$.

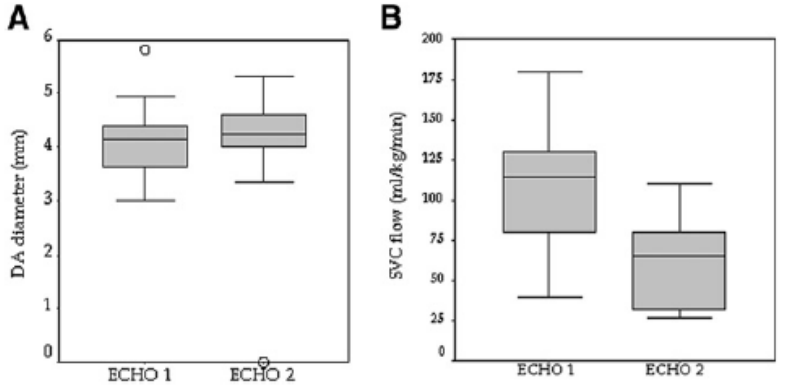


Figure. Internal diameters of **A,** DA and **B,** ECHO 1 and ECHO 2. **A,** DA diameters were similar at ECHO 1 and ECHO 2 (1 DA was closed at ECHO 2). **B,** SVC flow values were lower after 24 hours of restricted fluid intake than the baseline values ($P < .001$). Values are median ± IQ. $P < .05$.

Table II. Comparison between the echocardiographic variables for ECHO 1 and ECHO 2 (N = 18)

	ECHO 1	ECHO 2
Maximal flow-velocity in DA (m/s)	1.18 ± 0.38	1.23 ± 0.58
Mean flow-velocity in LPA (m/s)	0.58 ± 0.14	0.60 ± 0.12
End-diastolic flow-velocity in LPA (m/s)	0.22 ± 0.04	0.26 ± 0.04
LA:Ao	1.68 ± 0.28	1.65 ± 0.21
Mean flow-velocity in ascending aorta (m/s)	0.46 ± 0.10	0.43 ± 0.08
LVSF (%)	54 ± 9	51 ± 8
Mean blood flow-velocity in the MCA (m/s)	0.17 ± 0.05	0.13 ± 0.04
RI in the MCA	0.92 ± 0.09	0.98 ± 0.04
Mean blood flow-velocity in the SMA (m/s)	0.24 ± 0.04	0.15 ± 0.03*
RI in the SMA	0.79 ± 0.08	0.96 ± 0.09*

LVSF, left ventricular shortening fraction; *SMA*, superior mesenteric artery.
Data are expressed as mean ± SD.
*$P < .05$.

CONCLUSIONS:

Our results do not support the hypothesis that fluid restriction has beneficial effects on pulmonary or systemic hemodynamics in

preterm newborns.	
AIM: To determine whether routine echocardiography increases diagnosis and treatment for patent ductus arteriosus (PDA) and whether randomized nondisclosure is a feasible strategy for studying PDA management. **METHODS:** Two-centre, pilot randomized, controlled trial. 88 infants with birth weights ≤1250 grams and gestational ages ≤30 weeks were randomized to disclosure or nondisclosure of serial echocardiogram findings. Echocardiograms were performed at 3-5 and 7-10 days of life. The primary outcome was time to regain birth weight. **RESULTS:** 100% of echocardiograms in the disclosure group were disclosed; 16% (echocardiogram #1) and 29% (echocardiogram #2) were disclosed in the nondisclosure group. There was a statistically nonsignificant decrease in drug therapy for PDA in the nondisclosure group (adjusted odds ratio [AOR] 0.56, 95% confidence interval [CI] 0.24-1.34). There was no difference in time to regain birth weight or in other important neonatal outcomes. However, infants in the nondisclosure group were more likely to demonstrate appropriate weight loss and then regain birth weight within 7-14 days (AOR 2.64, 95% CI 1.08-6.44). **CONCLUSION:** Randomized nondisclosure of echocardiograms is a feasible strategy for evaluation of approaches to PDA management in verypreterm infants. Avoidance of routine echocardiography may reduce drug therapy for PDA without adverse clinical effects.	DeMauro SB[1], Cohen MS, Ratcliffe SJ, Abbasi S, Schmidt B. Serial echocardiography in very preterm infants: a pilot randomized trial. Acta Paediatr. 2013 Nov;102(11):1048-53. doi: 10.1111/apa.12389. Epub 2013 Sep 13.
OBJECTIVE: To determine the accuracy of the patent ductus arteriosus:left pulmonary artery ratio (PDA:LPA) on echocardiogram (ECHO) at 3-day postnatal in predicting spontaneous PDA closure in neonates ≤ 30 weeks gestational age (GA). **STUDY DESIGN:** ECHOs were performed at 72 h to characterize PDA size as closed-to-small (PDA:LPA <0.5) or moderate-to-large (PDA:LPA ≥ 0.5) and at 10 days to determine spontaneous closure (defined as closed-to-small in the absence of medical and/or surgical treatment). Caretakers were blinded to results; treatment was based on standard care. Neonates were prospectively enrolled and stratified: <27 weeks (n=31) and 27 to 30 weeks (n=65). **RESULT:** Neonates <27 weeks with closed-to-small PDAs had 60%	Thankavel PP, Rosenfeld CR, Christie L, Ramaciotti C. Early echocardiographi prediction of ductal closure in neonates ≤ 30 weeks gestation J Perinatol. 2013 Jan;33(1):45-51. doi: 10.1038/jp.2012.41. Epub 2012 Apr 12. .

spontaneous closure vs 9% when moderate-to-large (positive predictive value (PPV) 60%, negative predictive value (NPV) 91%). Neonates 27 to 30 weeks had 95% spontaneous closure vs 27%, respectively (PPV 95%, NPV 73%). Inter-observer variability for the initial ECHO was 0.84. **CONCLUSION:** PDA size defined by PDA:LPA at 3 days postnatal in combination with GA predicts spontaneous PDA closure.	
IMPORTANCE: There is currently no consensus for the screening and treatment of patent ductus arteriosus (PDA) in extremely preterm infants. Less pharmacological closure and more supportive management have been observed without evidence to support these changes. OBJECTIVE: To evaluate the association between early screening echocardiography for PDA and in-hospital mortality. DESIGN, SETTING, AND PARTICIPANTS: Comparison of screened and not screened preterm infants enrolled in the EPIPAGE 2 national prospective population-based cohort study that included all preterm infants born at less than 29 weeks of gestation and hospitalized in 68 neonatal intensive care units in France from April through December 2011. Two main analyses were performed to adjust for potential selection bias, one using propensity score matching and one using neonatal unit preference for early screening echocardiography as an instrumental variable. EXPOSURES: Early screening echocardiography before day 3 of life. MAIN OUTCOMES AND MEASURES: The primary outcome was death between day 3 and discharge. The secondary outcomes were major neonatal morbidities (pulmonary hemorrhage, severe bronchopulmonary dysplasia, severe cerebral lesions, and necrotizing enterocolitis). RESULTS: Among the 1513 preterm infants with data available to determine exposure, 847 were screened for PDA and 666 were not; 605 infantsfrom each group could be paired. Exposed infants were treated for PDA more frequently during their hospitalization than nonexposed infants (55.1% vs 43.1%; odds ratio [OR], 1.62 [95% CI, 1.31 to 2.00]; absolute risk reduction [ARR] in events per 100 infants, -12.0 [95% CI, -17.3 to -6.7). Exposedinfants had a lower hospital death rate (14.2% vs 18.5% ; OR, 0.73 [95% CI, 0.54 to 0.98]; ARR, 4.3 [95% CI, 0.3 to 8.3]) and a lower rate of pulmonary hemorrhage (5.6% vs 8.9%; OR, 0.60 [95% CI, 0.38 to 0.95]; ARR, 3.3 [95% CI, 0.4	Rozé JC, Cambonie G, Marchand-Martin L, Gournay V, Durrmeyer X, Durox M, Storme L, Porcher R, Ancel PY; Hemodynamic EPIPAGE 2 Study Group. Association Between Early Screening for Patent Ductus Arteriosus and In-Hospital Mortality Among ExtremelyPreterm Infants.JAMA. 2015 Jun 23-30;313(24):2441-8. doi: 10.1001/jama.2015.6734.

to 6.3]). No differences in rates of necrotizing enterocolitis, severe bronchopulmonary dysplasia, or severe cerebral lesions were observed. In the overall cohort, instrumental variable analysis yielded an adjusted OR for in-hospital mortality of 0.62 [95% CI, 0.37 to 1.04]. CONCLUSIONS AND RELEVANCE: In this national population-based cohort of extremely preterm infants, screening echocardiography before day 3 of life was associated with lower in-hospital mortality and likelihood of pulmonary hemorrhage but not with differences in necrotizing enterocolitis, severe bronchopulmonary dysplasia, or severe cerebral lesions. However, results of the instrumental variable analysis leave some ambiguity in the interpretation, and longer-term evaluation is needed to provide clarity.	

Otsingud	
Kuupäev	31.12.2015
Andmebaas	Pubmed, mesh
Otsingusõnad	Premature infant, premature infants, patent ductus arteriosus, prevention of patent ductus arteriosus, prophylactic ibuprofen, prophylactic paracetamol, prophylactic indometacin, conservative treatment, early enteral nutrition, CPAP treatment, non invasive ventilation, fluid restriction, diuretics, echocardiography
Filtrid	5 years, review, systematic review, meta-analyse, randomized controlled trial, english language
Vasteid	227
Sobivaid	1 konsensusdokument, 5 metaaanalüüsi, 5 artiklit

Muu leitud tõendusmaterjal (ravijuhendid):

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

Evans, N. **Guideline. Management of Patent Ductus Arterisosus in Preterm infants**. Health Sydney Local Health District. March 2014. http://www.slhd.nsw.gov.au/rpa/neonatal/content/pdf/guidelines/PDA_2014_guideline.pdf

The Swedish National Board of Health and Wlefare. Care of extremely premature infants **A guideline for the care of children born before 28 full weeks of pregnancy have passed.** Published www.socialstyrelsen.se, September 2014