Kliiniline küsimus nr 25

Kas kofeiini manustamine vastsündinule esmase stabiliseerimise käigus võrreldes kofeiini mittemanustamisega aitab parandada ravitulemusi enneaegsetel vastsündinutel?

Kriitilised tulemusnäitajad: lapse peamised tulemusnäitajad, surfaktantravi vajadus, õhktüsistused, hingamistoetuse kestus.

Kokkuvõte

Ravijuhendite, metaanalüüside ning randomiseeritud kontrolluuringute alusel parandab kofeiinravi võrreldes kofeiini mittemanustamisega enneaegsete laste varast ning hilist ravitulemit. Kofeiinravi saanud enneaegsetel esineb statistiliselt oluliselt vähem BPD-d 36 GN-l ning nad vajasid nädal aega vähem positiivse rõhuga ventilatsiooni kui kontrollgrupp. Kofeiiniravi saanud laste psühhomotoorne areng oli 18 kuu vanuses parem kui kofeiinravi mittesaanud lastel. 5 aasta vanuses see erinevus küll kadus, kuid võib järeldada, et kofeiinravi on ohutu ja ei põhjusta olulisi elukvaliteeti mõjutavaid kesknärvisüsteemi kõrvaltoimeid.

Kofeiinravi alustatakse traditsiooniliselt küllastusannuses 20 mg/kg/die (kofeiintsitraat) ning jätkatakse säilitusannuses 5-10 mg/kg/die i.v või p.o. Mitmes RCT-s on näidatud, et kõrgem kofeiini doos (küllastus 80 mg/kg/die ning säilitusannus 20 mg/kg/die) on periekstubatsiooniperioodis efektiivsem võrreldes tavadoosiga. Kofeiini seerumikontsentratsiooni monitooring ei ole rutiinselt vajalik.

Kofeiini manustamist esmase stabiliseerimise käigus on käsitletud vaid ühes randomiseeritud uuringus, kus uuriti 21 vastsündinut (< 29 GN). Leiti, et varase ja hilise/rutiinse kofeiini manustamise vahel ei esine erinevust hilisema intubatsiooni vajaduse osas. Leiti, et paraneb küll hemodünaamika, kuid kindlasti on vajalikud edasised uuringud. Tõendusmaterjali puudulikkuse tõttu ei ole antud ülevaates käsitletud kofeiini manustamist vaid esmase stabiliseerimise käigus, vaid kofeiinravi tervikuna.

Ravijuhendid

Soovitused kofeiinravi kohta enneaegsetel vastsündinutel on käsitletud ühes ravijuhendis (European Consensus Guidelines on the Manangement of Neonatal Respiratory Distress Syndrome in Preterm Infants, Update 2013). Soovitused põhinevad 2007-2012 avaldatud tõendusmaterjalil (Cochrane andmebaasi ülevaated), millele on andnud hinnangu Euroopa neonatoloogia ekspertide konsensus.

Metüülksantiine on kasutatud alates 1970ndatest (Henderson-Smart and De Paoli, 2010) enneaegsete laste apnoede ravis, et soodustada ekstubatsiooni ja võõrutamist kopsude mehaanilisest ventilatsioonist (KMV).

Mainitud ajavahemikul on avaldatud suur randomiseeritud kontrolluuring (The Caffeine for Apnea of Prematurity (CAP) Study), mis uurib kofeiinteraapia lähi- ja kaugtulemit. Uuringusse kaasati 2006 enneaegset vastsündinut, sünnikaaluga < 1250 g, kes randomiseeriti enne 10. elupäeva vastavalt kofeiinravi või platseebo gruppi ning ravi kestvuse määras raviarst, vastavalt lapse seisundile.

TULEMUSED:

Varane ravitulem (enne esmast kojukirjutamist) – kofeiinravi saanud lapsed vajasid KMV-d 1 nädal vähem kui platseebo grupis olevad lapsed. Samuti esines neil statistiliselt oluliselt vähemal määral bronhopulmonaalset düsplaasiat (BPD).

Hiline ravitulem 18 kuu vanuses – kofeiinravi saanud lastel esineb vähem tserebraalparalüüsi ja kognitiivse arengu mahajäämust

Kokkuvõtteks soovitab ravijuhend: kofeiinravi on vajalik enneaegsete laste apnoede raviks, sh võõrutamiseks KMV-st (A).

Ravijuhend soovitab kaaluda kofeiinravi alustamist ka sünnijärgselt mitteinvasiivsel ventilatsioonil olevatel enneaegsetel vastsündinutel sünnikaaluga < 1250 g, kellel on kõrge risk hilisemaks KMV vajaduse tekkeks (B).

Antud ravijuhend ei anna soovitusi optimaalsete ravidooside ega annustamisskeemide kohta. Vajalik informatsioon on kirjeldatud tõendusmaterjali kokkuvõtte hilisemates lõikudes.

Grades of recommendation: GRADE

A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating consistency of results or Extrapolated evidence from studies such as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating consistency of results or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+

GRADE = Grading of recommendations assessment, development and evaluation [5]; RCT = randomized controlled trial.

Süstemaatilised ülevaated/meta-analüüsid

Teema kohta leiti otsingukriteeriumide järgi 3 meta-analüüsi/süstemaatilist ülevaadet (koostatud 2009–2015).
Antud kokkuvõttest jäeti välja profülaktilist metüülksantiinravi (apnoede profülaktikas) käsitlev süstemaatiline ülevaade, kuna selle tõenduspõhisus jäi ebapiisavaks uuringute väikse arvu ja vastuoluliste tulemuste tõttu.

Kaks meta-analüüsi (Henderson-Smart, D.J., De Paoli, A.G., 2010 ja Henderson-Smart, D.J., Davis, P.G., 2010) näitavad, et metüülksantiinide (kofeiin, aminofülliin, teofülliin) kasutamine vähendab ekstubatsiooni ebaõnnestumiste arvu (RR 0.48 (95%CI 0.32 to 0.71), on tõhus ravimeetod vähendamaks apnoehoogude arvu ja mehaanilise ventilatsiooni vajadust esimese kahe kuni seitsme päeva jooksul peale ravi alustamist.

Soovitatakse eelistada kofeiinravi, kuna kofeiin on vähem toksiline ja esineb vähem kõrvaltoimeid.

Kofeiinraviga seostatakse ka paremaid kaugtulemusi:
Väheneb DAPi (*Ductus Arterious Persistens*) ligeerimise vajadus (RR 0.37; 95%CI 0.21 to 0.66). On leitud, et väheneb postmenstruaalvanus, mil viimati esineb
-- lisahapniku (mean difference, RR -0.90 weeks; 95%CI -1.54 to -0.26),
-- intubatsiooni (mean difference RR -0.60 weeks; 95%CI -1.03 to -0.17),

-- IPPV (*intermittent positive pressure ventilation*) (mean difference, RR -0.90; 95%CI -1.32 to -0.48) vajadus.
Ka meta-analüüsides tuuakse esile, et kofeiinravi saanud lastel esineb statistiliselt oluliselt vähemal määral bronhopulmonaalset düsplaasiat (BPD) 36. gestatsiooninädalal.

Randomiseeritud kontrolluuringud (RCT)

Andmebaasis PubMed teostatud otsingul leiti ajavahemikus 2009 – 2015 enneaegsetel vastsündinute kofeiinravi/profülaktika kohta 8 RCT-d.
Varasematel aastatel (2006, 2007) on avaldatud Caffeine for Apnea of Prematurity (CAP) uuringugrupi poolt suured mitme-keskuse RCT-d, mis on olulisemad tõendused antud valdkonnas, mistõttu otsustati need uuringud antud tõendusmaterjali kokkuvõttesse kaasata. CAP uuringusse kaasati 2006 enneaegset vastsündinut (sünnikaal 500-1250 g), kes randomiseeriti esimese 10 elupäeva jooksul juhuslikult kofeiinravi ja platseebogruppi. Kofeiinravi saavas grupis esines oluliselt vähem BPD-d võrreldes kontrollgrupiga (36% vs 47%, OR 0.63, 95%CI 0.52-0.76, P<0.001). Positiivse rõhuga ventilatsioon lõpetati kofeiinravi grupis 1 nädal varem, kui kontrollgrupis (mediaan PMA 31 GN vs 32 GN, P<0.001). Kofeiinravi saavas grupis esines väiksem positiivne kaaluiive võrreldes kontrollgrupiga (keskmine kaaludiferents -23 g, 95% CI -32 kuni – 13 g, P<0.001).
Kofeiinravi pikaajalist ohutust hinnati 18–21 kuu möödudes ning kofeiinravi grupis oli võrreldes platseebogrupiga väiksem suremus/vähem raske psühhomotoorse arengu mahajäämust (40.2 vs 46.2%, P= 0.008) ning esines vähem tserebraalparalüüsi (4.4 vs 7.3%, P=0.009).
Samas 5 aasta vanuses, aastal 2012 teostatud uuring samale uuringugrupile ei andnud enam erinevusi suremuse, neuroloogilise mahajäämuse, käitumisraskuste osas kofeiinravi ja platseebogrupi vahel.

CAP uuringule teostati 2010. a *post-hoc* analüüs alagruppide kaupa (hingamistoetuse puudumine/ mitte-invasiivne ventilatsioon/ endotrahheaalne intubatsioon; varane vs hiline kofeiinravi; kofeiinravi alustamise eesmärk (apnoe profülaktika, apnoe ravi, ekstubatsiooni kergendamine). Selgus, et kofeiinravist saavad enam neuroprotektiivset kasu igasugust hingamistoetust vajavad vastsündinud (NIV ja IPPV). Varasem kofeiinravi alustamine vähendas enam hingamistoetuse päevade arvu. Autorid rõhutavad, et alagruppide analüüsi tulemustesse peaks suhtuma ettevaatlikult, kuna CAP uuring ei olnud disainitud vastavate analüüside teostamiseks.
Eelnevates uuringutes näidati, et kofeiin parandab VLBW enneaegsetel neuroloogilist kaugtulemit, kuid on ebaselge läbi millise mehhanismi. Doyle LW et al. avaldasid 2010.a uuringu, kus hinnati 70 CAP uuringus osalenud enneaegse lapse MRI-sid korrigeeritud vanuses 38-42 GN (keskmiselt 40.2 GN) hindamaks kofeiini mõju aju mikro- või makrostruktuursele arengule. Selgus, et kofeiini saanud laste ajus esinesid difusioonimuutused, mis viitavad paremale valgeaine mikrostruktuursele arengule ning need muutused ei ole vahendatud üle BPD vähenemise.

Skouroliakou M et al avaldasid 2009 a RCT, milles võrdlesid kofeiini ja teofülliini efektiivsust apnoe profülaktikas või ravis 70-l spontaanhingamisel oleval enneaegsel vastsündinul (<33 GN). Samuti määrati metüülksantiinide seerumikontsentratsiooni esimesel, kolmandal ja seitsmendal ravipäeval. Uuringust selgus, et kofeiin on võrreldes teofülliiniga efektiivsem esimesel elunädal, edasi see eelis kaob. Mõlema ravimi

seerumikontsentratsiooni monitooring esimesel 3 ravinädalal ei ole üldjuhul vajalik, kui puuduvad toksilisusele viitavad tunnused ning saavutatakse raviefekt.

OPTIMAALNE DOOS JA SOOVITUSLIK ANNUSTAMISSKEEM
Kuigi kofeiinravi on kasutatud apnoede raviks ja profülaktikaks aastakümneid, on optimaalne küllastus- ja säilitusannus ebaselge. Kofeiinravi alustatakse traditsiooniliselt küllastusannusega 20 mg/kg i.v kofeiintsitraati (võrdne 10 mg/kg kofeiin-alusega) ning säilitusannuseks on 5-10 mg/kg i.v või p.o. Arvatakse, et suurem kofeiinidoos võiks olla efektiivsem nii apnoede profülaktikas kui ka periekstubatsiooniperioodis. Kuna ajavahemikus 2009-2015 on kofeiini ravidooside kohta avaldatud vaid 1 RCT, kaasati antud kokkuvõtesse ka varasemaid RCT-sid.

Steer P et al avaldasid 2004. a randomiseeritud kontrolluuringu, mis hõlmas 234 enneaegset vastsündinut (<30 GN), kes vajasid KMVd rohkem kui 48 tundi. Uuringus võrreldi periekstubatsiooniperioodis tavapärast kofeiintsitraadi säilitusannust 5 mg/kg/die kõrgema annusega 20 mg/kg/die, küllastusannuseks oli vastavalt 80 mg/kg/die või 20 mg/kg/die. Kõrgemat kofeiinidoosi saanud lastel esines võrreldes tavadoosi grupiga statistiliselt oluliselt vähem ebaõnnestunud ekstubatsioone. (15.0 vs 29.8%, RR 0.51, 95%CI 0.21-0.85. Alla 28 GN vastsündinutel vähenes kõrget kofeiini doosi saanud lastel oluliselt KMV päevade arv (14.4 vs 22.1, P<0.01). Kõrvaltoimete (suremus, oluline neonataalne haigestumus, surm või raske puue 12 kuu vanuses) esinemissagedus kõrge doosi rühmas ei suurenenud.

Charles BG et al uurisid kofeiini farmakokineetikat eelnevalt mainitud RCT alarühmal (110/234-st enneaegsest vastsündinust) ning leidsid, et kofeiini eliminatsioon on ELBW vastsündinutel tugevalt langenud, kuid tõuseb mitte-lineaarselt sünnist kuni 6. elunädalani. Kofeiini biosaadavus suukaudsel manustamisel on 100%. Antud uuringus manustati kofeiini küllastusannuses 80 mg/kg või 20 mg/kg ning säilitusannuseks oli 20 mg/kg või 5 mg/kg. Antud dooside juures ei esinenud olulisi kõrvaltoimeid ning rutiinne kofeiini kontsentratsiooni monitoorimine ei ole otstarbekas.

Mohammed S et al võrdlesid kõrge (küllastusdoos 40 mg/kg/die, säilitusannus 20 mg/kg/die) ja madala kofeiinidoosi (küllastusannus 20 mg/kg/die ja säilitusdoos 10 mg/kg/die) efektiivsust ja ohutust 120 vastsündinul gestatsioonivanusega alla 32 GN, kel esines apnoe esimese 10. elupäeva jooksul. Kõrgdoosis kofeiin vähendas statistiliselt oluliselt ebaõnnestunud ekstubatsioone, apnoede esinemissagedust ja apnoe päevade arvu. Kõrvaltoimetest esines kõrge kofeiinidoosi grupis oluliselt enam tahhükardiat, gruppide vahel ei olnud erinevust neonataalse suremuse, BPD, NEK-i, IVH ja ROP-i esinemissageduse ning hospitaliseerimise kestuse osas.

Viited

Kokkuvõte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
META-ANALÜÜS I The six included trials (Sims 1985; Murat 1981; Peliowski 1990; Gupta 1981; Erenberg 2000; CAP Trial 2006) studied a total of 959 infants.	Henderson-Smart, D.J., De Paoli, A.G., 2010. ***Methylxanthine treatment for apnoea in***

All trials utilizing random or quasi-random patient allocation were included. Participants were preterm infants with recurrent apnoea. Six trials reported on the effect of methylxanthine in the treatment of apnoea (three trials of theophylline and three trials of caffeine). Outcome measures: **Primary** 1. Failed treatment (less than 50% reduction in apnoea, or use of IPPV, or death during study). 2. Use of IPPV. 3. Death before hospital discharge. **Secondary** 1. Acute drug side effects (tachycardia or feed intolerance leading to omission of treatment). 2. Neonatal morbidity such as - patent ductus arteriosus requiring treatment, intracranial haemorrhage, necrotizing enterocolitis. 3. Duration of IPPV. 4. Duration of oxygen therapy. 5. Chronic lung disease indicated by respiratory support (oxygen &/or positive airway pressure) still given at 36 weeks postmenstrual age. 6. Longer term outcomes, such as growth and neurodevelopmental outcome. Results were meta-analysed using a fixed effect model and treatment effects were expressed as relative risk (RR) and risk difference (RD) and their 95% confidence intervals. For significant results, we used the inverse of the risk difference (1/RD) to calculate the number needed to treat (NNT). If there was significant heterogeneity based on I^2 statistic that is unresolved by subgroup analyses, the random effects RR was also reported. <u>The results were similar across trials.</u> • Analysis of the three trials in which theophylline was used also showed significantly less treatment failure [summary RR 0.42 (95%CI 0.28 to 0.63), RD -0.50 (95%CI -0.67 to -0.33), NNT 2 (95%CI 1 to 3)] and a reduction in use of IPPV that nearly reaches statistical significance. The two trials evaluating caffeine found significantly less treatment failure [summary RR 0.46 (95%CI 0.27 to 0.78), RD -0.31 (95%CI -0.49 to -0.12), NNT 3 (95%CI 2 to 8)]. • The difference in the low rate of death before discharge (methylxanthine 3/81 versus control 6/73, RR 0.49, 95%CI 0.14 to 1.78) reported in three trials (Gupta 1981; Sims 1985; Erenberg 2000) is not significant. • Short term side effects were reported in three trials. Two reported that there were none (Peliowski 1990; Sims 1985) and one trial (Gupta 1981) reported that two infants in the theophylline group developed tachycardia. • The relative risk of having patent ductus arteriosus ligation was reduced in the caffeine group (RR 0.37; 95%CI 0.21 to 0.66).	***preterm infants.*** Cochrane Database Syst Rev CD000140. doi:10.1002/14651858.CD000140.pub2

• The postmenstrual age at last oxygen use was reduced in the caffeine group (mean difference, RR -0.90 weeks; 95%CI -1.54 to -0.26). • The postmenstrual age at the time of last endotracheal tube use was reduced in the caffeine group (mean difference RR -0.60 weeks; 95%CI -1.03 to -0.17). • The postmenstrual age at last positive pressure ventilation was lower in the caffeine group (mean difference, RR -0.90; 95%CI -1.32 to -0.48). • The risk ratio of chronic lung disease (BPD) at 36 weeks PMA was significantly less in the caffeine group (RR 0.72; 95%CI 0.58 to 0.89). • The risk ratio of cerebral palsy in long term follow up in infancy was lower, but not significantly (RR 0.60; 95% CI 0.29 to 1.25). • The risk ratio of death or major disability by late infancy was not significantly different, but there was a trend favouring the caffeine group (RR 0.85; 95%CI 0.71 to 1.01). In these studies, methylxanthine therapy led to a reduction in apnoea and use of intermittent positive pressure ventilation (IPPV) in the first two to seven days. The *post-hoc* analysis of the large CAP Trial comparing caffeine to control in a subgroup of infants being treated for apnoea reported significantly reduced rates of PDA ligation; postmenstrual age at last oxygen treatment, last endotracheal tube use, last positive pressure ventilation; and reduced chronic lung disease at 36 weeks. Methylxanthine is effective in reducing the number of apnoeic attacks and the use of mechanical ventilation in the two to seven days after starting treatment. Caffeine is also associated with better longer term outcomes. In view of its lower toxicity, caffeine would be the preferred drug for the treatment of apnoea.	

DATA AND ANALYSES

Comparison 1. Any methylxanthine vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed apnoea reduction after 2 - 7 days	5	192	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.32, 0.60]
1.1 Theophylline vs. control	3	92	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.28, 0.63]
1.2 Caffeine vs. control	2	100	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.27, 0.78]
2 Use of mechanical ventilation	5	192	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.12, 0.97]
2.1 Theophylline vs. control	3	92	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.13, 1.16]
2.2 Caffeine vs. control	2	100	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.66]
3 Tachycardia or feed intolerance	4	149	Risk Ratio (M-H, Fixed, 95% CI)	4.69 [0.24, 89.88]
3.1 Theophylline vs. control	2	49	Risk Ratio (M-H, Fixed, 95% CI)	4.69 [0.24, 89.88]
3.2 Caffeine vs. control	2	100	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 PDA ligation	1	827	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.21, 0.66]
4.1 Caffeine vs. control	1	827	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.21, 0.66]
5 PMA at last oxygen therapy	1	797	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.54, -0.26]
5.1 Caffeine vs. control	1	797	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.54, -0.26]
6 PMA at last endo-tracheal tube	1	797	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.03, -0.17]
6.1 Caffeine vs. control	1	797	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.03, -0.17]
7 PMA at last positive pressure ventilation	1	797	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.32, -0.48]
7.1 Caffeine vs. control	1	797	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.32, -0.48]
8 Cognitive delay	1	715	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.69, 1.06]
8.1 Caffeine vs. control	1	715	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.69, 1.06]
9 Chronic lung disease (BPD)	1	805	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.58, 0.89]
9.1 Caffeine vs. control	1	805	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.58, 0.89]
10 Death before discharge	3	154	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.14, 1.78]
10.1 Theophylline vs. control	2	72	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.05, 1.52]
10.2 Caffeine vs. control	1	82	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.16, 17.43]
11 Cerebral palsy	1	729	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.29, 1.25]
11.1 Caffeine vs. control	1	729	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.29, 1.25]
12 Death or major disability by late infancy	1	767	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.71, 1.01]
12.1 Caffeine vs. control	1	767	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.71, 1.01]

META-ANALÜÜS II

Seven studies were identified for inclusion (Barrington 1993; CAP 2006; Durand 1987; Greenough 1985; Muro 1992; Pearlman 1991; Viscardi 1985).

All published trials utilising random or quasi-random patient allocation in which treatment with methylxanthines (theophylline or caffeine) was compared with placebo or no treatment to improve the chances of successful extubation of preterm or low birth weight infants were included.

Meta-analysis of all randomised trials evaluating prophylactic methylxanthine used to limit the duration of mechanical ventilation. The standard method of Neonatal Review Group was used to synthesise the data. Results are expressed as relative risk (RR) and risk difference (RD) and from 1/RD the number needed to treat. The fixed effects model was used unless there was significant heterogeneity based on I2 statistic, that is unresolved by subgroup analysis. In this case, the random effects RR was also reported.

Results:

Treatment consisted of aminophylline or theophylline in four trials (Barrington 1993; Durand 1987; Greenough 1985; Viscardi 1985), and caffeine in two trials (Muro 1992; CAP 2006).

There was a wide range of gestational ages and birth weights in the infants enrolled in the studies. Although all trials had the aim of improving the chances of successful extubation, protocols differed considerably. In three studies, the infants were extubated at a set time

Henderson-Smart, D.J., Davis, P.G., 2010. ***Prophylactic methylxanthines for endotracheal extubation in preterm infants.*** Cochrane Database Syst Rev CD000139. doi:10.1002/14651858.CD000139.pub2

and then the need for reintubation within five days (Viscardi 1985; Pearlman 1991; Muro 1992), seven days (Barrington 1993) or at any time (Durand 1987) evaluated.The remaining trial (Greenough 1985) examined how many infants were still intubated at 48 hrs. Three trials (Durand 1987; Muro 1992; Viscardi 1985) found significant reductions in failure of extubation within one week of commencing treatment. Overall analysis of the six trials that reported on extubation failure showed that methylxanthine treatment results in a reduction in the incidence of failed extubation [summary RR 0.48 (95%CI 0.32 to 0.71)]. Overall there is an absolute reduction of 27 % in the incidence of failed extubation [summary RD -0.27 (95%CI - 0.39 to -0.15)]. There is significant heterogeneity in the Rd-metaanalysis (p = 0.007, I2 = 68.6) possibly related to the large variation in baseline rate in the control group (range 20 to 100%). Two trials reported side effects of methylxanthine treatment. Greenough 1985 found 2/18 of the treatment group and 0/20 of the control infants had tachycardia or agitation leading to cessation of treatment. The other small trial (Muro 1992) reported an increase in mean heart rate in infants treated with caffeine, but treatment was not withheld in any infant. The number of infants with reported side effects was small and the differences not significant. Methylxanthines are effective in assisting endotracheal extubation and improve long term neurodevelopmental and in-hospital respiratory outcomes. Methylxanthines increase the chances of successful extubation of preterminfantswithin oneweek of age.	
RCT **Background** Methylxanthines reduce the frequency of apnea of prematurity and the need for mechanical ventilation during the first seven days of therapy. It is uncertain whether methylxanthines have other short- and long-term benefits or risks in infants with very low birth weight. **Methods** We randomly assigned 2006 infants with birth weights of 500 to 1250 g during the first 10 days of life to receive either caffeine or placebo, until drug therapy for apnea of prematurity was no longer needed. We evaluated the short-term outcomes before the first discharge home. **Results** Of 963 infants who were assigned to caffeine and who remained alive at a postmenstrual age of 36 weeks, 350 (36 percent) received supplemental oxygen, as did 447 of the 954 infants (47 percent) assigned to placebo (adjusted odds ratio, 0.63; 95 percent confidence interval, 0.52 to 0.76; P<0.001). Positive airway pressure was discontinued one week earlier in the infants assigned to caffeine (median postmenstrual age, 31.0 weeks; interquartile range, 29.4 to 33.0) than in the infants in the placebo group (median postmenstrual age, 32.0 weeks;	Schmidt B[1], Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W; ***Caffeine for Apnea of Prematurity Trial Group Caffeine therapy for apnea of prematurity.*** N Engl J Med. 2006 May 18;354(20):2112-21.

interquartile range, 30.3 to 34.0; P<0.001). Caffeine reduced weight gain temporarily. The mean difference in weight gain between the group receiving caffeine and the group receiving placebo was greatest after two weeks (mean difference, −23 g; 95 percent confidence interval, −32 to −13; P<0.001). The rates of death, ultrasonographic signs of brain injury, and necrotizing enterocolitis did not differ significantly between the two groups. **Conclusions** Caffeine therapy for apnea of prematurity reduces the rate of bronchopulmonary dysplasia in infants with very low birth weight.	
RCT **Background** Methylxanthine therapy is commonly used for apnea of prematurity but in the absence of adequate data on its efficacy and safety. It is uncertain whether methylxanthines have long-term effects on neurodevelopment and growth. **Methods** We randomly assigned 2006 infants with birth weights of 500 to 1250 g to receive either caffeine or placebo until therapy for apnea of prematurity was no longer needed. The primary outcome was a composite of death, cerebral palsy, cognitive delay (defined as a Mental Development Index score of <85 on the Bayley Scales of Infant Development), deafness, or blindness at a corrected age of 18 to 21 months. **Results** Of the 937 infants assigned to caffeine for whom adequate data on the primary outcome were available, 377 (40.2%) died or survived with a neurodevelopmental disability, as compared with 431 of the 932 infants (46.2%) assigned to placebo for whom adequate data on the primary outcome were available (odds ratio adjusted for center, 0.77; 95% confidence interval [CI], 0.64 to 0.93; P = 0.008). Treatment with caffeine as compared with placebo reduced the incidence of cerebral palsy (4.4% vs. 7.3%; adjusted odds ratio, 0.58; 95% CI, 0.39 to 0.87; P = 0.009) and of cognitive delay (33.8% vs. 38.3%; adjusted odds ratio, 0.81; 95% CI, 0.66 to 0.99; P = 0.04). The rates of death, deafness, and blindness and the mean percentiles for height, weight, and head circumference at follow-up did not differ significantly between the two groups. **Conclusions** Caffeine therapy for apnea of prematurity improves the rate of survival without neurodevelopmental disability at 18 to 21 months in infants with very low birth weight.	Schmidt B[1], Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W; Caffeine for Apnea of Prematurity Trial Group ***Long-term effects of caffeine therapy for apnea of prematurity.*** N Engl J Med. 2007 Nov 8;357(19):1893-902.
RCT **Objective** To determine whether the benefits of caffeine vary in three subgroups of 2006 participants in the Caffeine for Apnea of Prematurity (CAP) trial. **Study design** Post-hoc subgroup analyses were performed on the basis of: (1) indication for commencement of study drug: treat apnea, prevent apnea, or facilitate extubation; (2) positive pressure ventilation (PPV) at randomization: endotracheal tube (ETT), noninvasive ventilation, or none; and (3) timing of commencement of study drug: early or late (<=	Davis PG1, Schmidt B, Roberts RS, Doyle LW, Asztalos E, Haslam R, Sinha S, Tin W; ***Caffeine for Apnea of Prematurity Trial Group Caffeine for Apnea of Prematurity trial: benefits may vary in***

3 versus >3 days). Outcomes assessed were those showing treatment effects in the original analyses. We investigated the consistency of caffeine effects by using regressionmodels that incorporated treatment/subgroup factor interactions. **Results** There was little evidence of a differential treatment effect of caffeine in subgroups defined by the clinical indication for starting study drug. The size and direction of the caffeine effect on death or disability differed depending on PPV at randomization (P = .03). Odds ratios (95% CI) were: no support, 1.32 (0.81-2.14); noninvasive support, 0.73 (0.52-1.03); and ETT, 0.73 (0.57-0.94). Adjustment for baseline factors strengthened this effect (P = .02). Starting caffeine early resulted in larger reductions in days of respiratory support. Postmenstrual age at time of discontinuing PPV was shorter with earlier treatment (P = .01). Mean differences (95% CI) were: early, 1.35 weeks (0.90-1.81); and late 0.55 weeks (–0.11-0.99). Adjustment for baseline factors weakened this effect (P = .03). **Conclusions** There is evidence of variable beneficial effects of caffeine. Infants receiving respiratory support appeared to derive more neurodevelopmental benefits from caffeine than infants not receiving support. Earlier initiation of caffeine may be associated with a greater reduction in time on ventilation. (J Pediatr 2010;156:382-7).	***subgroups.*** J Pediatr. 2010 Mar;156(3):382-7

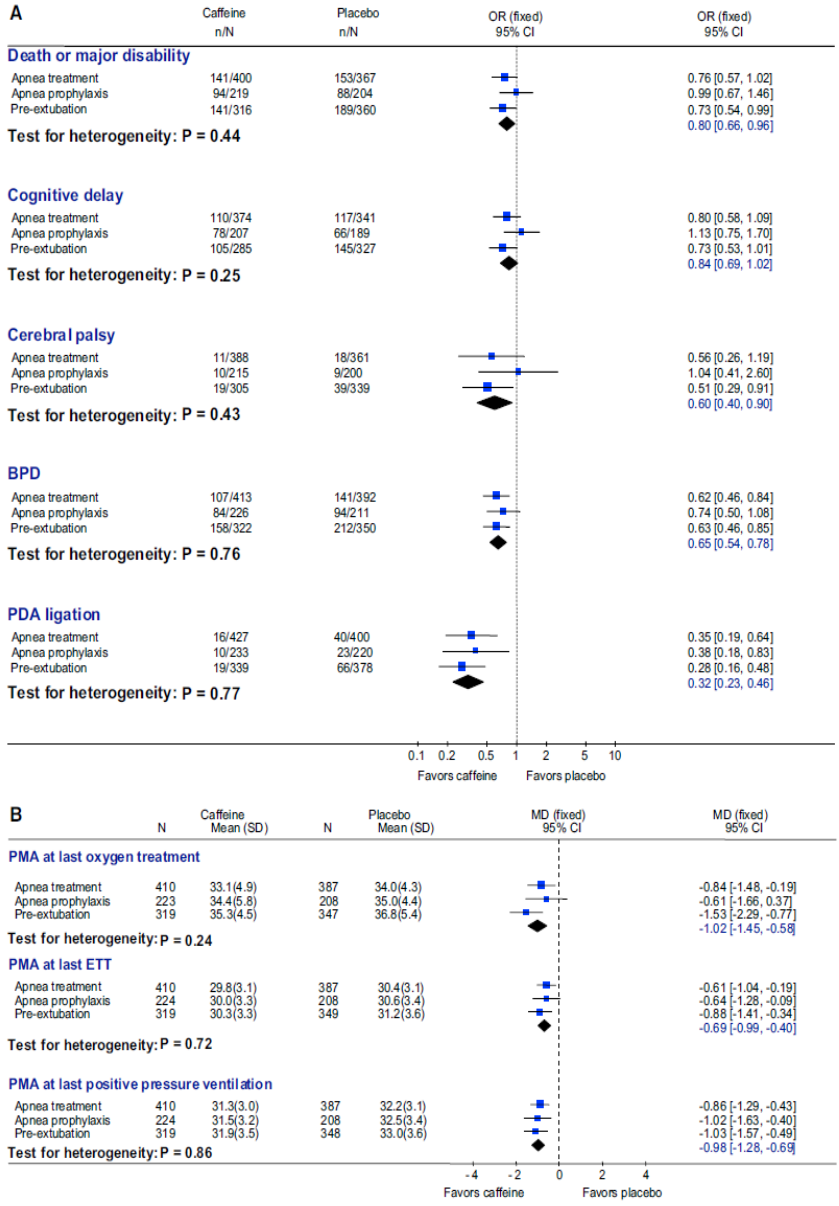

Figure 1. **A,** Neonatal morbidities and long-term impairments by reason for treatment. **B,** PMA at last use of respiratory supports by reason for treatment. Each black diamond represents the overall treatment effect for that outcome.

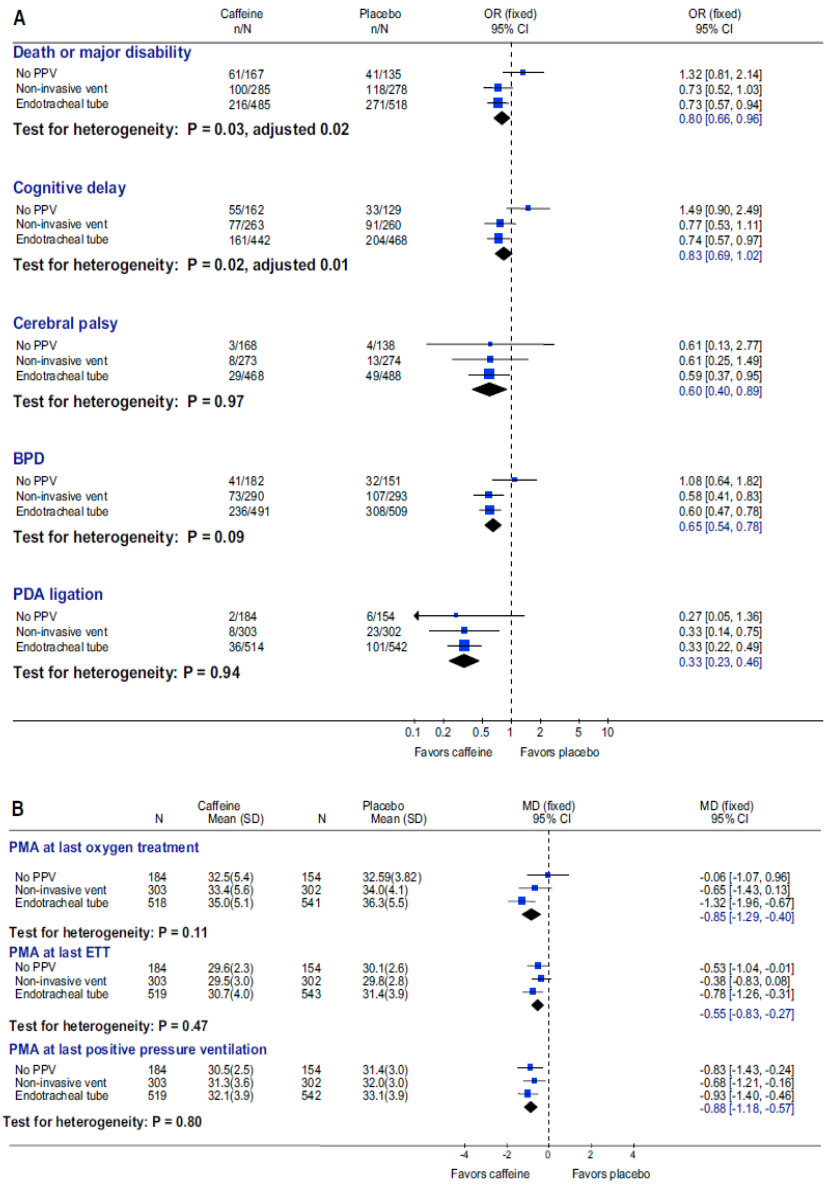

Figure 2. **A,** Neonatal morbidities and long-term impairments by level of respiratory support at randomization **B,** PMA at last use of respiratory supports by level of respiratory support at randomization. Each black diamond represents the overall treatment effect for that outcome.

RCT

Objective: Caffeine improves neurological outcome in very preterm infants, but the mechanisms responsible for this neurological benefit are unknown. The objective of this study was to assess whether caffeine influenced brain macro or microstructural development in preterm infants.

Methods: Seventy preterm infants <1,251 g birthweight randomly allocated to either caffeine (n ¼ 33) or placebo (n ¼ 37) underwent brain magnetic resonance imaging (MRI) at term-equivalent age; white and gray matter abnormalities were qualitatively scored, global and

Doyle, LW, Cheong J, Anderson PJ et al. ***Caffeine and brain development in very preterm infants.*** Ann Neurol. 2010 Nov; 68(5): 167-72

regional brain volumes were measured, and white matter microstructure was evaluated using diffusion-weighted imaging. **Results:** There were no significant differences between the groups in the extent of white matter or gray matter abnormality, or in global or regional brain volumes. In contrast, although only available in 28 children, caffeine exposure was associated with reductions in the apparent diffusion coefficient, and radial and axial diffusivity with the greatest impact in the superior brain regions. The alterations in diffusion measures were not mediated by lowering the rate of lung injury, known as bronchopulmonary dysplasia. **Interpretation:** These diffusion changes are consistent with improved white matter microstructural development in preterm infants who received caffeine.	
RCT **Aim:** To compare standard doses of theophylline and caffeine for apnea of prematurity in terms of apnea frequency and assess the need for therapeutic drug monitoring. **Methods:** Seventy neonates less than 33 weeks gestation, breathing spontaneously, were randomly assigned (open-label) to receive either theophylline or caffeine for treatment or prevention of apnea. The primary outcome measure was the difference in apnea frequency between theophylline and caffeine patient groups. Methylxanthine serum levels were measured on the 1st, 3rd and 7th days of therapy and every 7 days thereafter. **Results:** Thirty-seven neonates received theophylline (T) and 33 caffeine (C) for treatment (8 T/10 C) or prevention of apnea (29 T/23 C). Treatment with either methylxanthine significantly decreased apnea events (T, $P = 0.012$; C, $P = 0.005$) while only C prophylaxis appeared to control apnea in infants at risk. Analysis of combined (treatment plus prophylaxis) data showed a significant decrease in apnea frequency only in those infants receiving caffeine ($P = 0.001$). However, there was no sustained benefit of C over T beyond the first week of therapy. T and C concentrations (2.2–13.9 mg/L; 5.5–23.7 mg/L, respectively) in the majority of cases fell within the recommended therapeutic ranges and were not significantly associated with apnea events. **Conclusions:** This study shows an advantage of C over T for premature infants □33 weeks gestation during the first week of therapy. Standard regimens of both methylxanthines do not seem to require routine concentration monitoring in the first 3 weeks of treatment unless indicated by clinical effect	Skouroliakou M, Bacopoulou F, Markantonis SL ***Caffeine versus theophylline for apnea of prematurity: a randomised controlled trial.*** J Paediatr Child Health. 2009 Oct;45(10):587-92.
RCT The optimum caffeine dose in preterm infants has not been well investigated. We aimed to compare the efficacy and safety of high versus low-dose caffeine citrate on apnea of prematurity (AOP) and successful extubation of preterm infants from mechanical ventilation. We compared high-dose (loading 40 mg/kg/day and maintenance of 20	Mohammed S[1], Nour I, Shabaan AE, Shouman B, Abdel-Hady H, Nasef N. ***High versus low-dose***

mg/kg/day)versus low-dose (loading 20 mg/kg/day and maintenance of 10 mg/kg/day) caffeine citrate in preterm infants <32 weeks gestation, presented with AOP within the first 10 days of life. A total of 120 neonates (60 in each group) were enrolled. High-dose caffeine was associated with a significant reduction in extubation failure in mechanically ventilated preterm infants ($p<0.05$), the frequency of apnea ($p<0.001$), and days of documented apnea ($p<0.001$). High-dose caffeine was associated with significant increase in episodes of tachycardia ($p<0.05$) without a significant impact on physician decision to withhold caffeine. **Conclusion:** The use of higher, than current standard, dose of caffeine may decrease the chance of extubation failure in mechanically ventilated preterm infants and frequency of AOP without significant side effects.	***caffeine for apnea of prematurity: a randomized controlled trial.*** Eur J Pediatr. 2015 Feb 3.
RCT **Objective**: To compare two dosing regimens for caffeine citrate in the periextubation period for neonates born at less than 30 weeks gestation in terms of successful extubation and adverse effects. **Design:** A multicentre, randomised, double blind, clinical trial. **Setting:** Four tertiary neonatal units within Australia. **Patients:** Infants born less than 30 weeks gestation ventilated for more than 48 hours. **Interventions:** Two dosing regimens of caffeine citrate (20 v 5 mg/kg/day) for periextubation management. Treatment started 24 hours before a planned extubation or within six hours of an unplanned extubation. Main outcome measure: Failure to extubate within 48 hours of caffeine loading or reintubation and ventilation or doxapram within seven days of caffeine loading. **Results**: A total of 234 neonates were enrolled. A significant reduction in failure to extubate was shown for the 20 mg/kg/day dosing group (15.0% v 29.8%; relative risk 0.51; 95% confidence interval (CI) 0.31 to 0.85; number needed to treat 7 (95% CI 4 to 24)). A significant difference in duration of mechanical ventilation was shown for infants of less than 28 weeks gestation receiving the high dose of caffeine (mean (SD) days 14.4 (11.1) v 22.1 (17.1); $p = 0.01$). No difference in adverse effects was detected in terms of mortality, major neonatal morbidity, death, or severe disability or general quotient at 12 months. **Conclusions**: This trial shows short term benefits for a 20 mg/kg/day dosing regimen of caffeine citrate for neonates born at less than 30 weeks gestation in the periextubation period, without evidence of harm in the first year of life.	P Steer, V Flenady, A Shearman, B Charles, P Gray, D Henderson-Smart, G Bury, S Fraser, J Hegarty, Y Rogers, S Reid, L Horton, M Charlton, R Jacklin, and A Walsh ***High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial*** Arch Dis Child Fetal Neonatal Ed. 2004 Nov; 89(6): F499–F503.
RCT The objective of this study was to develop a population model of the pharmacokinetics (PK) of caffeine after orogastric or intravenous administration to extremely premature neonates with apnea of prematurity who were to undergo extubation from ventilation. Infants of gestational age <30 weeks were randomly allocated to receive	Charles BG, Townsend SR, Steer PA, Flenady VJ, Gray PH, Shearman A. ***Caffeine citrate treatment for extremely***

maintenance caffeine citrate dosing of either 5 or 20 mg/kg/d. Four blood samples were drawn at prerandomized times from each infant during caffeine treatment. Serum caffeine was assayed by enzyme-multiplied immunoassay technique. Concentration data (431 samples, median: 4 per subject) were obtained from 110 (52 male) infants of mean birth weight of 1009 g, current mean weight (WT) of 992 g, mean gestational age of 27.6 weeks, and mean postnatal age (PNA) of 12 days. Of 1022 doses given, 145 were orogastric, permitting estimation of absolute bioavailability. A 1-compartment model with first-order absorption was fitted to the data in NONMEM. Patient characteristics were screened ($P < 0.01$) in nested models for pharmacokinetic influence. Model stability was assessed by nonparametric bootstrapping. Clearance (CL) increased nonlinearly with increasing PNA, whereas volume of distribution (Vd) increased linearly with WT, according to the following allometric models: CL (L/h) = 0.167 (WT/70) (PNA/12); Vd (L) = 58.7 (WT/70). The mean elimination half-life was 101. Interindividual variability (IIV) of CL and Vd was 18.8 % and 22.3 %, respectively. Interoccasion variability (IOV) of CL and Vd was 35.1% and 11.1%, respectively. This study established that the elimination of caffeine was severely depressed in extremely premature infants but increased nonlinearly after birth up to age 6 weeks. Caffeine was completely absorbed, which has favorable implications for switching between intravenous and orogastric routes. The interoccasion variability about CL was twice the interindividual variability, which, among other factors, indicates that routine serum concentration monitoring of caffeine in these patients is not warranted.	***premature infants with apnea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring.*** Ther Drug Monit. 2008 Dec;30(6):709-16**.**
RCT Five-year follow-up from 2005 to 2011 in 31 of 35 academic hospitals in Canada, Australia, Europe, and Israel, where 1932 of 2006 participants (96.3%) had been enrolled in the randomized, placebo-controlled **Caffeine for Apnea of Prematurity (CAP) trial** between 1999 and 2004. A total of 1640 children (84.9%) with birth weights of 500 to 1250 g had adequate data for the main outcome at 5 years. The combined outcome of death or disability was not significantly different for the 833 children assigned to caffeine from that for the 807 children assigned to placebo (21.1% vs 24.8%; odds ratio adjusted for center, 0.82; 95% CI, 0.65-1.03; *P*=.09). The rates of death, motor impairment, behavior problems, poor general health, deafness, and blindness did not differ significantly between the 2 groups. The incidence of cognitive impairment was lower at 5 years than at 18 months and similar in the 2 groups (4.9% vs 5.1%; odds ratio adjusted for center, 0.97; 95% CI, 0.61-1.55; *P*=.89). Neonatal caffeine therapy was no longer associated with a significantly improved rate of survival without disability in children with very low birth weights who were assessed at 5 years.	Schmidt, B., Anderson, P.J., Doyle, L.W., Dewey, D., Grunau, R.E., Asztalos, E.V., Davis, P.G., Tin, W., Moddemann, D., Solimano, A., Ohlsson, A., Barrington, K.J., Roberts, R.S., Caffeine for Apnea of Prematurity (CAP) Trial Investigators, 2012. ***Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity.*** JAMA 307, 275–282. doi:10.1001/jama.2011.2024

RCT Motor dysfunction, including cerebral palsy and the more common motor impairment of developmental coordination disorder (DCD) without cerebral palsy occurs more frequently in children born either with very low birth weight (<1500 g birth weight) or very preterm (<32 weeks' gestation) than in children of either normal birth weight (>2499 g birth weight) or born at term. It is known from the international randomized controlled trial of caffeine for apnea of prematurity, the **Caffeine for Apnea of Prematurity (CAP) trial**, that caffeine treatment in the first weeks after birth in infants <1250 g birth weight reduces the incidences of cognitive impairment and of cerebral palsy at 18 months of age. By 5 years of age the reduction in rates of cerebral palsy with caffeine treatment was no longer statistically significant, but overall function on the Gross Motor Function Classification System was improved in the caffeine group. Motor dysfunction not associated with cerebral palsy or cognitive impairment is referred to as DCD. Children in the Caffeine for Apnea of Prematurity trial were assessed for motor performance (Movement Assessment Battery for Children [MABC]), clinical signs of cerebral palsy, and Full-Scale IQ at 5 years of age by staff who were unaware of the children's treatment group. DCD was defined as MABC <5th percentile in children with a Full-Scale IQ >69 who did not have a diagnosis of cerebral palsy. There were 1433 children with known MABC corrected-age percentile as well as known Full-Scale IQ at 5 years and cerebral palsy status, of whom 735 had been randomly assigned to caffeine and 698 to placebo therapy. The rate of DCD was lower in those treated with caffeine (11.3%) than in the placebo group (15.2%) (OR adjusted for center and baseline covariates, 0.71, 95% CI, 0.52-0.97; P = .032). Neonatal caffeine therapy for apnea of prematurity reduces the rate of DCD at 5 years of age. As more children have DCD than have cerebral palsy, this is an important additional benefit from neonatal caffeine treatment.	Doyle, L.W., Schmidt, B., Anderson, P.J., Davis, P.G., Moddemann, D., Grunau, R.E., O'Brien, K., Sankaran, K., Herlenius, E., Roberts, R., Caffeine for Apnea of Prematurity Trial Investigators, 2014. ***Reduction in developmental coordination disorder with neonatal caffeine therapy.*** J. Pediatr. 165, 356–359.e2. doi:10.1016/j.jpeds.2014.04.016
Objective This study aims to compare the effects of early and late (routine) initiation of caffeine in nonintubated preterm neonates. **Study Design** A total of 21 neonates < 29 weeks gestational age were randomized to receive intravenous caffeine citrate (20 mg/kg) or placebo either before 2 hours of age (early) or at 12 hours of age (routine). This was an observational trial to determine the power needed to reduce the need for endotracheal intubation by 12 hours of age. Other outcomes included comparisons of cerebral oxygenation, systemic and pulmonary blood flow, hemodynamics, hypotension treatment, oxygen requirement, and head ultrasound findings.	Katheria, A.C., Sauberan, J.B., Akotia, D., Rich, W., Durham, J., Finer, N.N., 2015. ***A Pilot Randomized Controlled Trial of Early versus Routine Caffeine in Extremely Premature Infants.*** Am J Perinatol.

Results There was no difference in the need for intubation ($p = 0.08$), or vasopressors ($p = 0.21$) by 12 hours of age. Early caffeine was associated with improved blood pressure ($p = 0.03$) and systemic blood flow (superior vena cava flow, $p = 0.04$ and right ventricular output, $p = 0.03$). Heart rate, left ventricular output, and stroke volume were not significantly affected. Cerebral oxygenation transiently decreased 1 hour after caffeine administration. There were no differences in other outcomes. **Conclusion** This pilot study demonstrated the feasibility of conducting such a trial in extremely preterm neonates. We found that early caffeine administration was associated with improved hemodynamics. Larger studies are needed to determine whether early caffeine reduces intubation, intraventricular hemorrhage, and related long-term outcomes	doi:10.1055/s-0034-1543981

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Andmebaas	Medline (PUBMED)
Otsingustrateegia: (Key words + Mesh)	((("Caffeine"[Mesh]) OR caffeine)) AND ((((((((((((("premature infant") OR "premature infants") OR "premature newborn") OR "premature newborns") OR "premature neonate") OR "premature neonates") OR "preterm infant") OR "preterm infants") OR "preterm newborn") OR "preterm newborns") OR "preterm neonate") OR "preterm neonats")) OR (("Infant, Premature"[Mesh]) OR "Infant, Low Birth Weight"[Mesh]))
Tulemuste arv	Meta-analysis 3; SR 13; RCT 7
Filtrid	Systematic Review, Meta-analysis Randomised Controlled Trial
Ajaline piirang	5 aastat
Muud piirangud	English language