Neuroprotektion inte bara Hypotermi

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23 April 2010

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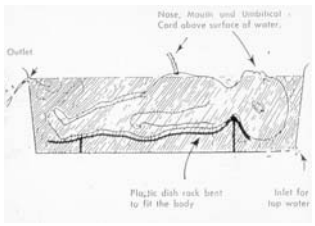


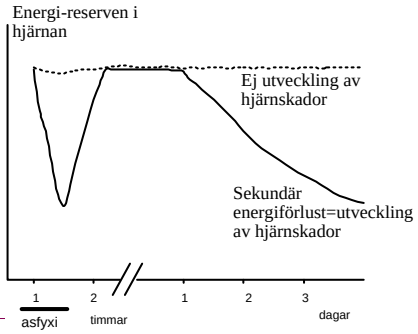
Westin 1959

Perinatal asfyxi

- 1-2 barn/1000 HIE
- 0.5-1/1000 moderate-severe HIE

	Mortalitet	Motoriska handikap
Måttlig	10%	30%
Svår	60%	30-40%

Sekundär nervcellskada



Intensivvård

Kan optimal behandling förbättra prognos?

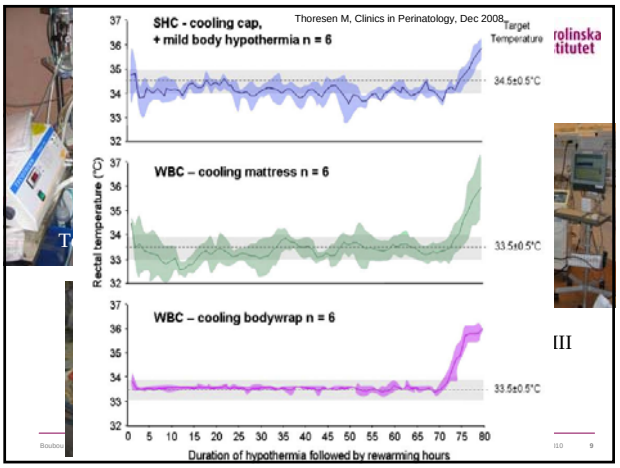
- Normoventilation ($PaCO_2$ 5.5- 8 kPa)
- Normoxi (PaO_2 7-9 kPa)
- Normalt blodtryck (>35-40 mm Hg)
- B-glukos >2.6 mmol/L
- Tidig krampbehandling
- Normotermi (36.5-37.5 C)

NEUROPROTEKTION

- Fria syreradikaler (t.ex. allopurinol
- Intracellulärt calcium (calciumkanal-blockerare)
- Glutamatantagonister, (Mg^{2+})
- Apoptos (hypotermi)
- Inflammation
- Tillväxtfaktorer (EPO, IGF1)
- Oxidativ stress (FiO2 0,21)
- Krampbehandling

Mechanism of cell injury	Pathway or condition influenced by treatment	Clinical studies	Protective effect
Programmed cell death, Apoptosis	Caspase activation	Hypothermia *Edwards BMJ 2010*	+
Inflammatory second messenger activation	Cytokines e.g. interleukin ILs	Hypothermia	+
Oxidative stress Free radical release	O2 -> hypoxanthine release	Room air vs 100% ox *Saugstad 2009*	+
	NO	Hypothermia	+
	Xantine oxidase	Allopurinol *Benders Archives2008*	+/-/*
Excitatory amino acid release	Glutamate/ NMDA receptor inhibitor HT induction	HT Animal exp Magnesium Pilot Magnesium RCT *Bhat Pediatrics 2009* Xenon animal/RCT *Thoresen Stroke 2009*	+/- + +! -!/+ +/*
Ca 2+ influx -> cell membrane injury		Ca 2+ blocker[125] Bumetanide/ *NEMO*	- */?
Ischemia/Reperfusion	Fe 2+ scavenger	Erythropoietin EPO *Zhu Peditrics 2009*	+/*
Cytotoxic edema	Reduce cerebral edema	Mannitol [129] Dexamethasone [129, 130]	- -
Seizures	Antiepileptic treatment AED	Barbiturates Thiopental Phenobarbitone	- -

- (+)Significantly reduced neurological impairment, (–) Non significant or harmful, (!) Adverse event study stopped, (*) Ongoing study, (?) Study planned.



BMJ RESEARCH

Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data

Study or subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
TOBY	74	163	86	162		39.0	0.86 (0.68 to 1.07)
NICHD	45	102	64	106		28.3	0.73 (0.56 to 0.95)
CoolCap	59	116	73	118		32.7	0.82 (0.65 to 1.03)
Total (95% CI)		381		386		100.00	0.81 (0.71 to 0.93)
Total events	178		223				

0.2 0.5 1 2 5
Favours hypothermia | Favours normothermia

Fig 1 | Forest plot of the effect of therapeutic hypothermia compared with standard care (normothermia) on death or disability ("events"). All infants randomly assigned to either study arm were included in the analysis. A Mantel-Haenszel fixed effects model was used to calculate risk ratios and 95% confidence intervals. Test for heterogeneity: χ^2=0.82, degrees of freedom=2 (P=0.66); I^2=0%. Test for overall effect: Z=3.03 (P=0.002). Studies shown are the Total Body Hypothermia (TOBY) trial,[4] the National Institute of Child Health and Human Development (NICHD) trial,[5] and the CoolCap trial[6]

BMJ | ONLINE FIRST | bmj.com

BMJ 2010;340:c363

BMJ RESEARCH

Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data

Study or subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
CoolCap	29	116	20	118		22.9	1.48 (0.89 to 2.45)
NICHD	32	102	22	106		24.9	1.51 (0.94 to 2.42)
TOBY	71	163	45	162		52.2	1.57 (1.16 to 2.12)
Total (95% CI)		381		386		100.00	1.53 (1.22 to 1.93)
Total events	132		87				

0.1 0.2 0.5 1 2 5 10
Favours normothermia | Favours hypothermia

Fig 2 | Forest plot of the effect of therapeutic hypothermia compared with standard care (normothermia) on survival with normal neurological function ("events"). All infants randomly

Måttlig HT i 72 timmar efter förlossningsasfyxi minskar hjärnskadan, förbättrar motoriska och kognitiva funktioner och är säker. Fördubblar chansen till frisk överlevnad.

BLFs kriterier för kylbehandling

A. Över v 36+0 med minst ett av följande fyra kriterier är uppfyllt:

Apgar ≤ 5 vid 10 minuter.
Pågående HLR vid 10 minuters ålder.
pH ≤ 7,0/ BE ≤ -16 första 60 minuterna

B. Anfall ("kramper") eller tecken på **måttlig till svår encefalopati** vilket här definieras av:

- förändrad **vakenhetsgrad** (letargi, stupor eller koma), OCH
- förändrad **tonus**; hypoton, helt slapp eller opistotonus, OCH
- påverkan på **primitiva reflexer** (svag eller avsaknad av sugreflex /morореflex).

Nedkylning protokoll

- Kylning så fort vi kan, senast 6 tim
- Mål temperaturen 33,5 grader C (mellan 33 och 34 grader)
- 72 timmar
- Långsam uppvärmning (minst 12 timmar)

Kylbehandling i Sverige
Nationellt register 2007-2009

- 188 HT behandlade barn
- 2007: 0.36 (range 0-0.9) (39/108.000)
- 2008: 0.64 (range 0-0,9) (71/110.000)
- 2009: 0.67 (range 0-0.9) (78/115.000)

- 1 ECMO
- 20 iNO
- 10 % Mortalite – OBS! Mycket lägre än tidigare rapporterat.

- 2 allvarliga arrytmier - lidokain

Passive induction of hypothermia during transport of asphyxiated infants: a risk of excessive cooling

Boubou Hallberg[1,2], Linus Olsen[1,2], Marco Bartocci[1,2], Ingela Edqvist[1,2], Mats Blennow (mats.blennow@ki.se)[1,2]

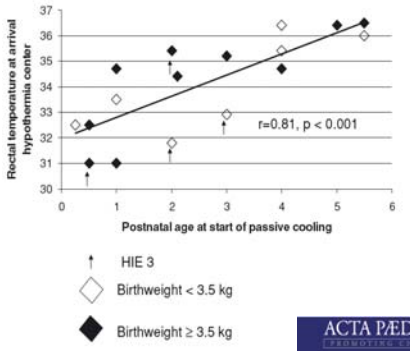
ACTA PÆDIATRICA
PROMOTING CHILD HEALTH
2009 Jun;98(6):942-6

- Dec 2006- April 2008
- Förlossningar 40,350
- 37 barn upfyllde B-krit
- 34 HT behandlade
- Median tid för start av passiv kylning 2.5 timmar
- 6 barn passivt kylda före 1 timmes ålder

Temperatur vid ankomst

	35.0–37.0°C	33.1–35.0°C	<33°C	Total
n	8	4	6	18
Passive cooling started in DR	0	1	5	6
Outdoor temp. <10°C at transport	5	2	5	12
Outdoor temp. <0°C at transport	2	1	1	4
Birth weight <3.5 kg	4		4	8
Birth weight ≥3.5 kg	4	4	2	10
Ventilated during transport	2	0	4	6
HIE moderate-to-severe	6	2	6	14
Mortality	1	0	2	3

HIE = hypoxic–ischaemic encephalopathy.



ACTA PÆDIATRICA
PROMOTING CHILD HEALTH
2009 Jun;98(6):942-6

The prognostic value of early aEEG in asphyxiated infants undergoing systemic hypothermia treatment

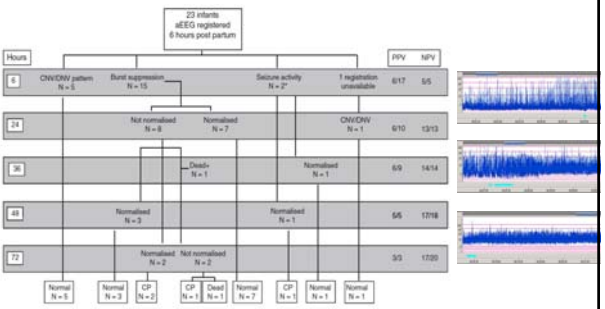
B Hallberg (boubou.hallberg@ki.se)[1,2], K Grossmann[3], M Bartocci[1,2], M Blennow[1,2]

ACTA PÆDIATRICA
PROMOTING CHILD HEALTH
Acta Paediatrica 2010 99, pp. 531–536

Table 3 Baseline patient characteristics and outcome data

GA	Weeks + days	40 + 1	36 + 5–41 + 6	Mean (range)
BW	kg	3.56	2.45–4.99	Mean (range)
Apgar 5'		2	0–6	Median (range)
Apgar 10'		4	1–6	Median (range)
Sex	Girls/Boys	8/15		
Inborn/Outborn		12/11		
pH umb		6.92	6.57–7.30	Mean (range)
BE umb		−16.3	−24–−4.5	Mean (range)
pH infant <1 h		6.89	6.6–7.08	Mean (range)
BE infant <1 h		−20.6	−25–−10	Mean (range)
Age at HTstart	h	3.15	0.5–10	Mean (range)
HIE	Mild/moderate/severe	3/16/4		
AIMS at 4–6 months	<5, 5–25, 25–74, >75 percentile	3/1/12/4		
Neurological exam. 12 months	CP/Delayed/Normal	4/1/15		
Mortality		2		

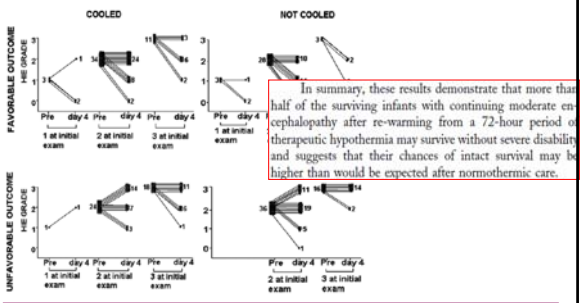
Prognos instrument- aEEG



Karolinska Institutet

Therapeutic Hypothermia Changes the Prognostic Value of Clinical Evaluation of Neonatal Encephalopathy

J Pediatr 2008;152:55-8



In summary, these results demonstrate that more than half of the surviving infants with continuing moderate encephalopathy after re-warming from a 72-hour period of therapeutic hypothermia may survive without severe disability and suggests that their chances of intact survival may be higher than would be expected after normothermic care.

FN

Early postnatal allopurinol does not improve short term outcome after severe birth asphyxia

M J N L Benders, A F Bos, C M A Rademaker, et al.

Arch Dis Child Fetal Neonatal Ed 2006 91: F163-F165 originally published online January 20, 2006
doi: 10.1136/adc.2005.086652

Allopurinol; 32 Asfyktiska barn

Interim analys- ingen effekt

Studien avbruten

Nu pågår Holländsk RCT med Allopurinol till mödrar före förlossning.

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Magnesium Sulfate in Severe Perinatal Asphyxia: A Randomized, Placebo-Controlled Trial

Mushtaq Ahmad Bhat, Bashir Ahmad Charoo, Javeed Iqbal Bhat, Sheikh Mushtaq Ahmad, Syed Wajid Ali and Masood-ul-Hassan Mufti

Pediatrics 2009;123;e764-e769; originally published online Apr 6, 2009;

- 40 fullgångna asfyktiska barn; placebo kontrollerad studie.
- 3 doser av magnesium sulfat infusion; 250 mg/kg per dos) eller 3 doser of NaCl. 1x1 (3x24)
- Behandlings gruppen: moderat HIE 35% (7 av 20) svår HIE; 65% (13 av 20)
- Vid utskrivning: 22% (4 av 18) i beh. gruppen hade neurologiska abnormalitet, jämfört med 56% (10 of 18) i placebo gruppen.

- **Konklusion:** *"Good short-term outcomes at discharge occurred for 77% of the patients in the treatment group, compared with 37% of the patients in the placebo group."*

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Erythropoietin Improved Neurologic Outcomes in Newborns With Hypoxic-Ischemic Encephalopathy

Changlian Zhu, Wenqing Kang, Falin Xu, Xiuyong Cheng, Zhan Zhang, Liting Jia, Ling Ji, Xiaoyan Guo, Hong Xiong, George Simbruner, Klas Blomgren and Xiaoyang Wang

Pediatrics 2009;124:e218-e226; originally published online Jul 27, 2009;

•167 fullgångna barn: moderate/svår HIE.
•Erythropoietin (N = 83) 300 U/kg (N = 52) or 500 U/kg (N = 31),
•Recombinant human erythropoietin, v.a.d. i 2veckor imom < 48 timmar efter födelse

•Död eller moderate/svår neurohandikap: 35 (43.8%) av 80 i kontroll gruppen; 18 (24.6%) av 73 i erythropoietin gruppen (P = .017) vid 18 månaders ålder.
•Subgrupp analys visade effekt endast vid moderate HIE (P = .001)

•**Konklusion:** *"Repeated, low-dose, recombinant human erythropoietin treatment reduced the risk of disability for infants with moderate HIE, without apparent "side effects.*

Zhu et al. Pediatrics 2009;124:e218-e226

Erythropoietin Improved Neurologic Outcomes in Newborns With Hypoxic-Ischemic Encephalopathy

TABLE 4 Outcomes at 18 Months of Age for Erythropoietin and Control Groups

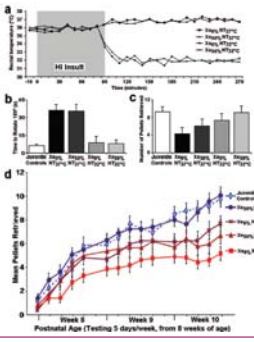
	n/N (%)		Relative Risk (95% Confidence Interval)	P
	Erythropoietin (N = 73)	Control (N = 80)		
Primary outcome				
Death	3/73 (4.1)	4/80 (5.0)	0.89 (0.37–2.13)	> .999
Disability	15/70 (21.4)	31/76 (40.8)	0.59 (0.38–0.93)	.013
Secondary outcome				
Death or Disability	18/73 (24.6)	35/80 (43.8)	0.62 (0.41–0.94)	.017
Moderate HIE	3/47 (6.4)	19/59 (32.2)	0.26 (0.09–0.76)	.001
Severe HIE	15/26 (57.7)	16/21 (76.2)	0.70 (0.47–1.15)	.227
Male	17/57 (29.8)	25/55 (45.5)	0.71 (0.47–1.08)	.118
Female	1/16 (6.3)	10/25 (40.0)	0.18 (0.03–1.22)	.029
MDI of <70	7/70 (10.0)	17/76 (22.4)	0.56 (0.30–1.08)	.048
Moderate HIE	2/47 (4.3)	9/57 (15.8)	0.38 (0.11–1.34)	.106
Severe HIE	5/23 (21.7)	8/19 (42.1)	0.62 (0.29–1.30)	.193
Cerebral palsy	5/70 (6.8)	14/76 (18.4)	0.51 (0.23–1.11)	.051
Moderate HIE	1/47 (2.1)	8/57 (14.0)	0.23 (0.04–1.47)	.039
Severe HIE	4/23 (17.4)	6/19 (31.6)	0.67 (0.30–1.52)	.468

Xenon and Hypothermia Combine Additively, Offering Long-Term Functional and Histopathologic Neuroprotection After Neonatal Hypoxia/Ischemia

Catherine Hobbs, PhD; Marianne Thoresen, MD, PhD; Alexander Tucker, BA; Kristian Aquilina, FRCS; Ela Chakkarapani, MRCPCH; John Dingley, MD

Xenon – NMDA antagonist
Addidativ effekt HT
Reducerar skade utbredning
-Råtta, Gris

-UCL/Imperial College planerar Klinisk studie



A Closed-Circuit Neonatal Xenon Delivery System: A Technical and Practical Neuroprotection Feasibility Study in Newborn Pigs

Ela Chakkarapani, MRCPCH*
Marianne Thoresen, MD, PhD, FRCPCH*
Catherine E. Hobbs, PhD*
Kristian Aquilina, FRCS*
Xun Liu, PhD*
John Dingley, MD†

Figure 1. Full neonatal closed-circuit assembly (overall height 122 cm). A neonatal ventilator set to deliver 100% O_2 is attached to lower chamber of the circuit. During inspiration, bag (A) is compressed. Gas passes to upper part of

Cochrane Report: Neonatal Seizures

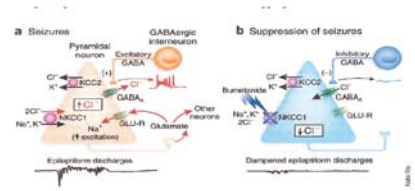
Conclusion:

Little evidence from randomised trials to support the use of any AED currently in use in the neonatal period

No recommendation can be made regarding choice of AED based on available data

Booth and Evans 2004 (Cochrane Database Syst Rev)

Seizure Mechanism of Action



Fukuda, Atsuo, Nature Medicine 2005;11:1153-1154

NEMO 1 - fas I/IIa:
- Farmakokinetisk, säkerhets och dos studie av bumetanide.
- Behandling av neonatala kramper som ej svarar på Fenobarbital
- Optimal dos av bumetanid som antiepileptiskt läkemedel vid neonatala kramper.

NEMO 2 - Fas IIb/III,
- RCT, placebo-kontrollerad, dubbel-blind, klinisk studie.
- Evaluera effekt och säkerhet av Bumetanid.
- Lång tids uppföljning.

- HIE och HT
- Kramper
- Fenobarbital
- Bumetanide

www.nemo-europe.com


Ingela Edqvist

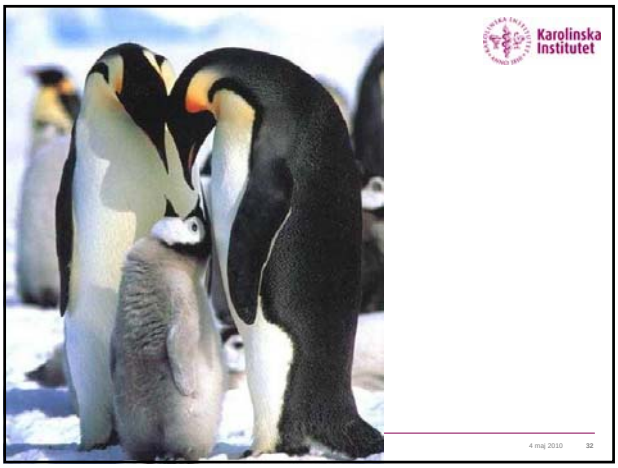

Linus Olson


Marco Bartocci


Mats Blennow


Boubou Hallber

NeoCool group in Stockholm



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