Kliiniline küsimus nr 23

Kas enneaegsete vastsündinute parema ravitulemuse saavutamiseks on varase parenteraalse toitmise eelistamine parem võrreldes hilise parenteraalse toitmise alustamisega?

- vedeliku vajadus gestatsiooninädala ja elupäevade kaupa
- süsivesikute, valkude ja rasvade pakkumine parenteraalsel toitmisel kilogrammi kehakaalu kohta

Tulemusnäitajad: lapse peamised tulemusnäitajad

Ravijuhendid

Kokkuvõte ravijuhendites leiduvast:

Soovitused enneaegsete vastsündinute parenteraalse toitmise kohta on leitavad kolmes AGREE-ga hinnatud ravijuhendis:

European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Halliday HL; European Association of Perinatal Medicine. Neonatology. 2013;103(4):353-68. (AGREE 82%) **(1)**

Care of extremely premature infants: A guideline for the care of children born before 28 full weeks of pregnancy have passed. *(*originaal rootsi keeles: *Vård av extremt för tidigt födda barn. En vägledning för vård av barn födda före 28 fullgångna graviditetsveckor.)* **2014.** (AGREE 70%) **(2)**

Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). Koletzko B1, Goulet O, Hunt J, Krohn K, Shamir R; Parenteral Nutrition Guidelines Working Group; European Society for Clinical Nutrition and Metabolism;European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005 Nov;41 Suppl 2:S1-87. (AGREE 91%) **(3)** – See ravijuhend on võetud soovituste koostamisel kasutusele, kuna on antud teemal kõige põhjalikum ning usaldusväärsem kättesaadav ravijuhend, millel põhinevad suuresti ka hiljem avaldatud ja käesolevalt kasutatud ravijuhendid.

Euroopa 2013. a. ravijuhend:

Esitatud soovitused on Euroopa juhendis koostatud GRADE süsteemi kasutades ja põhinevad kuni 2012. a. lõpuni publitseeritud teaduskirjandusel.

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

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

Intensiivse toitmisega tuleks alustada alates sünnist, sest on teada, et see vähendab sünnijärgset kaalulangust ja pikemaajalist postnataalselt kasvupeetust. Algul, kui enteraalse toitmise mahud on piiratud, tuleks toitaineid manustada parenteraalselt – eesmärgiga pakkuda piisavalt energiat ja aminohappeid, et vältida negatiivset (lämmastiku)bilanssi ja soodustada varast kasvamist suurendades valgusünteesi ja lämmastiku säilitamist. Nii vara kui võimalik tuleks alustada minimaalse enteraalse või troofilise toitmisega (rinnapiimaga 10-20 ml/kg/päevas), et parandada seedekulgla küpsemist ja talitlust.

Enamus kasutusel olevatest protokollidest sisaldab kindlat varast vedelikupakkumist järk-järgult suurenevas mahus, kasutades individuaalset lähenemist ning võttes arvesse vedelikubilanssi, kaalumuutust ja seerumi elektrolüütide väärtusi.

Enamusel lastel niisutatud kuvöösitingimustes tuleks alustada intravenoosse vedelikupakkumisega 70-80 ml/kg/päevas, ent väga ebaküpsed enneaegsed vastsündinud võivad vajada rohkem vedelikku. (D)

Vedelikupakkumist tuleb kohandada individuaalselt, arvestades seerumi naatriumikontsentratsiooni ja kaalulangust. (D)

Esimestel elupäevadel tuleks naatriumipakkumist piirata, alustades sellega pärast diureesi vallandumist, hoolikat vedelikubilansi ja elektrolüütide taseme jälgimist. (B)

Parenteraalse toitmisega tuleks alustada esimesel elupäeval, suurendades kiiresti valgupakkumist 3,5 g/kg/päevas ja lipiidide pakkumist taluvuse korral 3,0 g/kg/päevas. (C)

Minimaalse enteraalse toitmisega tuleks alustada esimesest elupäevast (B)

<u>Rootsi ravijuhend 2014:</u>

põhineb kuni 2014. a. (k.a.) avaldatud teaduskirjanduse süstemaatilisel analüüsil ja riigi neonatoloogia ekspertide arvamusel, seda küsimuste osas, mille kohta ei ole piisavalt tõendusmaterjali.

Parenteraalne toitmine on invasiivne ravivõte, millega kaasneb suur risk tüsistusteks (peamiselt hooldusega klaasnevad infektsioonid) ja seetõttu on oluline kogemus, hästitoimiv tegutsemisviis ning hoolikas jälgimine/monitooring.

Enneaegse lapse kiire kasvamise tõttu on vajalik suur energia ja toitainete pakkumine juba esimestest elutundidest. See on võimalik kasutades kontsentreeritud lahuste manustamist tsentraalse veenitee kaudu ja enteraalselt pakutava rinnapiima hulga kiiret suurendamist.

Parenteraalse toitmisega tuleb alustada sünni järgselt võimalikult varakult (esimestel elutundidel), lisaks alustada varase enteraalse toitmisega rinnapiimaga. (*The assessment is based on systematic charting.***)**

Adekvaatne vedeliku- ja elektrolüütide tasakaal on vajalik, et vältida dehüdratatsiooni, ülehüdratatsiooni, elektrolüütide häireid ja metaboolset atsidoosi, mis omakorda võivad suurendada suremust ja haigestumust.

Sügavalt enneaegsete laste kogu keha vedelik moodistab ligi 90% kaalust. Nende laste neerufunktsioon on ebaküps ja piiratud. Seetõttu on esimestel elunädalatel vedeliku ja elektrolüütide tasakaal väga õrn; häired ja ka väikesed nihked selles tasakaalus võivad tingida tõsisesid tagajärgi.

Võimalusel tuleb alustada varase fosfori, kaltsiumi ja magneesiumi pakkumisega. Naatriumi ja kaaliumi taluvus väikeses hulgas on seotud küllaldase toitmisega. Kolmel esimesel elupäeval peab vedeliku ja naatriumkloriidi pakkumine olema piiratud (vt. tabel).

Vee ja elektrolüütide tasakaalu peab hoolikalt jälgima, eriti esimesel elunädalal. (*The assessment is based on consensus between the chairpersons of the expert groups.***)**

<u>Soovitatud toitainete tarbimine enneaegsel vastsündinul</u>

Agostoni, C, Buonocore, G, Carnielli, VP, De Curtis, M, Darmaun, D, Decsi, T, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010; 50(1):85-91.

Koletzko, B, Goulet, O, Hunt, J, Krohn, K, Shamir, R, Parenteral Nutrition Guidelines Working Group, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005; 41 Suppl 2:S1-87.

Koletzko, B, Poindexter, B, Uauy, R. Nutritional care of preterm infants: scientific basis and practical guidelines; 2014.

Toitaine (kg/päevas)[a]	Elupäev 0[b]	Elupäev 4[c]	Täielik ET[d]	Täieleik PT[e]
Vedelik (ml)	80-100	130-160	135-200	135-180
Energia (kcal)	50-60	105-125	115-135	90-115
Valk/aminohapped (g)	2-2.4	3.5-4.5	4.0-4.5	3.5-4
Süsivesikud (g)	7-10	11-16	9-15	13-17
Glükoos (mg/kg/min)	5-7	-	-	9-12
Rasv (g)	1.0-1.5	4-6	5-8	3(-4)
Dokosaheksaeenhape (mg)	-	-	12-60	11-60
Arahhidoonhape (mg)	-	-	18-45	14-45
Na (mmol)	0-1	2-4	3-7	3-7
P (mmol)	0-1	1.0-2.5	2-3	2-3
Cl (mmol)	0-1	2-4	3-7	3-7
Ca (mmol)	0.5-1.5	2.2-2.7	3.0-3.5	1.5-2
P (mmol)	0.5-1.5	1.7-2.5	2-3	1.5-1,9
Mg (mg)	0-4	6-11	8-15	4,3-7,2

Fe (mg)	-	0	2-3	0,1-0.2
Zn (mg)	-	1-1.5	1.5-2.5	0.4-0.45
Cu (µg)	-	70-110	120-200	20-25
Se (µg)	-	2-5	2-7	2-5
Mn (µg)	-	0-4	1.0-7.5	0-1
I (µg)	-	10-30	10-50	10
Vit A (RÜ)	-	1 000-2 300	1 300-3 300	700-1 500
Vit D (RÜ)	-	220-600	400-1 000	40-160
Vit E (mg)	-	2.2-7	2.2-11	2.8-3.5
Vit K (µg)	-	4.4-20	4.4-28	4.4-16
Vit C (mg)	-	13-35	11-46	15-25
Tiamiin B1 (µg)	-	140-300	140-300	200-350
Riboflaviin B2 (µg)	-	150-300	200-400	150-200
Püridoksiin B6 (µg)	-	45-250	45-300	150-200
Niatsiin (mg)	-	0.4-7,0	0.4-5,5	4-7
Pantoteen (mg)	-	0.3-2,0	0.3-2,1	1-2
Biotiin (µg)	-	1.7-12,0	1.7-16,5	5-8
Folaat (µg)	-	35-90	35-100	35-80
Vit B12 (µg)	-	0.1-0.6	0.1-0/77	0.1-0.5

[a] Kilogrammi kehakaalu kohta päevas kõikide ühikute kohta. Kasutada võimalikult täpset kaalu v.a. esimestel elupäevadel, mil kasutada sünnikaalu, kuni sünnikaal on saavutatud ja ületatud.

[b] Elupäev 0 all mõistetakse sündimise kuupäeva s.t. sünnist kuni järgmise päeva hommikuni. Soovitus kehtib terve päeva kohta ning tuleb individuaalselt kohandada vastavalt lapse sünniajale.

[c] Enneaegne laps peaks saama täisannuses toitaineid 4 elupäevaks (veel vähese vedelikupiiranguga). Selle tulba soovitused on ligikaudsed ja põhinevad 50% enteraalsel ja 50% parenteraalsel toitmisel. Täpne eesmärk (mida tuleb individuaalselt arvestada) sõltub parenteraalse ja enteraalse toitmise vahekorrast, näiteks parenteraalse toitmise suurema mahu korral on eesmärkväärtused madalamad.

[d] Soovitav pakkumine täielikul enteraalsel toitmisel (ET).

[e] Soovitav pakkumine täielikul pareneteraalsel toitmisel (PT).

ESPAGHAN 2005

Põhineb süstemaatilisel kirjanduse ülevaatel peamiselt ajavahemikust 1992-2003 detsember. Kui oli oluliseid anmeid varasemast ajast, siis kasutati ka neid allikaid. Esitatud soovitused on koostatud allpool toodud tõenduspõhisuse ja soovituste tugevuse kriteeriume järgides (SIGN 2000).

TABLE 1.2. *Grading of levels of evidence (LOE) according to the Scottish Intercollegiate Guideline Network (SIGN) 2000*

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 of RCTs, or RCTs with a low risk of bias.
1−	Meta analyses, systematic reviews of RCTs, 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, or chance and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2−	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3	Non-analytic studies, e.g. case reports, case series. Evidence from non-analytic studies e.g. case reports, case series.
4	Evidence from expert opinion.

TABLE 1.3. *Grading of recommendations (GOR) according to the Scottish Intercollegiate Guideline Network (SIGN) 2000*

A.	Requires at least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs, or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.
B.	Requires a body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+.
C.	Requires a body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall 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+.

Soovitused:

AH pakkumisega tuleks alustada esimesel elupäeval GOR B

Minimaalne AH pakkumine peaks olema vähemalt 1,5 g/kg/päevas, et ennetada negatiivset lämmastikubilanssi. Suurem pakkumine on vajalik, et saavutada füsioloogiline valgu talletamine. GOR A

Soovitav maksimaalne AH pakkumine on 4 g/kg/pävas. GOR B

Lipiidemulsioonide pakkumine ei tohiks olla suurem kui nende äratarvitamine (*lipid clearance*) ja hüperlipideemia puhul tuleb annuseid vähendada. GOR B

Lipiidemulsioone tuleks manustada 24 tunnise infusioonina. GOR B

Lipiidemulsioone saavatel patsientidel on vajalik triglütseriidide (TG) taseme jälgimine, eriti suurenenud hüperlipideemia riski korral (s.h. suurema lipiidide manustamise, sepsise, katabolismi ja ELBW vastsündinute puhul). GOR D

Lipiidemulsioonide vähendamist tuleks kaaluda, kui seerumi TG väärtus on >2,8 mmol/l. GOR D

Enneaegsetel vastsündinutel, kes ei saa piisavalt energiat enteraalsest toidust tuleks alustada lipiidide pakkumisega mitte hiljem kui kolmandal elupäeval, aga võib alustada ka esimesel elupäeval. GOR B

Varane lipiidemulsioonide manustamine esimestel elupäevadel võrreldes hilise lipiidemulsioonide manustamisega ei suurenda krooonilise kopsuhaiguse esinemist või suremust enneaegsetel lastel (LOE 1). Siiski peaks eraldi jälgima varase lipiide pakkumise puhul võimalike kõrvaltoimete esinemise osas VLBW lapsi (<800 g). LOE 2

Lipiidide manustamisel ei ole enneaegsete laste populatsioonis näidatud märkimisväärset toimet hüperbilirubineemiale (LOE 2). Seni on ebaselge, missugust bilirubiini taset

enneaegsetel vastsündinutel saab pidada ohutuks. Suurenenud hüeperbilirubineemia riskiga laste parenteraalse toitmise korral, on vajalik hoolikas TG ja bilirubiini jälgimine ja vastavalt sellele lipiidide infusioonimahu korrigeerimine. GOR D

Lipiidemulsioonide manustamine fototeraapia ajal peaks toimuma spetsiaalsete valguskaitstud infusiooniliinide abil, et vähendada hüdroperoksiidide tekkimist. GOR B

Glükoosi infusiooni tuleks alustada 4-8 mg/kg/min (5,8-11,5 g/kg/päevas) GOR C

Maksimaalne glükoosi oksüdatsioon enneaegsetel vastsündinutel sünnijärgselt on 8,3 mg/kg/min (12 g/kg/päevas). LOE 2-3

Insuliini infusiooni võib hüperglükeemiaga VLBW lastel kasutada PT ajal, kuid ohutus ja toimed kliinilisele tulemile ei ole käesolevalt teada. GOR D

ESPAGHAN-i ravijuhend ei käsitle erinevate lipiidlahuste manustamist EA vastsündinutel. Selle kohta on andmeid hilisemates RCT-des ja metaanalüüsides.

Samuti on insuliini kasutamise kohta viimasel ajal avaldatud 1 metaanalüüs.

Süstemaatilised ülevaated

Kokkuvõte süstemaatilistest ülevaadetest

Enneaegsete vastsündinute parenteraalse toitmise kohta olid vastavalt otsingukriteeriumitele kätteasaadavad 4 meta-analüüsi (avaldatud viimase 5 aasta jooksul).

Trivedi A, Sinn JK. Early versus late administration of amino acids in preterm infants receiving parenteral nutrition. *Cochrane Database Syst Rev. 2013* **(11)**

Moyses HE, Johnson MJ, Leaf AA, Cornelius VR. Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. *Am J Clin Nutr. 2013 Apr;97(4):816-26.* **(4)**

Vlaardingerbroek H, Veldhorst MA, Spronk S, van den Akker CH, van Goudoever JB. Parenteral lipid administration to very-low-birth-weight infants--early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis. *Am J Clin Nutr. 2012 Aug;96(2):255-68.* **(5)**

Sinclair JC, BottinoM, Cowett RM. Interventions for prevention of neonatal hyperglycemia in very low birth weight infants. *Cochrane Database Syst Rev. 2011***(13)**

Ülevaateartikleid oli väga mitmeid (kokku 17), kuid väga hea kvaliteediga uuematest süstemaatilistest ülevaateartiklitest väärib kasutamist

Uthaya S, Modi N. Practical preterm parenteral nutrition: systematic literature review and recommendations for practice. *Early Hum Dev. 2014 Nov;90(11):747-53.* **(6)** Selles ülevaateartiklis sisaldub ka allpool kommenteeritud metaanalüüside ja RCT-de ülevaade.

Mitmed ülevaateartiklid (**Recommended nutrient intake levels for stable, fully enterally fed very low birth weight infants.** Koletzko B, Poindexter B, Uauy R. World Rev Nutr Diet. 2014;110:297-9. doi: 10.1159/000360195. Epub 2014 Apr 11.

Approaches to growth faltering. Poindexter B. World Rev Nutr Diet. 2014;110:228-38. doi: 10.1159/000358471. Epub 2014 Apr 11. Review. **Preterm nutrition and the brain.** Ramel SE, Georgieff MK. World Rev Nutr Diet. 2014;110:190-200. doi: 10.1159/000358467. Epub 2014 Apr 11. **Practice of parenteral nutrition in VLBW and ELBW infants.** Embleton ND, Simmer K. World Rev Nutr Diet. 2014;110:177-89. doi: 10.1159/000358466. Epub 2014 Apr 11. Review. **Enteral and parenteral lipid requirements of preterm infants.** Lapillonne A. World Rev Nutr Diet. 2014;110:82-98. doi: 10.1159/000358460. Epub 2014 Apr 11. **Energy requirements, protein-energy metabolism and balance, and carbohydrates in preterm infants.** Hay WW Jr, Brown LD, Denne SC.World Rev Nutr Diet. 2014;110:64-81. doi: 10.1159/000358459. Epub 2014 Apr 11. Review. **Amino acids and proteins.** van Goudoever JB, Vlaardingerbroek H, van den Akker CH, de Groof F, van der Schoor SR. World Rev Nutr Diet. 2014;110:49-63. doi: 10.1159/000358458. Epub 2014 Apr 11. Review. **Nutrition, growth and clinical outcomes.** Ehrenkranz RA.World Rev Nutr Diet. 2014;110:11-26. doi: 10.1159/000358455. Epub 2014 Apr 11. Review. **Defining the nutritional needs of preterm infants.** Uauy R, Koletzko B. World Rev Nutr Diet. 2014;110:4-10. doi: 10.1159/000358453. Epub 2014 Apr 11. Review.) on avaldatud ühtse kogumikuna: **Koletzko, B, Poindexter, B, Uauy, R. Nutritional care of preterm infants: scientific basis and practical guidelines; 2014 (12)**	
2013 a. meta-analüüsi hõlmati 7 randomiseeritud kontrolluuringut (*Blanco 2008; Heimler 2010; Murdock 1995; Rivera 1993; Saini 1989; Tang 2009; te Braake 2005; van den Akker 2006 –viimane oli läbi viidud te Braake 2005 alagrupil)*, et võrrelda varase ja hilise aminohapete (AH) pakkumise mõju enneaegsete laste kasvule, neuroloogilisele arengule, suremusele ja kliiniliselt olulistele kõrvaltoimetele. Varaseks AH pakkumiseks loeti AH pakkumist esimese 24 elutunni jooksul (eraldi või koos teiste parenteraalsete lahustega); hiliseks AH pakkumiseks loeti AH manustamist pärast 24 elutundi. (Uuringute kvaliteet küsitav – kõik uuringud olid ühekeskuselised, väikese laste arvuga, ainult ühel RCT-l oli eelnevalt registreeritud protokoll; pimendamist ei olnud kasutatud ühelgi juhul. Uuringute disain oli väga erinev – AH pakkumine 0-2,4 g/kg/päevas esimesel päeval kuni maksimaalse annuseni 2,5-4,0 g/kg/päevas. Hiliseks AH pakkumiseks peeti uuringutes lapse vanust >24;>48 ja mõnedes uuringutes ka >72 tunni.) Ainult ühe RCT (*Saini 1989*) andmetel ei esinenud 10 päeva vanuselt erinevust pikkuse ja peaümbermõõdu juurdekasvu osas. (Selles uuringus olid ka kõige tagasihoidlikumad AH pakkumised ning lipiidide lisamine pärast 7 ep.) 4 RCT-d *(Rivera 1993; Saini 1989; van den Akker 2006; Heimler 2010)* (kokku 93 enneaegset last) näitasid positiivset lämmastikubilanssi - 95% CI oli 250.42 (224.91 - 275.93 P <0.00001). 4 RCT *(Rivera 1993; te Braake 2005;Tang 2009; Heimler 2010)* näitasid olulist erinevust vere uurea sisalduses esimese 48 tunni jooksul (P <0.00001).	**Early versus late administration of amino acids in preterm infants receiving parenteral nutrition.** Trivedi A, Sinn JK. Cochrane Database Syst Rev. 2013 Sisaldab üsna madala kvaliteediga RCT-sid.

Varase AH pakkumisega ei kaasnenud metaboolne atsidoos esimese 24 tunni jooksul. **Antud metanalüüsis järeldati, et ei ole piisavalt andmeid varase AH pakkumisega kaasnevatest soodsatest toimetest suremusele, varasele ja hilisele kasvule ja neuroloogilisele arengule. 4 RCT andmetel kaasneb varase AH pakkumisega positiivne lämmastikubilanss – kliiniline olulisus siinkohal jääb selgusetuks. Varase AH pakkumisega lastel esinesid normaalne happe-alustasakaal ja ammooniumi väärtused.** **Arvestades väikest laste arvu käesolevasse metanalüüsi hõlmatud RCT-des, uuringute heterogeensust ja puudulikku vastsust kliiniliselt olulise tulemuse osas, siis antud andmetele tuginedes, ei ole võimalik anda praktilisi soovitusi varase või hilise AH pakkumise osas <37 GN vanustel lastel.**	
Ainus praeguseks publitseeritud metaanalüüs, milles võrreldakse varase ja hilise PT mõju kasvamisele ja võimalikele riskidele. 2013. aasta metanalüüsi hõlmati 8 RCT-d ja 13 vaatlusuuringut (OS) (kokku vastavalt 553 ja 1796 last), eesmärgiks hinnata, kas varane PT alustamine parandab enneaegsete laste kasvamist. Käesoleva analüüsi puuduseks tuleb pidada kasvamise hindamiseks kasutatud erinevaid tulemeid. Võimalikke vigasid/mõjusid uuringutele oli raske hinnata, kuna neid ei olnud adekvaatselt kirjeldatud. Tulemused olid esitatud keskmise erinevusena (95% CI). Varane PT vähedas aega sünnikaalu taassaavutamiseni 2,2 päeva (1,1-3,2) RCT-de puhul ja 3,2 päeva (2,0-4,4) OS-de puhul. Maksimaalne kaalulangus oli madalam 3,1 % (1,7-4,5) RCT-des ja 3,5% (2,6-4,3) OS-des. Varane PT suurendas kaalu haiglast väljakirjutamisel või 36 GN (PMA) 14,9 g (5,3-24,5), andmed ainult OS-dest, kuid pikkuskasvule ja peaümbermõõdule ei kaasnenud positiivset mõju. Antud metanalüüsi hõlmatud uuringute andmetel ei kaasne varase PT-ga suurem risk suremuseks, NEK-i, sepsisesse, CLD, IVH-sse või kolestaasi haigestumiseks. Ainult ühes RCT-s (*Blanco 2008-2012*) oli hinnatud neuroloogilist kaugtulemit – varase PT-ga ei kaasne halvem neuroloogiline kaugtulem 2 a. vanuses. **Antud metanalüüsis** (mõnede puudustega) **järeldati, et varane PT alustamine tagab lühiajalise kasvu osas paremaid tulemusi. Varase PT-ga ei suurene suremus ja haigestumus.** Teadusuuringute paremaks läbiviimiseks neonatoloogias oleks abi süstematiseeritud kasvamise hindamisest.	**Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis.** Moyses HE, Johnson MJ, Leaf AA, Cornelius VR. Am J Clin Nutr. 2013 Apr;97(4):816-26. Sisaldab erineva kvaliteediga ja mitte eriti tugevaid RCT-sid ja vaatlusuuringuid. "-" erinevad PT lahused; varase ja hilise PT aegade osaline kattuvus (vt. allpool ingl. k. tabelid)
Varasemas Cochrane metanalüüsis *(2005)* võrreldi „varast" (<5 p) ja „mitte varast" (>5p) lipiiide alustamist enneaegsetel lastel – järeldati, et	**Parenteral lipid administration to**

ei esinenud gruppidevahelisi erinevusi kasvus, suremuses, BPD esinemises. ESPAGHAN (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition) 2005 juhistes soovitati vastsündinutel, keda ei ole võimalik piisavalt toita enteraalselt, alustada lipiidemulsioonide parenetraalset manustamist mitte hiljem kui 3. päeval, aga võiks alustada esimesel elupäeval. Käesoleva metanalüüsi eesmärgiks oli hinnata varase (≤2p) ning hilise (>2 p) lipiidide alustamisega ja erineva koostisega lipiidemulsioonide manustamise kaasnevaid mõjusid enneaegsete (VLBW) laste kasvule ja haigestumisele. 2012 a. metanalüüsi hõlmati 14 RCT-d. Varase lipiidide manustamisega ei kaasnenud erinevusi haigestumises ja suremuses. Leiti nõrk soodne seos mittetäielikult sojaoaõlil baseeruvate lipiidemulsioonide kasutamisel sepsise esinemissagedusele (RR: 0,75; 95% CI: 0,56-1,00). **Järeldati, et lipiidide alustamine VLBW lastel esimesel 2 elupäeval on turvaline ja hästi talutav; kuigi erinevate lipiidemulsioonide kasulikkust kasvamisele ei õnnestunud tõestada. Mittetäielikult sojaoaõlil baseeruvate lipiidemulsioonide kasutamine võib olla seoses väiksema sepsise esinemissagedusega**. Ulatuslikud RCT-d enneaegsetel lastel on vajalikud, et tõestada varase lipiidide manustamise ja mittetäielikult sojaoaõlil baseeruvate lipiidemulsioonide kasutamisega kaasnevat soodsat mõju pikaajalisele tulemile.	**very-low-birth-weight infants--early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis.** Vlaardingerbroek H, Veldhorst MA, Spronk S, van den Akker CH, van Goudoever JB. Am J Clin Nutr. 2012 Aug;96(2):255-68. Analüüsitud RCT-d varase ja hilise lipiidide alustamise kohta üsna vanad (aastatest 1978-1997); paljudel juhtudel AH pakkumine väga vähene või puudulik võrreldes tänapäevaste soovitustega.
Enneaegsete laste parenteraalse toitmise kohta on avaldatud vähe piisava tugevusega uuringud. Mitmed neist on vasturääkivad ja seetõttu kindlaid soovitusi enneaegsete laste parenteraalse toitmise kohta teha ei saa. Antud süstemaatiline ülevaade põhineb 1980. – 2014. a. (34. nädalani) avaldatud teaduskirjandusel enneaegsete laste PT kohta. 1) Varase ja hilise PT alustamise võrdlus (kättesaadav vaid üks metaanalüüs *Moyses 2013*) vt. tabelis ülalpool 2) Varase ja hilise AH manustamise võrdlus (kättesaadav vaid üks metaanalüüs *Trivedi, Cochrane Database Syst Rev. 2013*) vt. tabelis ülalpool 3) Vähene, astmeliselt suurevev AH manustamine võrreldes suurema AH pakkumisega (7 RCT-d väiksem vs suurem AH pakkumine) Vähene AH pakkumine varieerus 1,0 - 2,4 g/kg/päevas suurenedes	**Practical preterm parenteral nutrition: systematic literature review and recommendations for practice.** Uthaya S, Modi N. *Early Hum Dev. 2014 Nov;90(11):747-53.*

maksimaalselt kuni 2,5 g/kg/päevas. Suur AH pakkumine oli vahemnikus 3-4 g/kg/päevas. Mõnedes uuringutes alustati madalama pakkumisega ja jõuti mõne päevaga suurema pakkumiseni. Üks uuring ei näidanud paremust varase kasvamise osas (*Clark 2007*), ühe andmetel oli kasvamine halvem suurema AH pakkumisega grupis (*Balasubramanian 2013*) ja ühes ei esinenud täiendavat paranemist lämmastikubilansi osas võrreldes AH pakkumist 2,4 ja 3,6 g/kg/päevas, nagu see oli välja toodud samaaegse varase lipiidide pakkumisega (*Vlaardingerbroek 2013*). Ühes uuringus võrreldi varast ja hilist AH pakkumist ja teisese tulemina kirjeldati neuroloogilist tulemit 2 a. vanuses. Gruppidevahelist erinevust neuroloogilises tulemis ei esinenud, küll aga olid kõrge AH pakkumisega grupis kasvutulemused halvemad (*Blanco 2012*). Ühes mitte pimendatud RCT-s võrreldi väikest järk-järgult suurenevas annuses AH pakkumist (alustades 1,5 g/kg/päevas kuni maksimumannuseni 2,5 g/kg/päevas) suurema ja järk-järgult suurenevas annuses AH pakkumisega (alustades 2,5 g/kg/päevas kuni maksimumannuseni 4 g/kg/päevas). Kirjeldatud gruppides ei esinenud erinevusi 36 GN mõõdetud kehamõõtudes. 2. a. vanuses ei esinenud erinevusi neuroloogilises arengus (*Burattini 2013*). Ühes uuringus võrreldi kontrollgrupis standard PT lahuste (10% glükoos + valk ja lipiidid 2,8 g/kg/päevas) ja uuringugrupis standardiseeritud kontsentreeritud ja makroelementidega rikastatud PT (SCAMP-*Standardised Concentrated With Added Macronutrients Parenteral*) toitelahuste (12% glükoos + valk ja lipiidid 3,8 g/kg/päevas) kasutamise mõju varasele peakasvule. SCAMP grupis oli märgatavalt parem parem peaümbermõõdu (PÜ) juurdekasv sünnist kuni 28 päeva vanuseni (ΔPÜ $p< 0,001$) ning see jäi oluliselt erinevaks veel ka 36 GN vanuses.
Neuroloogilist arengut selles uuringus ei hinnatud (*Morgan 2014*).

4) Varase ja hilise lipiidide pakkumise võrdlus ja lipiidide koostis.
Varase ja hilise lipiidide alustamise kohta kättesaadav üks metanalüüs 14 RCT-st (*Vlaardingerbroek 2012*) vt. tabelis ülalpool. Järeldati, et lipiidide alustamine VLBW lastel esimesel 2 elupäeval on turvaline ja hästi talutav; kuigi erinevate lipiidemulsioonide kasulikkust kasvamisele ei õnnestunud tõestada. Mittetäielikult sojaoaõlil baseeruvate lipiidemulsioonide kasutamine võib olla seoses väiksema sepsise esinemissagedusega.

5) Standardiseeritud ja individualiseeritud PT võrdlus.
Antud teema kohta ei ole avaldatud metaanalüüse ega RCT-sid. Ei ole kindlalt teada ühe PT viisi eelised teise ees. Tehti ülevaade vaatlus- ja kohortuuringutest. Mõnedes uuringutes näidati standardiseeritud PT puhul suuremat manustatud valgu ja kalorite hulka (*Yeung 2003; Skouroliakou 2009; Lenclen 2006*). Teistes uuringutes aga leiti, et need, kellele manustati individuaalset PT, said rohkem toitaineid ja nende kasvamine oli parem (*Smolkin 2010; Eleni-dit-Trolli 2009; Dice 1981*).

Süstemaatiste ülevaadete kokkuvõtvad tõenduspõhised soovitused:

Enamus uuringuid, mis leiti enneaegsete vastsündinute PT kohta ja millele soovituste tegemisel saab tugineda, on keskendunud lühiajalisele tulemile, PT ohutusele ja taluvusele. Käesolevalt ei ole teada missugune oleks optimaalne viis enneaegsete toitainete vajaduse katmiseks ja PT-ks, et tagada parim pikaajaline tervisetulem. Seetõttu on keerukas anda kindlaid soovitusi.

Kliinilises praktikas on soovitav sünnijärgselt alustada PT nii kiiresti kui võimalik – see on ohutu ja hästi talutav. PT alustamise edasilükkamine kuni tsentraalne veenitee on rajatud, ei ole vajalik. Puuduvad tõendid, et osmolaarsuse/glükoosi kontsentratsiooniga kaasnevad riskid kaaluksid üle PT-st saadava kasu.

Vedelikuvajadust tuleks arvestada eraldi toitainete vajadusest. Rutiinselt ei peaks enneaegsetel vastsündinutel rakendama vedeliku piiramist, kui selleks ei esine näidustusi (neeru- või südamepuudulikkus). Vt. tabel. Vedelikuvajadus peaks olema mahus, mis tagab piisava/optimaalse toitainetega varustamise.

AH lahuste manustamine peaks algama sünnijärgselt võimalikult kiiresti ja mitte hiljem kui 24 tunni vanuses. Turvaline on alustada alates esimesest elupäevast AH pakkumisega 2-3,5 g/kg/päevas. Suurema AH pakkumisega kaasnevat soodsat mõju lühiajalisele ja kaugtulemile ei ole tõestatud.

Lipiidide manustamisega tuleks alustada esimesel elupäeval. Rutiinselt ei ole soovitatud kasutada III põlvkonna lipiidlahuseid (s.h. SMOF Lipid).

Süsivesikute pakkumist tuleks alustada annuses 8-10 g/kg/päevas ja edasiselt juhinduda hoolikast vere glükoositaseme monitooringust. Insuliini kasutamine hüperglükeemia ennetamiseks ei ole näidustatud.

Standardiseeritud PT eeliseks individuaalse PT ees toitmise erivajaduseta enneaegsetel vastsündinutel on väiksem risk vigadeks PT vajaduste arvutamisel, lahuste valmistamisel, samuti infektsiooniriski ning kulude vähenemine.

Suhteliselt vähe on avaldatud ja teostatud arvestatava tugevusega randomiseeritud kontrolluuringuid enneaegse vastsündinute varase ja hilise parenteraalse toitmise võrdlusest. Viimaste aastate uuringutes on enam keskendutud tasakaalustatud ja standardiseeritud toitmisele, sobivaima toitainetepakkumise suhtele PT puhul. Sagedamini on hinnatud PT mõju kasvamisele, metabolismile, varasele tulemile. Oluliselt vähem on andmeid hilise tervisetulemi s.h. neuroloogilise kaugtulemi kohta. Uuringute omavahelises võrdluses on piiranguks erinevused kasutatud lahuste osas.
Eestis oleks vajalik kontsentreeritumate aminohapete lahuste kasutamine (nt. Primene 10 % Baxter®) enneaegsete vastsünditnute populatsioonis (käesolevalt kasutusel Vaminolact 6 % Fresenius Kabi AB®), et vältida vedeliku ülekoormust ja tagada kasvamiseks ning optimaalseks arenguks vajalik AH pakkumine.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
ABSTRACT	**Interventions for**

Background Among very low birth weight (VLBW) infants, early neonatal hyperglycemia is common and is associated with increased risks for death and major morbidities. It is uncertain whether hyperglycemia per se is a cause of adverse clinical outcomes or whether outcomes can be improved by preventing hyperglycemia. **Objectives** To assess effects on clinical outcomes of interventions for preventing hyperglycemia in VLBW neonates receiving full or partial parenteral nutrition. **Search strategy** We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, issue 4 of 12, 2011; MEDLINE (1966 to April 2011); EMBASE (1980 to April 2011); CINAHL (1982 to Nov 2008); abstracts of Pediatric Academic Societies 2000 to 2011 and European Society for Pediatric Research 2005 to 2010. **Selection criteria** Randomized or quasi-randomized controlled trials of interventions for prevention of hyperglycemia in neonates with birth weight <1500 g or gestational age < 32 wk. **Data collection and analysis** Two review authors independently selected studies for eligibility and extracted data on study design, methods, clinical features, and treatment outcomes. Included trials were assessed for blinding of randomization, intervention and outcome measurement, and com- pleteness of follow-up. Treatment effect measures for categorical outcomes were relative risk and risk difference, and for continuous outcomes, mean difference, each with their 95% confidence intervals. **Main results** We detected four eligible trials. Two trials compared lower versus higher rates of glucose infusion in the early postnatal period. These trials were too small to assess effects on mortality or major morbidities. Two trials, one a moderately large multicentre trial (NIRTURE, Beardsall 2008), compared insulin infusion with standard care. Insulin infusion reduced hyperglycemia but increased death before 28 days and hypoglycemia. Reduction in hyperglycemia was not accompanied by significant effects on major morbidities; effects on neurodevelopment are awaited. **Authors' conclusions** **<u>Glucose infusion rate:</u> There is insufficient evidence from trials comparing lower with higher glucose infusion rates to inform clinical practice. Large randomized trials are needed, powered on clinical outcomes including death, major morbidities and adverse neurodevelopment.** **<u>Insulin infusion:</u> The evidence reviewed does not support the routine use of insulin infusions to prevent hyperglycemia in VLBW neonates. Further randomized trials of insulin infusion may be justified. They should enrol extremely low birth weight neonates at very high risk for hyperglycemia and neonatal death. They might use real time glucose monitors if these are validated for clinical use.**	**prevention of neonatal hyperglycemia in very low birth weight infants.** Sinclair JC, BottinoM, Cowett RM. Cochrane Database Syst Rev. 2011

Refinement of algorithms to guide insulin infusion is needed to enable tight control of glucose concentrations within the target range.	
A B S T R A C T **Background** Observational studies in preterm newborns suggest that delay in administering amino acids could result in a protein catabolic state and could impact on growth and development. **Objectives** To determine the effect of early administration of amino acids in premature newborns on growth, neurodevelopmental outcome, mortality and clinically important side effects. **Search methods** The standard search strategy of the Neonatal Review Group as outlined in *The Cochrane Library* was used. Relevant randomised controlled trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library 2012 Issue 9*), MEDLINE, EMBASE and CINAHL from their earliest dates to September 2012. The trial registry portal of the World Health Organization's International Cilinical Trial Registry Platform and ClinicalTrials.gov (US National Institute of Health) was searched to identify ongoing and completed but unpublished studies. **Selection criteria** Randomised controlled trials comparing early administration of amino acids with late administration in premature newborn infants were included. Early administration of amino acid solution was defined as the administration of amino acids in isolation or with total parenteral nutrition within the first 24 hours of birth; late initiation was defined as the administration of amino acids in isolation or with total parenteral nutrition after the first 24 hours of birth. The primary outcome measures were growth, neurodevelopmental outcome and mortality at 28 days. The secondary outcomes were biochemical abnormalities, sepsis and mortality. **Data collection and analysis** Both review authors independently selected trials, assessed trial quality and extracted data from the included studies. We contacted authors for further information. Fixed-effect analyses were performed. The treatment effect was expressed as mean difference for continuous variables and as risk difference and risk ratio for dichotomous variables. All results included 95% confidence intervals (CIs). **Main results** Seven randomised controlled trials were included in this review. One randomised controlled trial reported no difference in crownheel length and occipitofrontal head circumference by day 10. **Four trials that enrolled 93 premature infants showed positive nitrogen balance (The mean difference with 95%CI was 250.42 (224.91 to 275.93 P value < 0.00001).**	**Early versus late administration of amino acids in preterm infants receiving parenteral nutrition.** Trivedi A, Sinn JK. Cochrane Database Syst Rev. 2013

Analysis 2.1. Comparison 2 Nitrogen balance, Outcome 1 Nitrogen balance.

Review: Early versus late administration of amino acids in preterm infants receiving parenteral nutrition

Comparison: 2 Nitrogen balance

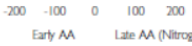
Outcome: 1 Nitrogen balance

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Heimler 2010	8	217 (109)	9	-132 (51)		9.6 %	349.00 [266.45, 431.55]
Rivera 1993	11	88 (54)	12	-135 (45)		39.1 %	223.00 [182.18, 263.82]
Saini 1989	10	122 (19)	11	-133 (76)		30.2 %	255.00 [208.57, 301.43]
van den Akker 2006	16	151 (105)	16	-99 (42)		21.2 %	250.00 [194.59, 305.41]
Total (95% CI)	**45**		**48**			**100.0 %**	**250.42 [224.91, 275.93]**

Heterogeneity: Chi^2 = 7.25, df = 3 (P = 0.06); I^2 =59%

Test for overall effect: Z = 19.24 (P < 0.00001)

Test for subgroup differences: Not applicable



Four trials showed a significant difference in the level of blood urea nitrogen (BUN) in the first 48 hours (P value < 0.00001).

Analysis 5.1. Comparison 5 BUN, Outcome 1 BUN levels in first two days.

Review: Early versus late administration of amino acids in preterm infants receiving parenteral nutrition

Comparison: 5 BUN

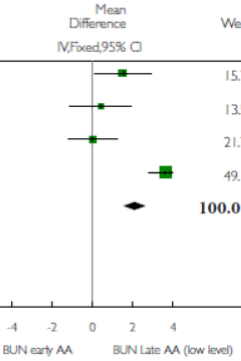
Outcome: 1 BUN levels in first two days

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Blanco 2008	30	7.3 (3.3)	31	5.8 (2.2)		15.7 %	1.50 [0.09, 2.91]
Rivera 1993	11	5.1 (2.2)	12	4.7 (1.4)		13.5 %	0.40 [-1.12, 1.92]
Tang 2009	34	5.78 (2.25)	32	5.77 (2.69)		21.7 %	0.01 [-1.19, 1.21]
te Braake 2005	66	9.6 (2.8)	69	6 (1.8)		49.1 %	3.60 [2.80, 4.40]
Total (95% CI)	**141**		**144**			**100.0 %**	**2.06 [1.50, 2.62]**

Heterogeneity: Chi^2 = 30.69, df = 3 (P<0.00001); I^2 =90%

Test for overall effect: Z = 7.22 (P < 0.00001)

Test for subgroup differences: Not applicable



Early administration of amino acids did not result in metabolic acidosis in the first 24 hours.

Analysis 3.1. Comparison 3 Metabolic acidosis, Outcome 1 pH within first 24 hours.

Review: Early versus late administration of amino acids in preterm infants receiving parenteral nutrition

Comparison: 3 Metabolic acidosis

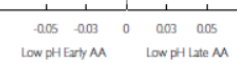
Outcome: 1 pH within first 24 hours

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Tang 2009	34	7.34 (0.07)	32	7.34 (0.07)		33.4 %	0.0 [-0.03, 0.03]
te Braake 2005	66	7.33 (0.08)	69	7.34 (0.06)		66.6 %	-0.01 [-0.03, 0.01]
Total (95% CI)	**100**		**101**			**100.0 %**	**-0.01 [-0.03, 0.01]**

Heterogeneity: Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 0.67 (P = 0.50)

Test for subgroup differences: Not applicable



Authors' conclusions

There is no available evidence of the benefits of early administration of amino acids on mortality, early and late growth and neurodevelopment. There is evidence from four randomised

controlled trials included in this review that early administration of amino acids is associated with a positive nitrogen balance. The clinical relevance of this finding is not known. Acid-base status and ammonia levels were normal in the infants who received amino acids early. Given the small number of infants in the randomised controlled trials included in this review, the clinical heterogeneity among them, and the lack of data on important clinical outcomes, there is insufficient evidence to guide practice regarding the early versus late administration of amino acids to infants less than 37 weeks gestation.

A B S T R A C T

Background:

The achievement of adequate nutritional intakes in preterm infants is challenging and may explain the poor growth often seen in this group. The use of early parenteral nutrition (PN) is one potential strategy to address this problem, although the benefits
and harms are unknown.

Objective:

We determined whether earlier administration of PN benefits growth outcomes in preterm infants.

Design:

We conducted a systematic review of randomized controlled trials (RCTs) and observational studies.

Results:

Eight RCTs and 13 observational studies met the inclusion criteria (n = 553 and 1796 infants).

TABLE 2
Characteristics of included studies[1]

First author, year of publication (reference)	Study type	Complex	No. of subjects		Gestational age		Birth weight		Timing of PN	
			Early	Late	Early	Late	Early	Late	Early	Late
					wk		*kg*			
Aroor, 2012 (16)	Retrospective	No	49	54	28.0	27.0	1.100	1.100	From birth	>48 h
Dinerstein, 2006 (17)	Retrospective	Yes	117	65	30.0	30.0	1.245	1.230	Day 1	Day 3
Donovan, 2006 (18)	Retrospective	Yes	57	23	27.3	27.1	0.946	0.929	<24 h	>48 h
García, 2012 (19)	Prospective	No	29	29	30.1	30.1	1.236	1.243	<24 h	>48 h
Ho, 2003 (20)	Retrospective	Yes	17	19	30.9	30.7	1.416	1.396	Day 1	>48 h
Elstgeest, 2010 (21)	Retrospective	No	73	70	26.0	26.0	0.915	0.907	<24 h	36–48 h
Geary, 2008 (22)	Retrospective	Yes	76	87	25.7	25.4	0.788	0.742	Birth	Days 2–4
Han, 2012 (23)	Retrospective	No	112	52	31.3	31.3	1.372	1.387	<24 h	>24 h
Janeiro, 2010 (24)	Retrospective and prospective	Yes	28	28	29.8	29.1	1.245	1.142	<24 h	Day 2
Kotsopoulos, 2006 (25)	Prospective	No	54	54	26.1	26.3	0.859	0.878	<6 h	12–30 h
Radmacher, 2009 (26, 27)	Retrospective	No	20	70	26.0	26.2	0.741	0.756	From birth	24 h
Trintis, 2012 (28)	Retrospective and prospective	No	85	88	27.6	27.8	0.973	1.103	From birth	24–48 h
Valentine, 2009 (29)	Retrospective and prospective	No	308	132	29.1	29.4	1.157	1.202	From birth	Day 2
Bai, 2005 (30)	RCT	No	20	20	32.0	32.3	1.390	1.410	Day 1	>48 h
Brownlee, 1993 (31)	RCT	No	63	66	29.0	29.0	1.144	1.147	<36 h	Day 6
Heimler, 2010 (32)	RCT	No	8	9	29.6	30.2	1.258	1.182	<24 h	>72 h
Ibrahim, 2004 (33)	RCT	No	16	16	27.0	26.8	0.846	0.968	From birth	>48 h
Wilson, 1997 (34)	RCT	Yes	64	61	27.0	27.4	0.925	0.933	12 h	Day 3
Blanco, 2008–2012 (35–37)	RCT	No	30	31	25.7	26.3	0.768	0.783	<24 h	24–36 h
te Braake, 2005 (38)	RCT	No	66	69	28.4	28.4	1.039	0.989	From birth	Day 2
Weiler, 2006 (39)	RCT	No	7	7	28.1	26.7	0.954	0.956	<24 h	Day 2

[1] PN, parenteral nutrition; RCT, randomized controlled trial.

The meta-analysis was limited by disparate growth-outcome measures. An assessment of bias was difficult because of inadequate reporting. Results are given as mean differences (95% CIs). **Early PN reduced the time to regain birth weight by 2.2 d (1.1, 3.2 d) for RCTs and 3.2 d (2.0, 4.4 d) in observational studies. The maximum percentage weight loss with early PN was lower by 3.1 percentage points (1.7, 4.5 percentage points) for RCTs and by 3.5 percentage points (2.6, 4.3 percentage points) for observational studies.**

Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis.

Moyses HE, Johnson MJ, Leaf AA, Cornelius VR.

Am J Clin Nutr. 2013 Apr;97(4):816-26.

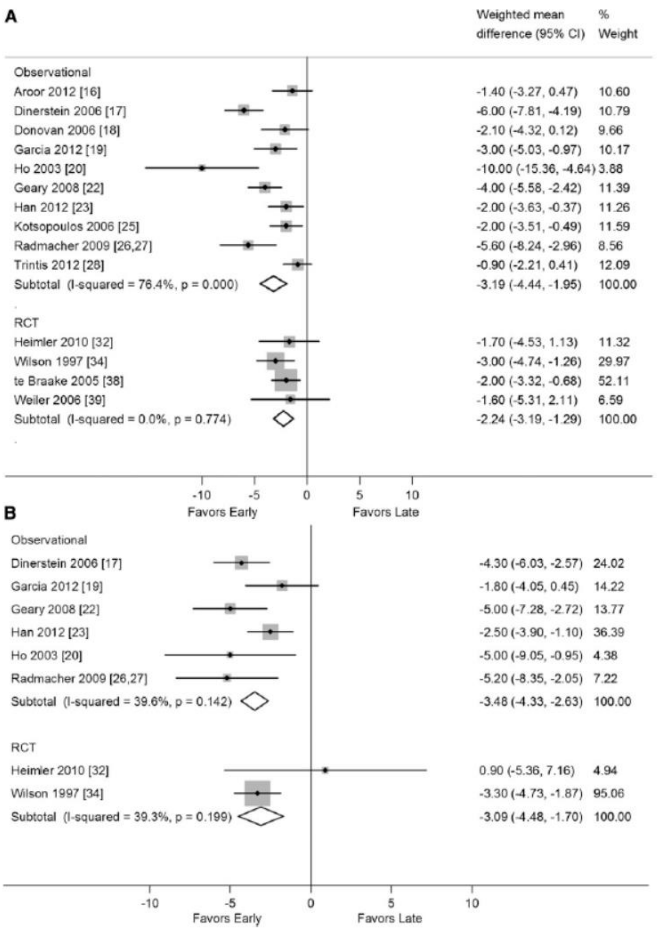


FIGURE 2. A: Time to regain birth weight (d). B: Maximum weight loss (in percentage points of birth weight). Open diamonds represent pooled mean differences (95% CIs) for each study type. Black circles represent the study mean differences, and the black bars are the 95% CIs. The size of the gray box is proportional to the weight of the study estimate in the meta-analysis. I-squared represents the percentage of variation attributable to heterogeneity. RCT, randomized controlled trial.

Early PN improved weight at discharge or 36 wk postmenstrual age by 14.9 g (5.3, 24.5 g) (observational studies only), but no benefit was shown for length or head circumference.

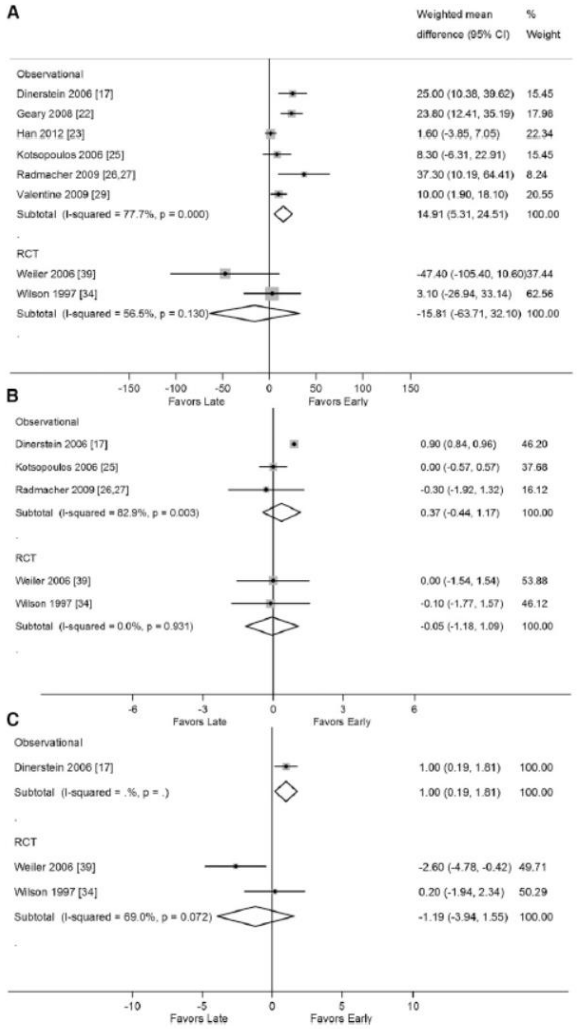


FIGURE 3. A: Weight at 36 wk or discharge (g). B: Head circumference (cm). C: Length (cm). Open diamonds represent pooled mean differences (95% CIs) for each study type. Black circles represent the study mean differences, and the black bars are the 95% CIs. The size of the gray box is proportional to the weight of the study estimate in the meta-analysis. I-squared represents the percentage of variation attributable to heterogeneity. RCT, randomized controlled trial.

There was no evidence that early PN significantly affects risk of mortality, necrotizing enterocolitis, sepsis, chronic lung disease, intraventricular hemorrhage, or cholestasis.

Conclusions: The results of this review, although subject to some limitations, show that early PN provides a benefit for some shortterm growth outcomes.

TABLE 5
Summary of meta-analyses of binary growth outcome measures[1]

Binary outcomes	First author, year of publication (reference)	Study design	Peto's OR (95% CI)	*P*	Favors
Weight <10th percentile at 36 wk, discharge, or death	Kotsopoulos, 2006 (25) Geary, 2008 (22)	Observational	0.43 (0.26, 0.71)	0.001	Early
	Wilson, 1997 (34)	RCT	0.34 (0.16, 0.73)	0.006	Early
Weight less than the third percentile at 36 wk, discharge, or death	Kotsopoulos, 2006 (25) Radmacher, 2009 (26)	Observational	0.57 (0.28, 1.14)	0.109	Early
	Wilson, 1997 (34)	RCT	0.48 (0.24, 0.97)	0.042	Early
Length <10th percentile at discharge or death	Wilson, 1997 (34)	RCT	0.47 (0.23, 0.97)	0.041	Early
Length less than the third percentile at discharge or death	Wilson, 1997 (34)	RCT	0.37 (0.18, 0.75)	0.006	Early
HC <10th percentile at discharge or death	Wilson, 1997 (34)	RCT	0.40 (0.17, 0.95)	0.037	Early
HC less than the third percentile at discharge or death	Radmacher, 2009 (26)	Observational	1.00 (0.19, 5.19)	0.999	Neither
	Wilson, 1997 (34)	RCT	0.29 (0.09, 0.90)	0.033	Early

[1] *P* values are for differences between early and late parenteral nutrition groups. HC, head circumference; RCT, randomized controlled trial.

No evidence that early PN increases morbidity or mortality was found. Neonatal research would benefit from the development of a set of core growth outcome measures.

A B S T R A C T

Parenteral lipid

Background:
The use of intravenous lipid emulsions in preterm infants has been limited by concerns regarding impaired lipid tolerance. As a result, the time of initiation of parenteral lipid infusioon to very-low-birth-weight (VLBW) infants varies widely among different
neonatal intensive care units. However, lipids provide energy for protein synthesis and supply essential fatty acids that are necessary for central nervous system development.

Objective:
The objective was to summarize the effects of initiation of lipids within the first 2 d of life and the effects of different lipid compositions on growth and morbidities in VLBW infants.

Design:
A systematic review and meta-analysis of publications identified in a search of PubMed, EMBASE, and Cochrane databases was undertaken. Randomized controlled studies were eligible if information on growth was available.

Results:
The search yielded 14 studies.

TABLE 1
Characteristics of studies assessing the effect of the early introduction of lipids[1]

First author, year (reference)	Study location	Study period	Design	Population	*n*	Intervention and duration	Quality[2]
Brownlee, 1993 (24)	UK	1990–1991	RCT	Premature infants, 24–36 wk gestational age	129	Start TPN with lipid (soybean oil emulsion 20%) and amino acids at <36 h vs at day 6	1
Gilbertson, 1991 (26)	UK	No data	RCT	Premature infants, birth weight <1500 g	29	Start lipid (soybean oil emulsion 20%) at day 1 vs day 8	1
Gunn, 1978 (25)	Canada	1974–1975	RCT	Premature infants	40	Start lipid (soybean oil emulsion 10%) and amino acids at day 2 vs after day 7	1
Sosenko, 1993 (27)	USA	1990–1991	RCT	Premature infants, birth weight 600–1000 g	133	Start lipid (soybean oil emulsion 20%) <12 h postnatally vs after day 7	3
Wilson, 1997 (28)	Northern Ireland	1990–1992	RCT	Premature infants, birth weight <1500 g	125	Start lipid (MCT–soybean oil emulsion 10% vs soybean oil emulsion 10%) at day 2 vs day 5, start amino acids at <12 h vs at day 3, early minimal enteral feeding	3

[1] MCT, medium-chain triacylglycerol; RCT, randomized controlled trial; TPN, total parenteral nutrition.
[2] Quality was assessed by using the Jadad et al (22) criteria (0–5-point rating scale, with 5 as the maximum score).

TABLE 3
Characteristics of studies comparing different lipid emulsions[1]

First author, year (reference)	Study location	Study period	Design	Population	*n*	Intervention	Quality[2]
D'Ascenzo, 2011 (32)	Italy	2007–2008	RCT	Premature infants, birth weight 500–1249 g	48	50% MCT–40% soybean–10% fish vs 50% MCT–50% soybean emulsion	3
Demirel, 2012 (36)	Turkey	2010	RCT	Premature infants, birth weight <1500 g, GA <32 wk	40	80% Olive–20% soybean vs 100% soybean	2
Deshpande, 2009 (29)	Australia	2006–2007	RCT	Premature infants, GA 23 to <28 wk	45	80% Olive–20% soybean vs 100% soybean	5
Lehner, 2006 (34)	Hungary	No data	RCT	Premature infants, GA 25–37 wk, birth weight <3000 g	12	20% MCT–80% soybean vs 100% soybean	1
Lima, 1988 (37)	UK	No data	RCT	Premature + term infants, combined analysis	51	50% MCT–50% soybean vs 100% soybean	3
Rayyan, 2012 (33)	Belgium	2004–2006	RCT	Premature infants, GA <34 wk, birth weight 500–2000 g	53	30% Soybean–30% MCT–25% olive–15% fish vs 100% soybean	5
Rubin, 1995 (30)	Israel	No data	RCT	Premature infants, GA <35 wk	33	50% MCT–50% soybean vs 100% soybean	1
Skouroliakou, 2010 (35)	Greece	2008–2009	RCT	Premature infants, GA <32 wk, birth weight <1500 g	32	30% Soybean–30% MCT–25% olive–15% fish vs 100% soybean	5
Tomsits, 2010 (31)	Hungary	2004–2006	RCT	Premature infants, GA <34 wk	60	30% Soybean–30% MCT–25% Olive–15% Fish vs 100% soybean	1
Wilson, 1997 (28)	Northern Ireland	1990–1992	RCT	Premature infants, birth weight <1500 g	125	50% MCT–50% soybean (10% solution) at day 2 (and start amino acids at <12 h, early minimal enteral feeding) vs 100% soybean (10% solution) at day 5 (and start amino acids at day 3)	3

[1] GA, gestational age; MCT, medium-chain triacylglycerol; RCT, randomized controlled trial.
[2] Quality was assessed by using the Jadad et al (22) criteria (0–5-point rating scale, with 5 as the maximum score).

No differences were observed in growth or morbidity with early lipid initiation. We found a weak favorable association of non–purely soybean-based emulsions with the incidence of sepsis (RR: 0.75; 95% CI: 0.56, 1.00).

Conclusions:
The initiation of lipids within the first 2 d of life in VLBW infants appears to be safe and well tolerated; however, beneficial effects on growth could not be shown for this treatment nor for the type of lipid emulsion. Emulsions that are not purely soybean oil–based might be associated with a lower incidence of sepsis. Large-scale randomized controlled trials in preterm infants are warranted to determine whether early initiation of lipids and lipid emulsions that are not purely soybean oil–based results in improved long-term outcomes.

administration to very-low-birth-weight infants--early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis.

Vlaardingerbroek H, Veldhorst MA, Spronk S, van den Akker CH, van Goudoever JB.

Am J Clin Nutr. 2012 Aug;96(2):255-68.

Table 1
Summary of studies included in this review.

Author	Year of publication	Aim	Methods	Results	Authors' conclusions
Early versus late introduction of PN					
Moyses, HE	2013	Whether earlier administration of PN benefits growth outcomes in preterm infants.	Systematic review of randomised controlled trials (RCTs) and observational studies.	Eight RCTs and 13 observational studies met the inclusion criteria. Early PN reduced the time to regain birth weight by 2.2 days (1.1, 3.2 days) for RCTs and 3.2 days (2.0, 4.4 days) in observational studies. Early PN improved weight at discharge or 36 weeks of postmenstrual age by 14.9 g (5.3, 24.5 g) (observational studies only), but no benefit was shown for length or head circumference.	Early PN provides a benefit for some short-term growth outcomes.
Early versus late administration of amino acids					
Trivedi, A	2013	To determine the effect of early administration of amino acids in premature newborns on growth, neurodevelopmental outcome, mortality and clinically important side effects.	Cochrane systematic review	Seven randomised controlled trials were included in this review. One randomised controlled trial reported no difference in crown-heel length and occipito-frontal head circumference by day 10. Four trials showed positive nitrogen balance (the mean difference with 95% CI was 250.42 (224.91 to 275.93) P value < 0.00001). Early administration of amino acids did not result in metabolic acidosis in the first 24 h.	There is no available evidence of the benefits of early administration of amino acids on mortality, early and late growth and neurodevelopment.
Low versus high intake of amino acids					
Thureen, PJ	2004	To study the efficacy and safety of more aggressive amino acid intake	Randomised controlled trial comparing low (LAA) 1 g/kg/day vs. high (HAA) 3 g/kg/day on protein balance (N = 28).	Protein balance was significantly lower in the LAA versus HAA groups by both nitrogen balance (-0.26 ± 0.11 versus 1.16 ± 0.15 g/kg/day, P < 0.00005) and leucine stable isotope (0.184 ± 0.17 versus 1.63 ± 0.20 g/kg/day, P < 0.0005) methods.	Parenteral HAA versus LAA intake resulted in increased protein accretion, primarily by increasing protein synthesis versus suppressing protein breakdown, and appeared to be well tolerated by very preterm infants in the first days of life.
Clark, RH	2007	To measure the effects of 2 strategies for parenteral nutrition on neonatal growth and blood amino acid profiles in premature infants	RCT. In one group amino acid supplementation was started at 1.0 g/kg per day and advanced by 0.5 g/kg per day to a maximum of 2.5 g/kg per day. The other group received amino acids starting at 1.5 g/kg per day and advancing by 1.0 g/kg per day to a maximum of 3.5 g/kg per day (N = 122).	There was no significant difference in growth by day 28 after birth (median weight gain: 12.9 and 11.4 g/kg per day for the 3.5 and 2.5 g/kg per day groups, respectively), and the incidences of secondary morbidities were similar in the 2 groups. On day 7, blood levels of several amino acids and the serum urea nitrogen level were higher in the 3.5 g/kg per day group, compared with the 2.5 g/kg per day group; none of the amino acid levels were lower.	Higher doses of amino acid supplementation did not improve neonatal growth and were associated with increased blood amino acid and urea nitrogen levels.
Balasubramanian, H	2013	To evaluate the effects of two different doses of parenteral amino acid supplementation on postnatal growth in very low birth weight (VLBW) infants receiving partial parenteral nutrition (PPN).	Double blind RCT. Two different initial doses of parenteral amino acids (AA) in the PPN solutions—low AA group: 1 g/kg/d versus high AA group: 3 g/kg/d from day 1 of life with increment by 1 g/kg every day till a maximum of 4 g/kg/d, until babies tolerated 75% enteral feeds (N = 150).	The gain in weight, length and head circumference at 28 days were significantly lower in the high AA group. The average weight gain at 28 days was 8.67 g/kg/d in the high AA group and 13.15 g/kg/d in the Low AA group (mean difference 123.12, 95% CI 46.67 to 199.37, P < 0.001).	Higher initial parenteral amino acid supplementation, in settings where partial parenteral nutrition is administered, results in poor growth in VLBW infants due to inadequate non-protein calorie intake.
Blanco, CL	2012	To examine the effects of early and high intravenous (IV) amino acid (AA) supplementation on growth, health, and neurodevelopment of extremely-low-birth-weight (ELBW) infants throughout their first 2 years of life.	Double blind RCT. Treatment for 7 days with either IV AA starting at 0.5 g/kg/day and increased by 0.5 g/kg/day every day to 3 g/kg/day or starting at 2 g/kg/day of IV AA and advanced by 1 g/kg/day every day to 4 g/kg/day (N = 43).	Mental Developmental Index (MDI) and Psychomotor Developmental Index were similar between groups; however, the early and high AA group had a lower MDI at 18 months. This difference disappeared at 2 years of age. The early and high AA group z score means for weight, length, and head circumferences were significantly lower than the standard AA group at most visits.	ELBW infants who received early and high IV AA during the first week of life were associated with poor overall growth at 2 years.
Vlaardingerbroek, H	2013	To assess the efficacy and safety of early parenteral lipid and high-dose amino acid (AA) administration from birth onwards in very low birth weight (VLBW, birth weight <1500 g) infants.	RCT. 2.4 g/kg/day of amino acid (control group), vs. 2.4 g/kg/day AA plus 2–3 g/kg/day lipids. (AA + lipid group), or 3.6 g/kg/day AA plus 2–3 g/kg/day lipids (high AA + lipid group) from birth onwards. The primary outcome was nitrogen balance (N = 144).	Nitrogen balance on day 2 was significantly greater in both intervention groups compared with the control group. Greater amounts of AA administration did not further improve nitrogen balance compared with standard AA dose plus lipids and was associated with high plasma urea concentrations and high rates of urea appearance. No differences in other biochemical variables, growth, or clinical outcomes were observed.	Parenteral AA combined with lipids from birth onwards improved conditions for anabolism and growth, as shown by improved nitrogen balance. Greater levels of AA administration did not further improve the nitrogen balance but led to increased AA oxidation.
Burattini, I	2013	To compare the effect of 2.5 vs. 4 g/kg/d of amino	RCT. Primary outcome was body size at 36 weeks	Body weight, length, and head circumference at	The high AA group had higher blood urea levels and

Table 1 *(continued)*

Author	Year of publication	Aim	Methods	Results	Authors' conclusions
		acid (AA) in PN of extremely low birth weight infants on metabolic tolerance, short-term growth, and neurodevelopment.	(N = 114).	36 weeks and 2 years were similar between groups. Bayley Scales of Infant and Toddler Development, Third Edition score was 94 ± 13 in the standard AA group and 97 ± 15 in the high AA group (P = .35).	better glucose control. An extra 8 g/kg of AA over the first 10 days of life did not improve growth and neurodevelopment.
Morgan, C	2014	To compare the change in HC (ΔHC) and HC SD score (ΔSDS) achieved at day 28 in infants <29 - weeks of gestational age randomly assigned to receive Standardised, Concentrated With Added Macronutrients Parenteral (SCAMP) nutrition or a control standardised, concentrated PN regimen.	RCT. Control PN (10% glucose, 2.8 g/kg per day protein/lipid) was started within 6 h of birth. Infants were randomly assigned to either start SCAMP (12% glucose, 3.8 g/kg per day protein/lipid) or remain on the control regimen (N = 148).	The SCAMP group had a greater ΔHC at 28 days (P < .001) that persisted to 36 weeks of corrected gestational age.	Early postnatal head growth failure in very preterm infants can be ameliorated by optimising PN.
Early versus late initiation of lipid and lipid composition					
Vlaardingerbroek, H	2013	The objective was to summarise the effects of initiation of lipids within the first 2 days of life and the effects of different lipid compositions on growth and morbidities in VLBW infants.	Systematic review of RCTs	The search yielded 14 studies. No differences were observed in growth or morbidity with early lipid initiation. A weak favourable association of non-purely soybean-based emulsions with the incidence of sepsis (RR: 0.75; 95% CI: 0.56, 1.00) was observed.	The initiation of lipids within the first 2 days of life in VLBW infants appears to be safe and well tolerated; however, beneficial effects on growth could not be shown for this treatment nor for the type of lipid emulsion.
Standardised versus individualised PN					
Yeung, MY	2003	To evaluate the difference in nutrient intakes and biochemical responses in newborn infants <33 weeks of gestation who received standardised versus individualised PN regimens.	RCT of standardised regime versus individualised PN regimens from day 2 to day 7 of life (N = 58).	Infants in the standardised PN group received less sodium (P < 0.01) and no potassium on day 2 as required, more protein (P < 0.02) every day, and more calcium and phosphate (P < 0.02 from day 4).	No significant clinical and statistical differences in biochemical responses in those who received standardised versus individualised PN regimes during the first week of life. The economic cost of PN provision using standardised PN formulation was approximately 30% lower
Skouroliakou, M	2009	Use of standardised computerised parenteral nutrition protocols and regimens compared to prescriptions by individual neonatologists on outcomes of weight changes, adequacy of parenteral nutrition, days of hospitalisation, clinical outcome.	Non-randomised comparison of two cohorts. Allocation not described (N = 60).	Standardised protocols provided more energy (P-value: 0.05), protein (P-value: 0.023) and micronutrients than the non-standardised. Neonates that received standardised PN gained more weight (+44 ± 114 g) than those in the individualised group during PN administration.	The use of standardised protocols in preterm neonates resulted in more adequate provision of nutrients, weight gain and better blood count profile compared with protocols prescribed by individual physicians.
Lenclen, R	2006	To evaluate the impact of a newly implemented standardised PN regimen	Retrospective observational study. Comparison with historical cohort (N = 20).	Amino-acid intakes on day 3 were higher in the standard group (1.5 +/−0.2 g/kg/d vs. 0.9 +/− 0.5, P < 0.001), and the calcium phosphate intakes were better balanced. The cumulative intake of amino acids for the first week was greater in the standard group (+20%; P = 0.0003). Biochemical parameters were similar in both groups. Insulin infusions were less frequent in the standard group (P < 0.06).	Standardised parenteral formulations provided higher early intakes of amino acid and glucose, a better calcium phosphate ratio, and a greater amount of amino-acid intakes during the first week while maintaining the same biochemical parameters.
Smolkin, T	2010	To compare individualised (IND-PN) and standard (STD-PN) on nutritional and growth parameters, complications and cost.	Retrospective comparative study (N = 140).	Infants receiving IND-PN showed significantly greater weight gain SDS during the 1st week (P = 0.036) and the 1st month of life (P = 0.0004), and higher discharge weight SDS (P = 0.012) and head circumference SDS (P = 0.006) and received higher mean daily caloric intakes. They also had significantly shorter durations of exclusive PN and needed less electrolyte corrections.	Infants receiving IND-PN achieved significantly better growth without added clinical or laboratory complications, had a shorter period of exclusive PN and less electrolyte corrections.
Eleni-dit-Trolli, S	2009	To determine the effects of computerising PN ordering on the composition of PN solutions and early clinical outcomes of preterm infants born < or =-28 weeks of gestation	Retrospective cohort study N = 40	Parenteral protein intake during the first week of life and parenteral lipid, glucose and energy intakes during the first and second weeks of life were significantly higher in infants assessed after the introduction of computerised parenteral nutrition ordering. There was significant reduction in the cumulative energy deficit over the first 28 days of life.	Computerising the PN ordering process improves the nutrient content of the PN solutions and early postnatal outcome.
Dice, JE	1981	To study the clinical contribution and cost effectiveness of pharmacist involvement in peripheral-vein PN in a neonatal intensive-care unit	Non-randomised trial. Alternate allocation. Group 1 received standardised PN with no pharmacist monitoring whereas Group 2 received individualised PN with pharmacist monitoring (N = 28).	The mean weight gain in Group 1 (4.9 g/day) was significantly less than in Group 2 (11.8 g/day) (P less than 0.02). The amount of protein provided to Group 2 (2.2 g/kg/day) was significantly greater than that to Group 1 (1.9 g/kg/day) (P less than 0.01). The number of calories provided per day was greater for Group 2 (63 kcal/kg/day) than for Group 1 (53 kcal/kg/day) (p less than 0.001). The mean daily cost was greater for Group 2.	Pharmacist monitoring of an individualised programme of PN in neonates provided a greater mean daily weight gain, allowed a greater amount of nutrients to be provided, and was cost effective.

In order to avoid catabolism, establish anabolism, achieve in utero protein accretion rates, and promote linear growth, it seems useful to initiate total parenteral nutrition on the first day of life with a high protein intake (>2 g amino acids/kg/day). It has been observed that high amino acid supply from the first day of life in VLBW infants decreases the frequency and severity of neonatal hyperglycaemia by stimulating endogenous insulin secretion, stimulates growth by enhancing the secretion of insulin and insulin-like growth factors, and is not associated with an increase in markers of amino acid overload, such as acidosis, hyperammonaemia, elevated blood urea nitrogen, or hyperaminoacidaemia. Modern amino acid solutions are able to provide equivalent proteiin intake of up to 3.5 g/kg/day in very preterm infants without apparent problems, and the administration of 2.5–3.5 g/kg/day of parenteral amino acids as soon as possible after birth is a reasonable recommendation. Table 1 shows the revised recommended protein intake and protein:energy ratio for preterm infants according to postconceptional age, and the need for catchup growth [9]. It should be stressed that these recommendations are derived especially from studies on preterm infants weighing more than 1000 g, rather than on extremely low birth weight infants (ELBW; less than 1000 g). Estimates for these ELBW infants are extrapolated from data involving larger premature infants. Glucose is the major energy source and the most widely used intravenous carbohydrate for neonates, because it is readily availability to the brain. Many other non-glucose carbohydrates have been tried, but with limited success. Newborn infants are often in a transitional stage of glucose homeostasis and are, therefore, subject to hyper or hypoglycaemia. Although the definition and the long-term consequences of neonatal hypoglycaemia remain controversial, plasma glucose concentration should be monitored and corrected should it fall below 50 mg/dl (2.8 mmol/l) during the first days of life [9]. In the first few days of life, VLBW infants are more susceptible to hyperglycaemia−often associated to glucosuria, which seems to be caused by a persistent endogenous hepatic glucose production secondary to the insensitivity of hepatocytes to insulin. The definition of hyperglycaemia varies, but it is generally set at a plasma level above 150–180 mg/dl (8.3–10 mmol/l). However, the upper “safe” limit of blood glucose concentration in the neonate is not well defined and, as for hypoglycaemia, there is a great variation in terms of diagnoosis and management of hyperglycaemia. In practice, 6 g/kg/day of intravenous glucose is generally well tolerated (4–5 mg/kg/min) even on thefirst day of life in VLBW infants. If this intake is tolerated, it may be increased to 8, 10, and up to 12–18 g/kg/day; otherwise, progressioon of glucose intake should be stopped and insulin perfusion should be considered according to clinical and nutritional status with an initial dose of 0.05 IU/kg/hour.	*Review* **The nutrition of preterm infants.** De Curtis M, Rigo J. Early Hum Dev. 2012 Mar;88 Suppl 1:S5-7. doi: 10.1016/j.earlhumdev.2011

Intravenous lipid emulsions are important constituents of total parenteral nutrition, as they provide energy and essential fatty acids to VLBW infants. Lipid emulsions consist of different oils, egg yolk phospholipids, and glycerol. The fat particles in the emulsions resemble endogenously produced chylomicrons in terms of size, physicochemical properties and metabolism, and are hydrolysed by lipoprotein lipase. Currently, intravenous lipids are started on the first day of life (0.5–1.0 g lipid/kg/day), even in very preterm, low birth weight infants, and increased rather quickly to 3 g/kg/day [9]. The rate of infused triglyceride clearance is determined by the available lipase activity and by the uptake of unesterified fatty acid products related to the adipose tissue mass and/or fatty acid oxidation in muscles. The normal sodium requirement is assumed to be 3–5 mmol/kg/day. During the first week of life, infants of less than 28 weeks' gestation often receive additional sodium supply from sources other than parenteral solution, i.e. blood transfusion, bicarbonate, or drugs, and lose more water than sodium. Therefore, to prevent hyperosmolar hypernatraemia, some authors propose very close monitoring of sodium intake during the first week of life, while others recommend completely avoiding sodium during the few first days of life in ELBW infants. The normal potassium requirement for growing preterm infants is assumed to be 1–2 mmol/kg/day. It should be withheld in the first 3 days after birth in those who are extremely preterm, because of the risk of developing non-oliguric hyperkalaemia from immature distal tubular function. The recommended chloride intake is 2–3 mmol/kg/day, with chloride maintenance intake not lower than 1 mmol/kg/day. Inadequate calcium and phosphorus intake has been associated with diminished bone mineralization in parenterally fed premature infants. It is advisable to supply a calcium content of 75–90 mg/kg/day, a phosphorus content of 60–67 mg/kg/day and a magneesium content of 7.5–10.5 mg/kg/day corresponding to a Ca:P ratio of 1.3:1 by weight and 1:1 by molar ratio in the total parenteral nutrition solution. Itmust be underlined that such a quantity of calcium provided by the parenteral route is about 60–75% of that deposited by the fetus during the last trimester of gestation (100–120 mg/kg/day), but is similar or higher than that obtained with enteral nutrition with the available preterm formula. Administering sufficient amounts of calcium and phosphorus in parenteral nutrition solutions is no longer a probleem in countries where organic phosphate preparations are available, and the amounts of calcium and phosphorus available with parenteral nutrition could be theoretically higher than that absorbed using the enteral route.	
	Parenteral Nutrition in Very Low Birth Weight Preterm Infants. Riskin A, Hartman C, Shamir R.

	Isr Med Assoc J. 2015 May;17(5):310-5.
Of the six reports listed in table 1 which support the statement that better nutritional support is associated with improved growth and less EUGR, only one was a randomized clinical trial. That trial, performed between 1990 and 1992 by Wilson et al. [30] - ülejäänud vaatlus- ja kohortuuringud **Table 1.** Findings in clinical investigations in extremely preterm infants Reference (first author) / Better nutritional support associated with improved growth and less EUGR / Improved growth is associated with improved neurodevelopmental outcomes / Better nutritional support is associated with improved neurodevelopmental outcomes Wilson, 1997 [30] X Pauls, 1998 [27] X Dinerstein, 2006 [31] X Maggio, 2007 [32] X Cormack, 2013 [33] X Shan, 2009 [34] X Ehrenkranz, 2006 [35] X Poindexter, 2013 [36] X Belfort, 2011 [37] X Poindexter, 2006 [39] X + (effect suggested) Stephens, 2009 [40] + X Eleni dit Trolli, 2012 [41] + X Tan, 2008 [43, 44] X X X Franz, 2009 [45] X X X	**Nutritional care of preterm infants: scientific basis and practical guidelines; 2014.** **Koletzko, B, Poindexter, B, Uauy, R.** *Peatükk/artikkel* ***Nutrition, Growth and Clinical Outcomes*** *Richard A. Ehrenkranz*
Practical Considerations with Regard to Enteral Protein Supplementation The transition from parenteral to enteral nutrition in preterm infants is a period where protein malnutrition can develop easily. Therefore, the initiation of tapering off parenteral amino acid intake should not start before at least 75 ml/(kg·day) of enteral nutrition is reached. When no growth faltering has occurred in the period before, aiming for 3.5–4.0 g protein/(kg·day) is advised for ELBW and VLBW infants. When catch-up growth is needed, intakes up to 4.5 g protein/(kg·day) are advised. **Conclusion** Amino acids and proteins are the major driving force for growth and therefore longterm outcome. Short-term studies show benefits of immediate commencement of amino acid supplementation to preterm infants following birth. Initial safe intake is at least 2.0–2.5 g/(kg·day), with a gradual increase to level of 3.5 g/(kg·day). Infants at full enteral nutrition need 3.5–4.5 g protein/(kg·day), either with supplemented human (donor) milk or, second best, formula. With these recommendations, the risk of developing growth retardation at the NICU becomes rare, and the discussion on the need of additional supplementation to establish catch-up growth becomes futile.	*Peatükk/artikkel* ***Amino Acids and Proteins*** *Johannes B. van Goudoever* *Hester Vlaardingerbroek* *Chris H. van den Akker* *Femke de Groof* *Sophie R.D. van der Schoor*
Energy and Carbohydrates: Nutritional Recommendations (1) Total energy intake for VLBW infants must be sufficient to support basal metabolism and net protein/fat balance (plus minor heat and stool	*Peatükk/artikkel* ***Energy***

losses) – 110–130 kcal/kg/day for enterally fed preterm infants (85–95 kcal/kg/day for parenterally fed infants) (LOE: moderate quality). (2) There is no evidence that energy intake above this level enhances neurological development or is required to achieve appropriate growth and body composition. High energy intakes in preterm infants results in greater fat accumulation compared to their normal fetal counterparts (LOE: moderate quality). (3) High infusion rates of glucose often results in hyperglycemia and may contribute to inflammatory injuries and fatty infiltration of liver and heart and other organs. Routine use of insulin to prevent hyperglycemia or promote growth is not beneficial and may be harmful (LOE: moderate quality).	***Requirements, Protein-Energy Metabolism and Balance, and Carbohydrates in Preterm Infants*** *William W. Hay, Jr.* *Laura D. Brown* *Scott C. Denne*
Recommendations • The initiation of lipids within the first 2 days of life in very preterm infants appears to be safe and well tolerated. When infused at a similar amount (g/kg/day) than that of amino acid, a dose of 2–3 g/kg/day of parenteral lipids can safely be used from birth onwards. • Lipid emulsions that are not purely soybean-based should be preferred over the soybean or soybean/sunflower-based emulsion since they reduce the risk of sepsis and promote more favorable LC-PUFA profile. • Lipid emulsions containing fish oil are potentially useful to favor better DHA status and improve various health outcomes. Their routine use is not recommended since their clinical benefits and safety have not yet been fully demonstrated in preterm infants.	*Peatükk/artikkel* ***Enteral and Parenteral Lipid Requirements of Preterm Infants*** *Alexandre Lapillonne*
Conclusions • There is evidence that careful restriction of fluid and sodium intake during the first postnatal days reduces the risk for CLD. • This fluid restriction is associated with an increased risk for hyponatremia. • A higher sodium intake after the first week of life may be beneficial for growth and mental development.	*Peatükk/artikkel* ***Water, Sodium, Potassium and Chloride*** *Christoph Fusch* *Frank Jochum*
Table 2. Suggested target intakes of nutrients from PN in first week Nutrient | Day 0[a] | Days 1–2 | Day 3[b] Amino acids[c], g/kg/day | ≥2 | ≥3.5 | 3.5–4 Lipid, g/kg/day | ≥2 | 3–4 | 3–4 Total energy intake, kcal/kg/day | 60–80 | 80–100 | ≥100 [a] First 24 h of life. [b] Assuming minimal contribution from enteral nutrition. [c] In g of protein equivalent. **Initiating Parenteral Nutrition and Introducing Enteral Nutrition: Suggestions for a Practical Approach** Individual units need to develop an approach that is sensitive to local circumstances, and that maximizes quality outcomes whilst minimizing harm. There are few adequately powered trials and meta-analyses are limited, but suggested intakes are **summarized in table 2 (Evidence base: low quality)** along with the following guide: (1) Develop unit-specific, evidence-based guidelines and facilitate access to professionals with expertise in nutrition, ideally including	*Peatükk/artikkel* ***Practice of Parenteral Nutrition in VLBW and ELBW Infants*** *Nicholas D. Embleton Karen Simmer*

neonatal dieticians as part of a multidisciplinary team. (2) Standardized PN and lipid solutions available 24 h/day either from the pharmacy or via the use of 'emergency' bags kept in a fridge on the NICU that are capable of providing at least 3.5 g/kg/day of amino acids. (3) **Start PN and lipid on admission to the NICU aiming to achieve intakes as listed in table 1 over the first few days**. (4) Commercially available bags that contain approximately 2.4–2.7 g/100 ml amino acids will meet suggested intakes if administered at 80–100 ml/day on day 1. If this is formulated with approximately 10% dextrose and co-administered with 2 g/kg/day of lipid then caloric intakes can also be met. (5) Promote the use of breast milk and aim to provide all infants (except those who are very unstable) with breast milk colostrum in the first 24 h. (6) Increase the volume of PN to approximately 150 ml/kg/day by day 3 along with 3–4 g/kg/day of lipid. At this volume a typical standardized PN bag will provide 3.6 g/kg/day of amino acids, and when combined with lipid will provide a total caloric intake of approximately 100 kcal/kg/day. (7) Individualize PN administration (composition, volume and/or concentration) in the presence of significant electrolyte disturbances, hyperglycemia, or fluid restrictions and when enteral nutrition is not tolerated. (8) Decrease PN as breast milk volume intakes increase so that total fluid intakes do not exceed 150–175 ml/kg/day in the first few days. Consider stopping PN when enteral volumes of 125–150 ml/kg/day are tolerated. (9) Audit outcomes on a regular basis. **Conclusion** Administration of PN to VLBW infants is now an essential component of care, and with careful formulation can meet all nutrient needs over the first few days. However, there are several risks associated with formulation, supply and administration that mean it must only be undertaken in specialist centers with adequate resource and expertise. Despite the clear benefits, data on long-term outcome are lacking and further research is needed.	
Randomiseeritud kontrolluuringud	
ABSTRACT **BACKGROUND:** Early postnatal head growth failure is well recognized in very preterm infants (VPIs). This coincides with the characteristic nutritional deficits that occur in these parenteral nutrition (PN) dependent infants in the first month of life. Head circumference (HC) is correlated with brain volume and later neurodevelopmental outcome. We hypothesized that a Standardized, Concentrated With Added Macronutrients Parenteral (SCAMP) nutrition regimen would improve early head growth. The aim was to compare the change in HC (DHC) and HC SD score (DSDS)	**Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study.** Morgan C, McGowan P,

achieved at day 28 in VPIs randomly assigned to receive SCAMP nutritionor a control standardized, concentrated PN regimen.

METHODS:

Control PN (10% glucose, 2.8 g/kg per day protein/lipid) was started within 6 hours of birth. VPIs (birth weight <1200 g; gestation < 29 weeks) were randomly assigned to either start SCAMP (12% glucose, 3.8 g/kg per day protein/lipid) or remain on the control regimen. HC was measured weekly. Actual daily nutritional Intake data were collected for days 1 to 28.

TABLE 1 Comparison Between Control and SCAMP Macronutrient Content and PN Fluid Volumes in a Total Fluid Volume of 150 mL/kg Per Day

PN Component in a Total Fluid Volume of 150 mL/kg per day	Control	SCAMP
Maximum protein, g/kg per day	2.8	3.8
Maximum lipid, g/kg per day	2.8	3.8
Maximum glucose, g/kg per day	13.5	15.6
Total calorie intake, kcal/kg per day	85	108
Maximum aqueous PN volume, mL/kg per day	85	100
Maximum intravenous lipid volume, mL/kg per day	15	20
Maximum supplementary dextrose volume, mL/kg per day)	50	30
Estimated combined osmolality, mOsmol/L water	855	1025
Electrolyte provision, mmoL/kg per day	Control formulation	As for control
Vitamin and trace element provision	Control formulation	As for control

RESULTS:

There were no differences in demographic data between SCAMP (n = 74) and control (n = 76) groups. Comparing cumulative 28-day intakes, the SCAMP group received 11% more protein and 7% more energy. **The SCAMP group had a greater DHC at 28 days (P <0.001). The difference between the means (95% confidence interval) for DHC was 5 mm (2 to 8), and DSDS was 0.37 (0.17 to 0.58). HC differences are still apparent at 36 weeks' corrected gestational age.**

TABLE 4 Comparison Between SCAMP and Control Groups

Age	SCAMP, *n* = 66	Control, *n* = 69	Mean difference (95% CI)	SCAMP, *n* = 66	Control, *n* = 69	Mean difference (95% CI)
Measurement		ΔHC (mm)			ΔSDS	
Day 28	31 (9)	26 (9)	5 (2 to 8) *P* < .001	+0.05 (0.66)	−0.32 (0.65)	0.37 (0.17 to 0.58) *P* = .001
Measurement		HC (mm)			SDS	
Randomization	240 (12)	240 (13)	—	−1.55 (0.70)	−1.48 (0.67)	—
Day 7	244 (12)	243 (14)	—	−1.64 (0.69)	−1.66 (0.69)	—
Day 14	252 (12)	250 (14)	—	−1.68 (0.63)	−1.78 (0.72)	—
Day 21	261 (14)	257 (16)	—	−1.67 (0.70)	−1.89 (0.75)	—
Day 28	271 (16)	265 (17)	6 (2 to 10) *P* = .007	−1.51 (0.87)	−1.81 (0.86)	0.30 (0.01 to 0.60) *P* = .042
36 weeks' CGA	316 (13) *n* = 63	311 (15) *n* = 63	5 (0.1 to 10) *P* = .046	−0.93 (1.06) *n* = 63	−1.32 (1.18) *n* = 63	0.40 (0.005 to 0.79) *P* = .047

CI, confidence interval. Mean (SD) ΔHC and ΔSDS between randomization and day 28 (28-d survivors); mean (SD) HC and SDS at randomization, 7, 14, 21, and 28 d (28-d survivors) and 36 weeks' CGA (survivors). *P* value controlling for stratum. *P* values are provided only for the primary outcome measure and major secondary outcomes.

CONCLUSIONS:

Early postnatal head growth failure in VPIs can be ameliorated by optimizing PN.

Herwitker S, Hart AE, Turner MA.

Pediatrics 2014;133(1):e120–8.

Hea kvaliteediga ühekeskuseline RCT, uurijad, hooldajad, vanemad pimendatud, turvalisuse kaalutlustel faramatseudid ei olnud pimendatud.

ABSTRACT

Objective

To compare the effect of 2.5 vs 4 g/kg/d of amino acid (AA) in parenteral nutrition of extremely low birth weight infants on metabolic tolerance, short-term growth, and neurodevelopment.

Study design

One hundred thirty-one infants with birth weight between 500 and 1249 g were randomized to

2.5 (standard AA [SAA] group) or 4 (high AA [HAA] group) g/kg/d

Targeting 2.5 versus 4 g/kg/day of amino acids for extremely low birth weight infants: a randomized clinical trial.

Burattini I, Bellagamba MP,

AA intake, with equal nonprotein energy. The primary outcome was body size at 36 weeks.

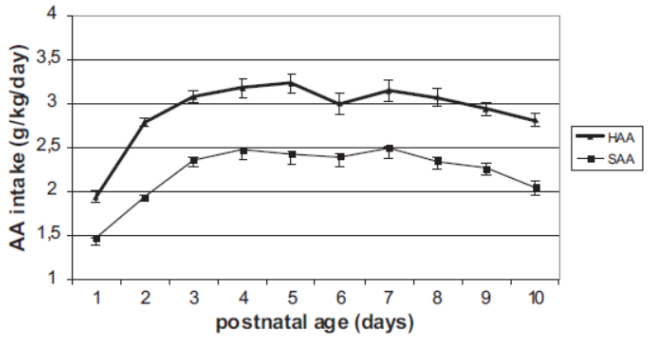


Figure 1. AA intake in g/kg/d (±SE); *P* = .000 by ANOVA.

Results

One hundred thirty-one patients were randomized and 114 analyzed (58 SAA group and 56 HAA group). Study groups had similar demographics and clinical characteristics.

Elevated blood urea (BU >70 mg/dL = BU nitrogen >32.6 mg/dL) occurred in 24% vs 59% (P = .000) and hyperglycemia (>175 mg/dL) in 34% vs 11% (P = .003) of the SAA and HAA patients, respectively.

Body weight, length, and head circumference at 36 weeks and 2 years were similar between groups.

Table II. Growth performances

	SAA group	HAA group	*P*
In-hospital	n = 58	n = 56	
Maximum weight loss %	11.3 ± 5.0	11.3 ± 5.2	.98
Age at regained BW, d	11.7 ± 4.1	11.2 ± 4.5	.59
Age at 1800 g, d	50.7 ± 15.1	51.1 ± 12.1	.88
Weight gain from birth to 1800 g, g/kg/d	12.1 ± 2.0	12.1 ± 2.0	.94
Weight gain from regained BW to 1800 g, g/kg/d	16.4 ± 2.5	16.4 ± 2.5	.91
Weight gain from regained BW to 36 wk PMA, g/kg/d	16.0 ± 2.7	16.6 ± 2.4	.32
36 wk PMA	n = 58	n = 56	
Weight, g	1847 ± 322	1865 ± 387	.79
Weight Z score	−1.95 ± 0.80	−1.88 ± 0.93	.68
Length, cm	42.7 ± 1.9	42.7 ± 2.4	.90
Length Z score	−1.86 ± 0.76	−1.82 ± 0.91	.80
Head circumference, cm	30.6 ± 1.3	30.5 ± 1.4	.55
Head circumference Z score	−1.53 ± 0.90	−1.59 ± 0.88	.74
Number of SGA	29 (50%)	27 (48%)	.64
2 y	n = 52	n = 48	
Weight, g	11822 ± 1661	11693 ± 1856	.71
Weight Z score	−0.17 ± 1.12	−0.22 ± 1.31	.84
Length, cm	87.4 ± 4.1	87.3 ± 4.6	.94
Length Z score	0.57 ± 1.12	0.61 ± 1.25	.86
Head circumference, cm	48.4 ± 1.6	48.1 ± 1.9	.43
Head circumference Z score	−0.56 ± 1.3	−0.57 ± 1.2	.97

Data are expressed as mean ± SD.

Bayley Scales of Infant and Toddler Development, Third Edition score was 94 ± 13 in the SAA group and 97±15 in the HAA group (P = .35).

Conclusions

The HAA group had higher BU levels and better glucose control.

Spagnoli C, D'Ascenzo R, Mazzoni N, Peretti A, et al.

J Pediatr 2013;163(5):1278–82 [e1].

Hea kvaliteediga ühekeskuseline (?) RCT, hindamise ja uuringutega seotud personal pimendatud, vahetud ravijad- hooldajad ei olnud pimendatud.

„+“ mõlemas uuringugrupis sarnane mitevalgulise energia pakkumine

BU >70 mg/dL = >24,99 mmol/L

Blood glucose 120 mg/dL = 6,66 mmol/L

80 mg/dL = 4,4 mmol/L

An extra 8 g/kg of AA over the first 10 days of life did not improve growth and neurodevelopment.

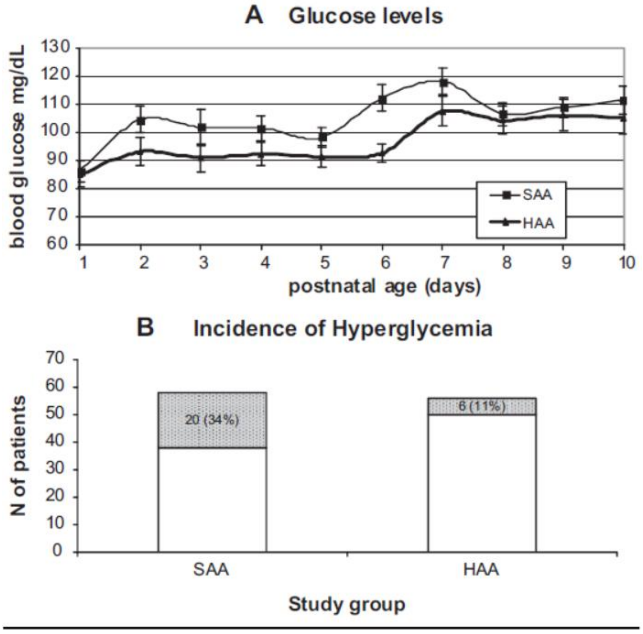


Figure 2. **A,** Mean daily blood glucose mg/dL (±SE) was significantly higher in the patients with SAA than in those with HAA; $P < .001$ by ANOVA. **B,** Number of subjects experiencing episodes of hyperglycemia (blood glucose >175 mg/dL in 2 consecutive occasions) were 20 (34%) in the SAA group and 6 (11%) in the HAA group; $P = .003$.

ABSTRACT

Objective

To assess the efficacy and safety of early parenteral lipid and high-dose amino acid (AA) administration from birth onwards in very low birth weight (VLBW, birth weight <1500 g) infants.

Study design

VLBW infants (n = 144; birth weight 862 ± 218 g; gestational age 27.4± 2.2 weeks) were randomized to receive 2.4 g of AA /g/d (control group), or 2.4 g AA kg/d plus 2-3 g lipids kg/d (AA + lipid group), or 3.6 g AA kg/d plus 2-3 g lipids kg/d (high AA + lipid group) from birth onwards. The primary outcome was **nitrogen balance**. The secondary outcomes were biochemical variables, urea rate of appearance, growth rates, and clinical outcome.

Table II. Total (parenteral + enteral) protein and nonprotein energy intake during the first week of life

	Control group			AA + lipid group			High AA + lipid group		
	Day 2	Day 4	Day 6	Day 2	Day 4	Day 6	Day 2	Day 4	Day 6
Total protein intake, g·kg^{-1}·d^{-1}	2.1 ± 0.6*	2.4 ± 0.9	2.6 ± 0.8	2.6 ± 0.4[a]	2.6 ± 0.6	2.5 ± 0.8	3.2 ± 0.9[a,b]	2.7 ± 1.3	3.0 ± 1.0[b]
Total nonprotein energy intake, kcal·kg^{-1}·d^{-1}	48.9 ± 11.0	71.4 ± 14.6	73.6 ± 16.8	62.4 ± 15.1[a]	75.4 ± 14.9	75.8 ± 22.1	62.7 ± 11.8[a]	71.3 ± 17.4	78.4 ± 19.0

*Data are presented as the mean ± SD.
[a]Significantly different from control group (ANOVA, $P < .05$).
[b]Significantly different from AA + lipid group (ANOVA, $P < .05$).

Results

The nitrogen balance on day 2 was significantly greater in both intervention groups compared with the control group.

Safety and efficacy of early parenteral lipid and high-dose amino acid administration to very low birth weight infants.

Vlaardingerbroek H, Vermeulen MJ, Rook D, van den Akker CH, Dorst K, Wattimena JL, et al.

J Pediatr 2013; 163(3):638–44 [e1-5].

Hea kvaliteediga ühekeskuseline (Rotterdam) RCT. Kõigil koheselt sünnijärgselt glükoos + AH. Pt. randomiseeriti esimese 6 tj

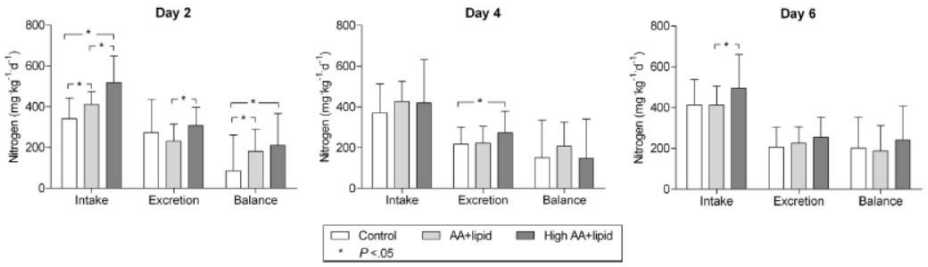


Figure 3. Nitrogen intake, excretion, and balance on postnatal days 2, 4, and 6 (mean ± SD), ANOVA tested.

Greater amounts of AA administration did not further improve nitrogen balance compared with standard AA dose plus lipids and was associated with high plasma urea concentrations and high rates of urea appearance.

Table III. Serum glucose, urea, and TG concentrations during the first week of life

	Control group			AA + lipid group			High AA + lipid group		
	Day 2	Day 4	Day 7	Day 2	Day 4	Day 7	Day 2	Day 4	Day 7
Glucose, mmol/L	5.5 ± 2.5*	7.1 ± 2.6	5.9 ± 1.6	7.1 ± 3.0[a]	6.4 ± 2.0	6.0 ± 2.5	6.6 ± 3.1	7.0 ± 2.9	6.3 ± 2.6
Urea, mmol/L	10.0 ± 4.3	8.2 ± 3.7	5.7 ± 2.8	8.3 ± 2.5[a]	7.6 ± 2.3	6.1 ± 1.9	11.7 ± 3.2[b]	9.9 ± 3.0[a,b]	7.7 ± 2.7[a,b]
TG, mmol/L	0.8 ± 0.5	2.2 ± 1.4	1.8 ± 0.9	2.0 ± 1.6[a]	2.0 ± 0.9	2.1 ± 1.4	1.8 ± 1.0[a]	2.2 ± 1.0	2.0 ± 1.2
Aspartate amino transaminase, U/L	62.2 ± 88.3	30.5 ± 27.4	23.8 ± 11.5	40.7 ± 17.2	21.1 ± 10.7	32.2 ± 24.2	37.5 ± 17.7	21.0 ± 8.1[a]	26.2 ± 12.2

*Data are presented as the mean ± SD.
[a]Significantly different from control group (ANOVA, $P < .05$).
[b]Significantly different from AA + lipid group (ANOVA, $P < .05$).

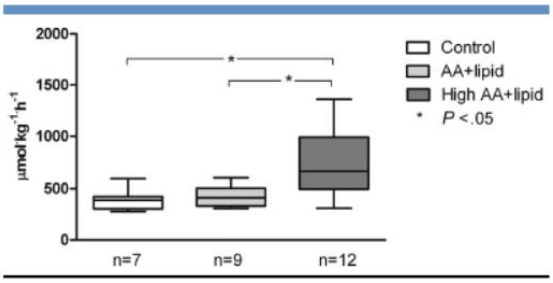


Figure 4. Urea rate of appearance on day 2 of life in a subset of infants. *Boxes* and *whiskers* indicate the medians, IQR, and 2.5th and 97.5th percentiles; tested with Kruskal-Wallis and Mann-Whitney *U* test.

No differences in other biochemical variables, growth, or clinical outcomes were observed.

Conclusions

In VLBW infants, the administration of parenteral AA combined with lipids from birth onwards

improved conditions for anabolism and growth, as shown by improved nitrogen balance. Greater levels of AA administration did not further improve the nitrogen balance but led to increased AA oxidation. Early lipid initiation and high-dose AA were well tolerated.

sünnijärgselt

„-„ Suurema AH ja lipiidide pakkumisega grupis vähendati pakkumist ravi käigus seoses kõrgemate uurea ja TG väärtustega. Seetõttu keerukas hinnata planeeritud suurema AH ja lipiidide pakkumise mõju.

ABSTRACT

Objectives:

To evaluate the effects of two different doses of parenteral aminoacid supplementation on postnatal growth in Very Low Birth Weight (VLBW) infants receiving partial parenteral nutrition (PPN).

Effect of two different doses of parenteral amino acid supplementation on postnatal growth of

Design:
Double blinded randomized controlled trial.
Settings:
Level 3 NICU between February 2008 to February 2010.
Participants:
150 inborn babies with birthweight between 900-1250 g, irrespective of gestational age, were randomized to either of the two interventions of amino acid supplementation.
Intervention:
Two different initial doses of parenteral amino acids (AA) in the PPN solutions- **Low AA group**: 1 g/kg/d *versus* **High AA group**: 3 g/kg/d from day 1 of life with increment by 1 g/kg every day till a maximum of 4 g/kg/d, until babies tolerated 75% enteral feeds.
Main outcome:
Average postnatal weight gain (in g/kg/d) by 28 days of life.
Results:
Both groups had similar baseline characteristics.
The gain in weight, length and head circumference at 28 days were significantly lower in the High AA group. The average weight gain at 28 days was 8.67g/kg/d in the High AA group and 13.15g/kg/d in the Low AA group (mean difference 123.12, 95% CI 46.67 to 199.37, *P*<0.001).

TABLE II POSTNATAL GROWTH AND NUTRITIONAL INTAKE AMONG THE STUDY SUBJECTS

Outcome	*Low AA Group (n=63)*	*High AA Group (n=60)*	*Mean difference (95% CI)*	*P value*
Weight gain at 28 days (g/kg/d)*	13.15 (5.25)	8.67 ± 4.28	4.48 (2.76-6.19)	<0.001
Weight in g at 28 days*	1494.7 (224.4)	1371.58 ± 202.64	123.12(46.67-199.57)	0.01
Length in cm at 28 days*	40.21 (2.34)	39.19 ± 1.8	1.02(0.27-1.77)	0.008
Length gain (cm/wk)*	0.63 (0.36)	0.36 ± 0.348	0.27(0.14-0.39)	<0.001
Head circumference in cm at 28 days†	29 (27.5-30.5)	28 (27-29)		0.42
Head circumference gain (cm/wk)†	0.625 (0.37-0.875)	0.25 (0.03-0.59)		<0.001
Total days of PPN†	12 (7-15)	10 (7-15)		0.31
Cumulative Enteral intake in first 28 days (kcal/kg/d)*	69.9 (3.99)	71.1 ± 3.34	-1.2(-2.52-0.11)	0.07
Cumulative non protein calorie from PPN (kcal)*	349.1 (55.34)	318.5 ± 60.43	30.6(9.93-51.27)	0.004
Time to regain BW (days)†	12 (10-14)	16 (11-20)		<0.001
Duration of hospital stay (days)†	21 (14-26)	19 (13-26)		0.25

*Data represented as mean (SD); †Data represented as median (IQR).

The incidences of neonatal morbidities associated with prematurity were similar in both groups.
Conclusion:
Higher initial parenteral aminoacid supplementation, in settings where partial parenteral nutrition is administered, results in poor growth in VLBW infants due to inadequate non-protein calorie intake.

very low birth weight neonates, a randomized controlled trial.

Balasubramanian H, Nanavati RN, Kabra NS.

Indian Pediatr 2013;50(12):1131–6.

Ühekeskuseline topeltpime RCT. (*resource limited settings* – Mumbai, India).
Randomiseerinine 24 tj. Sünnist.

„-“ Osaline PT, ilma lipiidlahuseid manustamata. Samas järelduseks, et suurem valgupakkumine, millega ei kaasne piisavas hulgas mittevalgulise kaloraaži tagamine (lipiidide näol), viib hoopiski vastupidisele tulemusele (väiksem kaaluiive). Lipiide manustati <1 kg lastele 0,5 g/kg/p annust suurendati + 0,5 g/kg/p

„-„ suhteliselt „suured“ >30 GN ja küpsed EA

PT lahused valmistas osakonna õde (nagu ka Eestis), kes ei osalenud ravitöös.

ABSTRACT

Impact of early and high amino acid

Objective:
The aim of the present study was to examine the effects of early and high intravenous (IV) amino acid (AA) supplementation on growth, health, and neurodevelopment of extremely-low-birth-weight (ELBW) infants throughout their first 2 years of life.

Methods:
Infants were prospectively randomized in a double-masked fashion and treated for 7 days with either **IV AA starting at 0.5 g/ kg/day** and increased by 0.5 g / kg/ every day **to 3 g/kg/ day** or **starting at 2 g/kg/ day of IV AA** and advanced by 1 g/kg every day **to 4 g/kg/day**. Plasma AA concentrations were determined by reverse-phase high-performance liquid chromatography. Survivors were longitudinally assessed with Bayley II Scales of Infant Development and physical, social, and global health.

Results:
Forty-three of 51 survivors were studied. **Mental Developmental Index (MDI) and Psychomotor Developmental Index were similar between groups; however, the early and high AA group had a lower MDI at 18 months.** This difference disappeared at 2 years of age.

TABLE 2. Nutritional characteristics and neurodevelopmental/health outcomes in children examined at 18–24 mo

	Standard, n = 16	Early and high, n = 16	*P*
Enteral feeds, mL·kg^{-1}·d^{-1}, DOL1	0	0	N/A
Enteral feeds, mL·kg^{-1}·d^{-1}, DOL3	2.5 ± 9.0	1.1 ± 2.9	0.5
Enteral feeds, mL·kg^{-1}·d^{-1}, DOL7	15 ± 23	10 ± 16	0.4
Parenteral caloric intake DOL1*	6.5 ± 4.3	7.8 ± 3.2	0.3
Parenteral caloric intake, DOL3*	18 ± 3	19 ± 5.3	0.8
Parenteral caloric, intake DOL7*	27 ± 6	29 ± 6	0.5
Weight gain by 28 d, g·kg^{-1}·d^{-1}	12.2 ± 4.6	10.8 ± 42	0.4
Time to full feeds, d	20 ± 8	23 ± 10	0.2
TPN days (initial, consecutive)	15 ± 7	18 ± 8	0.3
TPN days (total hospital stay)	21 ± 12	28 ± 19	0.1
Breast-feeding			
Discharge	14	15	0.6
3 mo CGA	1	2	0.5
6 mo CGA	0	2	0.4
Hospital readmission	1.4 ± 1.4	1.1 ± 1.2	0.6
Pulmonary medications			
6 mo CGA	4	3	0.8
12 mo CGA	3	4	0.8
Seizure medications	1	1	0.9
Blind	1	2	1.0
CP	1	3	0.5
Autistic	1	1	1.0
MDI			
6 mo CGA	88 ± 5	84 ± 14	0.3
12 mo CGA	84 ± 14	81 ± 9	0.5
18 mo CGA	84 ± 11	73 ± 15	0.03
24 mo CGA	63 ± 13	57 ± 11	0.2
PDI			
6 mo CGA	86 ± 13	82 ± 15	0.4
12 mo CGA	76 ± 12	71 ± 14	0.3
18 mo CGA	79 ± 12	74 ± 14	0.3
24 mo CGA	64 ± 12	67 ± 15	0.6
ECI services			
6 mo CGA	36%	43%	0.6
12 mo CGA	56%	59%	0.8
18 mo CGA	69%	69%	1.0
24 mo CGA	78%	69%	0.5

Data are presented as number of individuals, mean ± SD, or group percentage. CGA = corrected gestational age; CP = cerebral palsy; DOL = day of life; ECI = early childhood intervention; MDI = Mental Developmental Index; PDI = Psychomotor Developmental Index; TPN = total parenteral nutrition.
* Parenteral caloric intake is expressed in kcal·kg^{-1}·d^{-1}.

The early and high AA group z score means for weight, length, and head circumferences were significantly lower than the standard AA group at most visits.

supplementation on ELBW infants at 2 years.

Blanco CL, Gong AK, Schoolfield J, Green BK, Daniels W, Liechty EA, et al J

Pediatr Gastroenterol Nutr 2012;54(5):601–7.

San Antonio, Texas

Uuringuperiood 2002-2005 a. ELBW, randomiseeriti 12 tj sünnist.

„-„väike uuringurühm (43 last); Esialgselt ei olnud planeeritud kasvamise ja neuroloogilise arengu hindamine.

Järeldati, et 1 elunädalal suurema AH pakkumisega laste grupis kasvamine kõikide parameetrite osas halvem hinnatuna 2 a. vanuses.

Neuroloogiline tulem 2 a. sarnane (v.a. erinevus suurema AH pakkumise kahjuks 18 kuu vanuses).

Teiste peamiste haiguste esinemises vahet ei olnud v.a BPD, mille esinemissagedus statistiliselt oluliselt

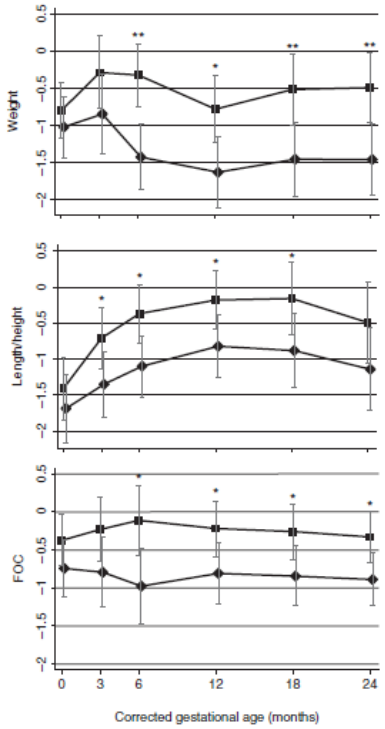


FIGURE 2. *z* Scores for weight, length/height, and fronto-occipital circumference (FOC) up to 2 years of age are shown. Diamonds represent early and high AA group, squares represent the standard AA group. $*P < 0.05$, $**P < 0.01$.

Cumulative and single plasma AA concentrations correlated negatively with MDI and postnatal growth.

suurem suurema AH grupis. Kuigi, on teada BPD-ga kaasnevaid kasvamise ja neuroloogilise arengu probleeme, ei saa seda võtta siinkohal otsese seosena.

Grupid liiga väikesed (vastavalt 20 ja 21 last)

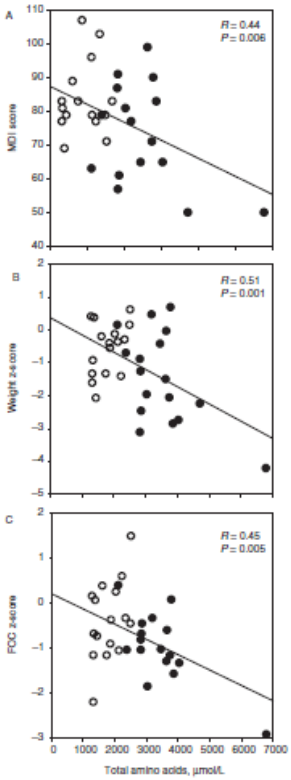


FIGURE 3. Correlation between total serum AA concentration and Mental Developmental Index at 18 months (A), total serum AA concentration and weight *z* scores (B), and total serum AA concentration and fronto-occipital circumference (FOC) *z* scores (C) at 18 to 24 months are shown. Open circles = standard AA group; dark circles = early and high AA group.

TABLE 1. Demographics and clinical outcomes at discharge from survivors who completed follow-up and those lost for follow-up

	Examined at 18–24 mo			Not examined at 18–24 mo		
	Standard, n = 16	Early and high, n = 16	*P*	Standard, n = 11	Early and high, n = 8	*P*
Birth weight, g	805 ± 145	820 ± 133	0.8	785 ± 140	711 ± 103	0.2
Gestational age, wk	26.3 ± 1.5	26.5 ± 1.9	0.8	27.0 ± 2.5	25.2 ± 1.2	0.07
SGA at birth	2	3	0.6	3	0	0.2
White race	1	0	1.0	4	2	0.6
Male sex	8	10	0.5	7	6	0.6
Antenatal steroids	10	11	0.6	8	6	0.9
CRIB score	5.1 ± 3.6	5.3 ± 2.7	0.8	5.4 ± 4.0	7.1 ± 2.6	0.3
Length of stay, days	74 ± 20	84 ± 22	0.2	78 ± 24	108 ± 79	0.2
IVH (3 and 4)	1	3	0.6	1	0	0.7
ROP, threshold	2	3	1.0	4	3	1.0
NEC	2	1	0.2	0	2	0.1
Sepsis	2	3	1.0	2	1	1.0
BPD	4	10	0.07	4	4	0.6
Home oxygen	2	2	1.0	2	2	1.0
Maternal education						
Elementary school	0	1	0.7	2	0*	0.5
High school	10	11	0.8	1	1*	0.8
College education	6	4	0.3	8	5*	0.5

Data are presented as number of individuals, means ± SD. Only survivors to discharge are included. BPD = bronchopulmonary dysplasia defined as oxygen therapy by 36 weeks postmenstrual age; CRIB = Clinical Risk Index for Babies; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; ROP = retinopathy of prematurity; SGA = small for gestational age.
* Missing information from 2 infants.

Conclusions:

ELBW infants who received early and high IV AA during the first week of life were associated with poor overall growth at 2 years.

Otsingustrateegia kliinilisele küsimusele 23

Andmebaas	Medline (PUBMED)
Otsingustrateegia: (Key words + Mesh)	Search ((((("parenteral nutrition") OR "Nutritional Requirements"[Mesh]) OR (("Parenteral Nutrition"[Mesh]) OR "Parenteral Nutrition Solutions"[Mesh]))) AND ((((((((((((("premature infant") OR "premature infants") OR "premature newborn") OR "premature newborns") OR "premature neonate") OR "premature neonates") OR "preterm infant") OR "preterm infants") OR "preterm newborn") OR "preterm newborns") OR "preterm neonate") OR "preterm neonates")) OR (("Infant, Premature"[Mesh]) OR "Infant, Low Birth Weight"[Mesh]))) Filters: Randomized Controlled Trial; Review; Systematic Reviews; published in the last 5 years; English
Tulemuste arv	**Meta-analüüsid: 4; SR: 17; RCT: 16**
Ajaline piirang	5 aastat
Muud piirangud	English language

Andmebaas	Cochrane Library http://onlinelibrary.wiley.com/cochranelibrary/search
Otsingustrateegia: (Key words)	„parenteral nutrition“
Tulemuste arv	**3 meta-analüüsi**
Ajaline piirang	5 aastat
Muud piirangud	English language