Evidence based analgesic and sedative drugs in infants:beyond the problem

ZonMw project 40-41500-98.9020

Intensive Care & Department of Paediatric Surgery

Erasmus MC - Sophia Children's Hospital Rotterdam

Evidence based analgesic and sedative drugs in infants;beyond the problem

- Randomized controlled trial of morphine versus IV paracetamol
- Optimal analgesic therapy in children on extracorporeal membrane oxygenation (ECMO)
- Dose finding of paracetamol in extreme low birth weight infants

Long term follow up after neonatal pain experiences and exposure to opioids

Evidence based analgesic and sedative drugs in infants;beyond the problem

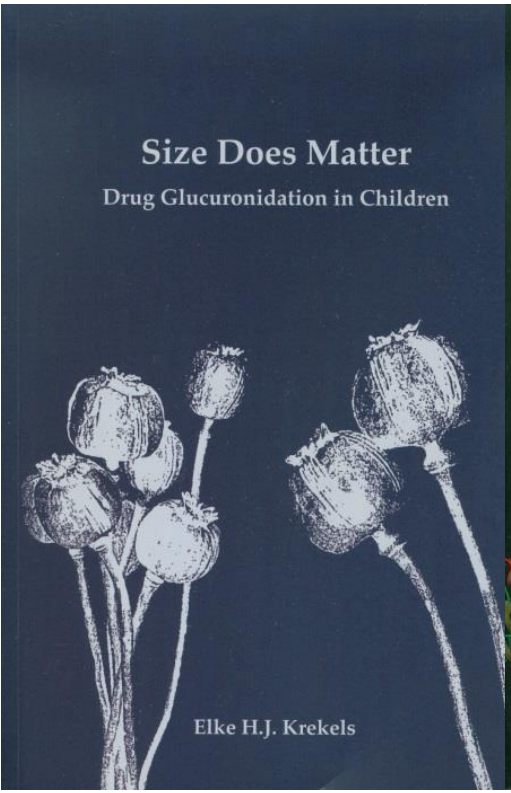
- Randomized controlled trial of morphine versus IV paracetamol
- Optimal analgesic therapy in children on extracorporeal membrane oxygenation (ECMO)
- Dose finding of paracetamol in extreme low birth weight infants

Long term follow up after neonatal pain experiences and exposure to opioids

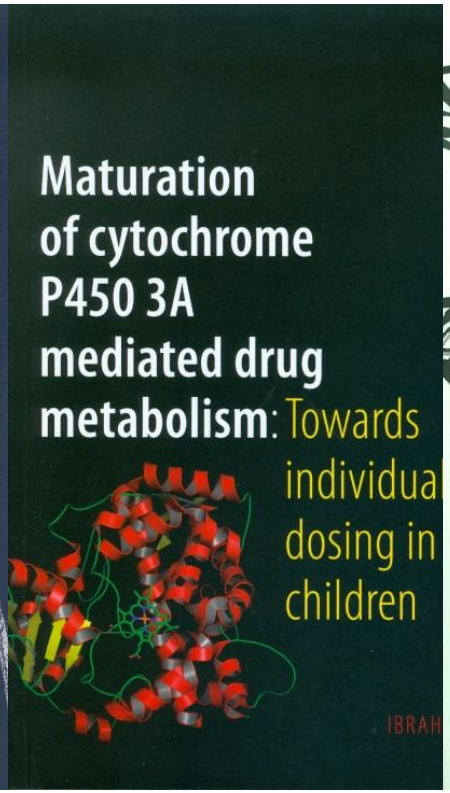
Towards evidence-based dosing regimens in children on the basis of population pharmacokinetic pharmacodynamic modelling

Rick Admiraal,[1,2,3,4] Charlotte van Kesteren,[1,2,3] Jaap Jan Boelens,[1,2] Robbert G M Bredius,[3] Dick Tibboel,[4] Catherijne A J Knibbe[2,4,5]

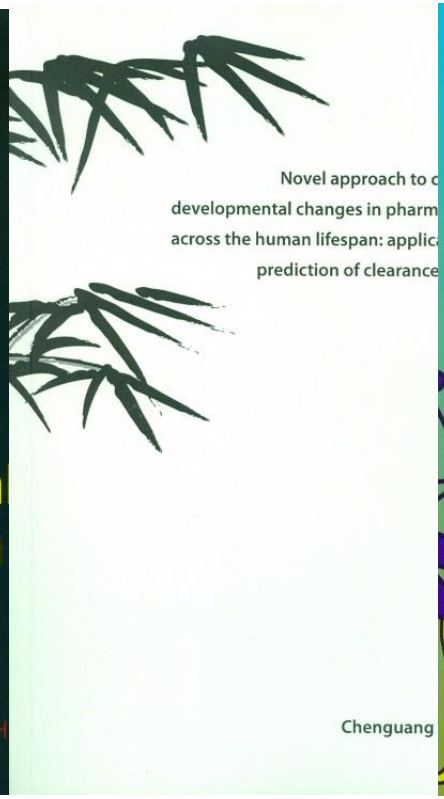
To cite: Admiraal R, van Kesteren C, Boelens JJ, *et al*. *Arch Dis Child* Published Online First: [*please include* Day Month Year] doi:10.1136/archdischild-2013-303721



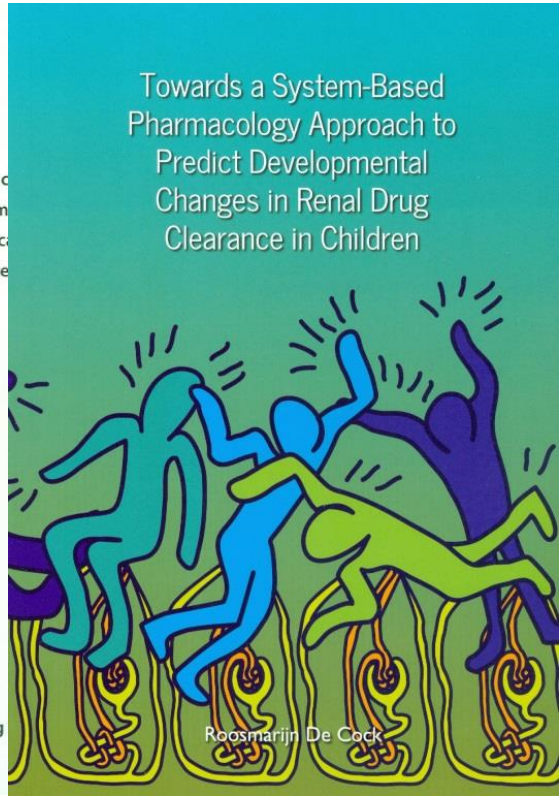
Morphine



Midazolam



Vancomycine



Renal clearance

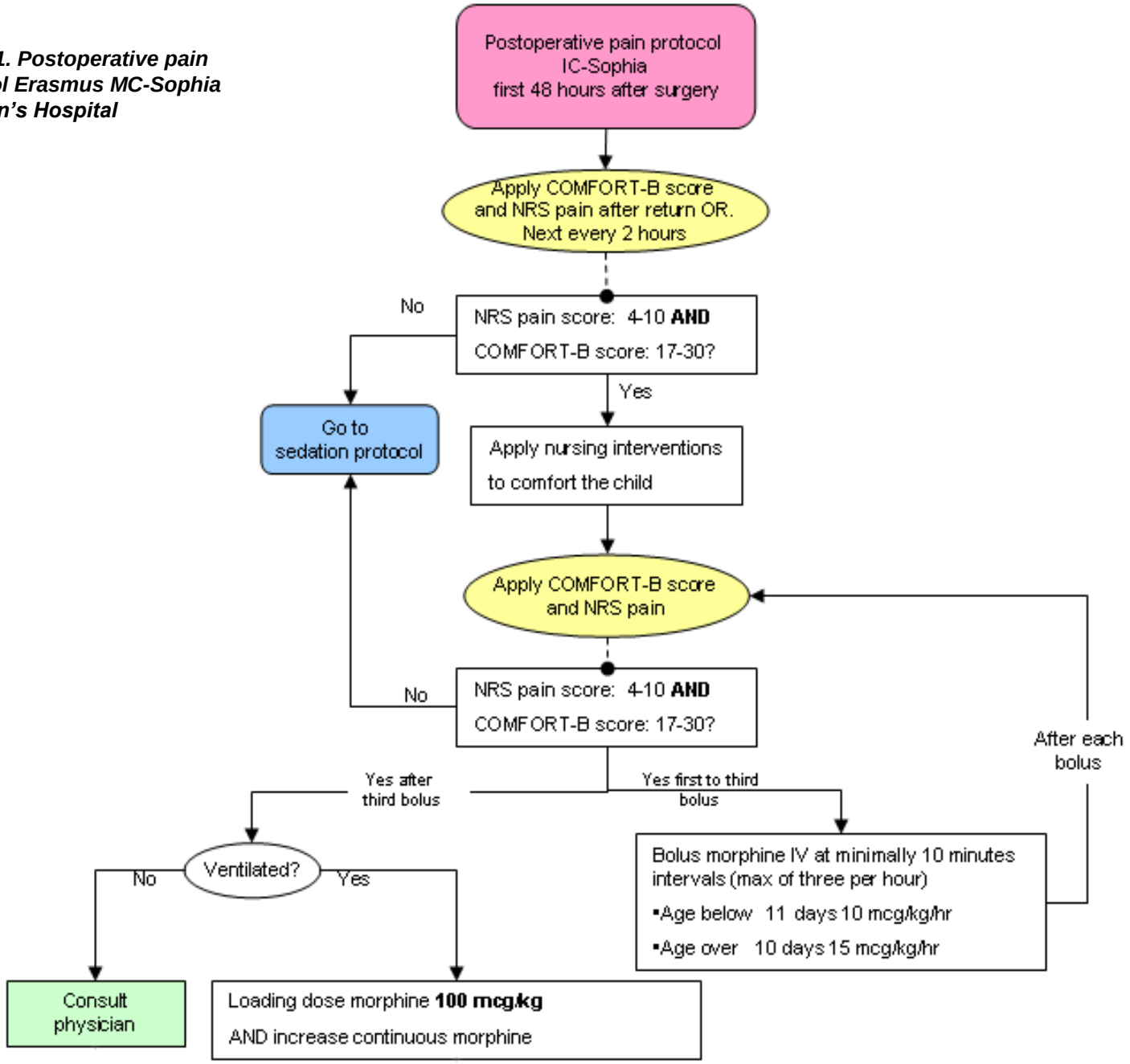
Morphine Glucuronidation in Preterm Neonates, Infants and Children Younger than 3 years

Conclusion:

Model-based simulations show that in newborns, including preterms, infants and children under the age of 3 years, a loading dose in µg/kg and a maintenance dose expressed in µg/kg 1.5/hr, with a 50% reduction of the maintenance dose in newborns younger than 10 days.

Knibbe CAJ, Krekels EHJ et al. Clin Pharmacokinet 2009:48:371-385

Figure 1. Postoperative pain protocol Erasmus MC-Sophia Children's Hospital



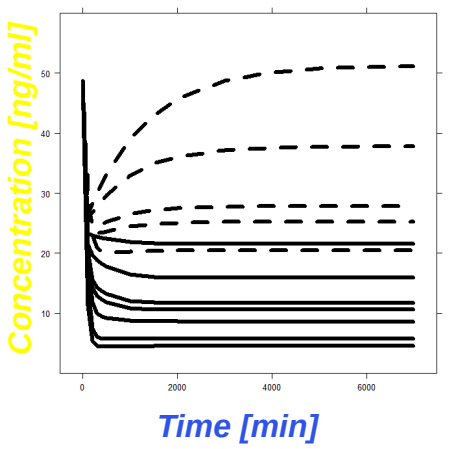
Validation of the proposed dosing regimen in a prospective trial *(NTR1438)*

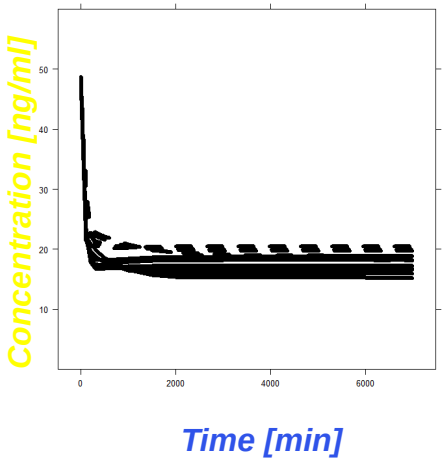
Erasmus MC

Traditional dosing scheme in ug/kg/h

Proposed dosing scheme µg/kg$^{1.5}$/h

Morphine





Validation of the proposed dosing regimen in a prospective trial (*NTR1438*)

BW kg	PNA < 10 2.5 µg/kg$^{1.5}$/h infusion rate µg/h	PNA > 10 5 µg/kg$^{1.5}$/h µg/h
0.5	0.9	1.8
1	2.5	5.0
1.5	4.6	9.2
2	7.1	14.1
2.5	9.9	19.8
3	13.0	26.0
3.5	6.4	32.7
	.0	40.0
	9	47.7
	.0	55.9
	32.2	64.5
6	36.7	73.5
6.5	41.4	82.9
7	46.3	92.6
7.5	.	102.7
8	.	113.1
8.5	.	123.9
9	.	135.0

75% dose reduction in neonates

Do we really need morphine?

Morphine i.v. versus Paracetamol i.v. in neonates and young infants undergoing major non-cardiac surgery.

Design: double blind RCT

Number of patients: 70

Age: 0 – 28 days

28 days – 6 months

6 months – 1 year

Rescue therapy: i.v. morphine

Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery

A Randomized Controlled Trial

Ilse Ceelie, MD, PhD
Saskia N. de Wildt, MD, PhD
Monique van Dijk, MSc, PhD
Margreeth M. J. van den Berg, MD
Gerbrich E. van den Bosch, MD
Hugo J. Duivenvoorden, PhD
Tom G. de Leeuw, MD
Ron Mathôt, PharmD, PhD
Catherijne A. J. Knibbe, PharmD, PhD
Dick Tibboel, MD, PhD

Importance Continuous morphine infusion as standard postoperative analgesic therapy in young infants is associated with unwanted adverse effects such as respiratory depression.

Objective To determine whether intravenous paracetamol (acetaminophen) would significantly (>30%) reduce morphine requirements in neonates and infants after major surgery.

Design, Setting, and Patients Single-center, randomized, double-blind study conducted in a level 3 pediatric intensive care unit in Rotterdam, the Netherlands. Patients were 71 neonates or infants younger than 1 year undergoing major thoracic (noncardiac) or abdominal surgery between March 2008 and July 2010, with follow-up of 48 hours.

Interventions All patients received a loading dose of morphine 30 minutes before the end of surgery, followed by continuous morphine or intermittent intravenous paracetamol up to 48 hours postsurgery. Infants in both study groups received morphine (boluses and/or continuous infusion) as rescue medication on the guidance of the validated pain assessment instruments.

Main Outcome Measures Primary outcome was cumulative morphine dose (study and rescue dose). Secondary outcomes were pain scores and morphine-related adverse effects.

Results The cumulative median morphine dose in the first 48 hours postoperatively was 121 (interquartile range, 99-264) μg/kg in the paracetamol group (n=33) and 357 (interquartile range, 220-605) μg/kg in the morphine group (n=38), $P<.001$, with a between-group difference that was 66% (95% CI, 34%-109%) lower in the paracetamol group. Pain scores and adverse effects were not significantly different between groups.

Conclusion and Relevance Among infants undergoing major surgery, postoperative use of intermittent intravenous paracetamol compared with continuous morphine resulted in a lower cumulative morphine dose over 48 hours.

Trial Registration trialregister.nl Identifier: NTR1438

JAMA. 2013;309(2):149-154 www.jama.com

THE TREATMENT OF PAIN IN young children has improved after the publications by Anand et al[1,2] in 1987 that made clear that neonates have well-developed nociceptive pathways and therefore are capable of experiencing pain. Because untreated pain is both an unwanted experience and ultimately may lead to adverse consequences,[3-6] opioids were introduced and have been used ever since.[7] Opioid therapy, however, is associated with adverse effects, in particular respiratory depression.[8] Re-

Table 2. End Points in First 48 Postoperative Hours

End Point	No. (%) Paracetamol (n = 33)	No. (%) Morphine (n = 38)	*P* Value	OR (95% CI)
Cumulative morphine dose, median (IQR), μg/kg	121 (99-264)	357 (220-605)	<.001	
Rescue morphine dose, median (IQR), μg/kg	25 (0-164)	20 (0-226)	.99	
Rescue morphine doses and infusions, median (IQR), No.	2 (0-6)	2 (0-5)	.97	
Patients receiving rescue morphine	22 (66.77)	23 (60.5)	.59	
Comedication				
Midazolam	5 (15.2)	3 (7.9)	.34	
Fentanyl	0	1 (2.6)	.35	
Vecuronium	1 (3.0)	0	.28	
Locoregional block	0	3 (7.9)	.10	
Adverse events				
Any adverse event	9 (27.3)	11 (28.9)		0.9 (0.3-2.6)
Reintubation	1 (3.0)	2 (5.3)		0.6 (0.1-6.5)
Apnea	4 (12.1)	10 (26.3)		0.5 (0.1-1.9)
Apnea with naloxone	0	3 (7.9)		0.5 (0.4-0.7)
Bradycardia	6 (18.2)	7 (18.4)		1.0 (0.3-3.3)
Urinary retention[a]	1	0		0.5 (0.4-0.6)

Abbreviations: IQR, interquartile range; OR, odds ratio.
[a] Twenty-six patients in the paracetamol group and 31 in the morphine group had a urinary catheter in place.

Do we really need morphine?

Morphine i.v. versus Paracetamol i.v. in neonates and young infants undergoing major non-cardiac surgery

Conclusion:

Equipotency between paracetamol and morphine as basic analgesic as the additional need for morphine showed no differences between the study groups

Clin Pharmacokinet
DOI 10.1007/s40262-014-0135-4

ORIGINAL RESEARCH ARTICLE

Evidence-Based Morphine Dosing for Postoperative Neonates and Infants

Elke H. J. Krekels · Dick Tibboel · Saskia N. de Wildt · Ilse Ceelie · Albert Dahan · Monique van Dijk · Meindert Danhof · Catherijne A. J. Knibbe

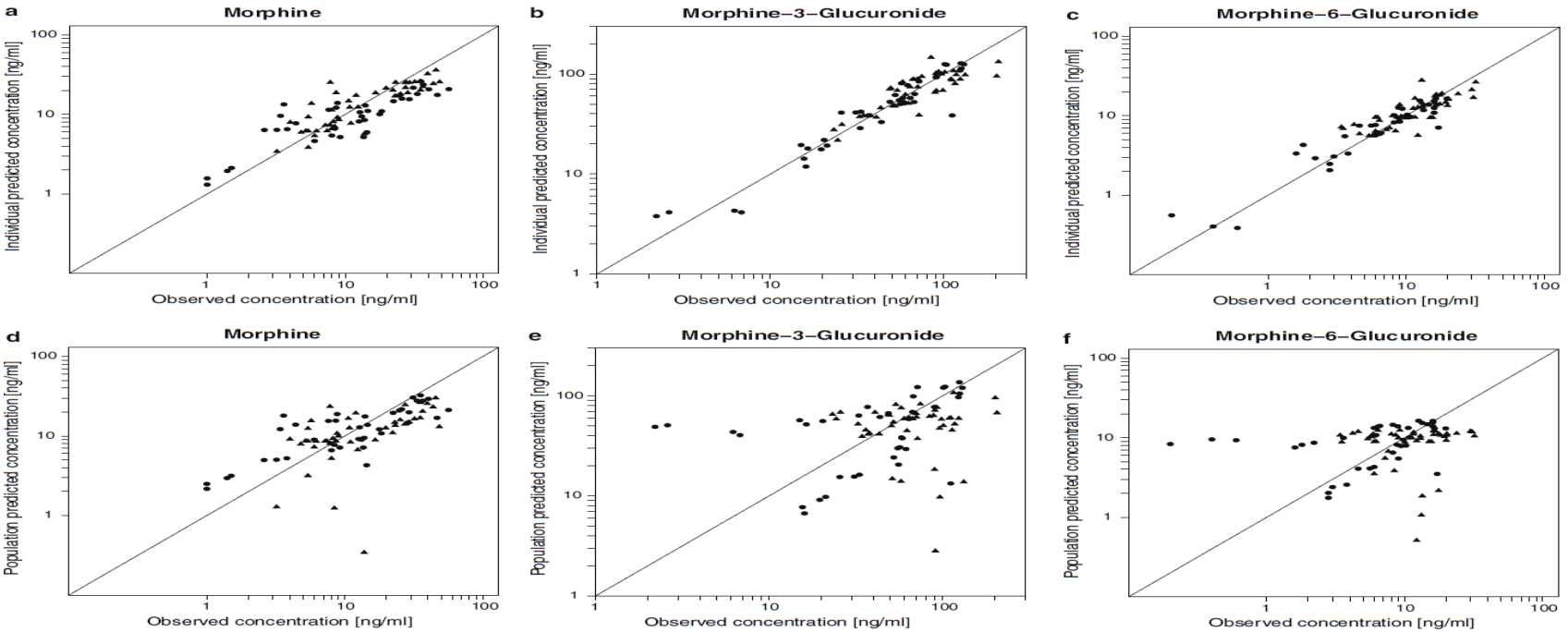


Fig. 1 Individual predicted concentrations obtained from a model fit to the observed concentrations versus observed concentrations of morphine (**a**), morphine-3-glucuronide (**b**) and morphine-6-glucuronide (**c**); and population predicted concentrations based on patients' bodyweight, age and dosing history alone versus observed concentrations of morphine (**d**), morphine-3-glucuronide (**e**) and morphine-6-glucuronide (**f**). *Triangles* and *circles* indicate datapoints from individuals in the morphine arm and the paracetamol arm of the study, respectively

Conclusions:

The role of morphine as primary choice for postoperative analgesia is controversial.

Dosing of morphine should be based on appropriate PK-PD modeling followed by “proof of principle” studies

The ultimate goal of (postoperative) analgesia is absence of pain evaluated by validated pain scores for the study population and circumstances

Long term effects of neonatal use of opioids should be evaluated

Background- Animal studies

Neonatal pain

- Acute hypersensitivity and increased duration of ipsilateral postoperative hypersensitivity (Knaepen et al. 2013)
- Decreased pain behavior (Sternberg et al. 2005)
- **Cell death** (Duhrsen et al. 2013)

NEUROPROTECTIVE EFFECT IN THE PRESENCE OF PAIN

Neonatal morphine administration

- Impaired cognitive functioning (McPherson et al. 2007)
- Prolonged pain hypersensitivity (Zhang et al. 2008)
- Increased nociceptive response in adult life (Rozisky et al. 2012)
- **Degeneration of neurons** (Atici et al. 2004)

Background- Human studies

Early Human Development 88 (2012) 487–491

Contents lists available at SciVerse ScienceDirect

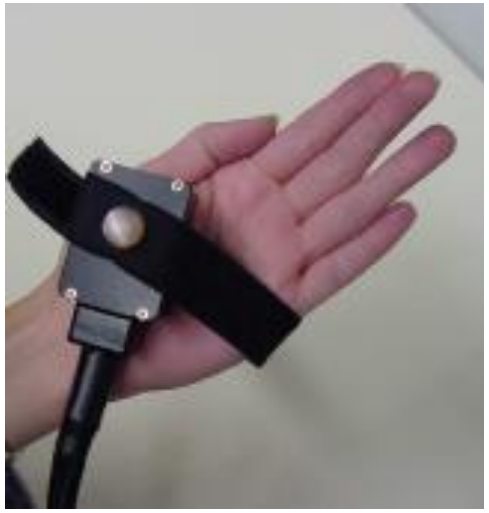
Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Thermal detection thresholds in 5-year-old preterm born children; IQ does matter

Joke de Graaf [a,*], Abraham J. Valkenburg [a,b], Dick Tibboel [a,b], Monique van Dijk [a]

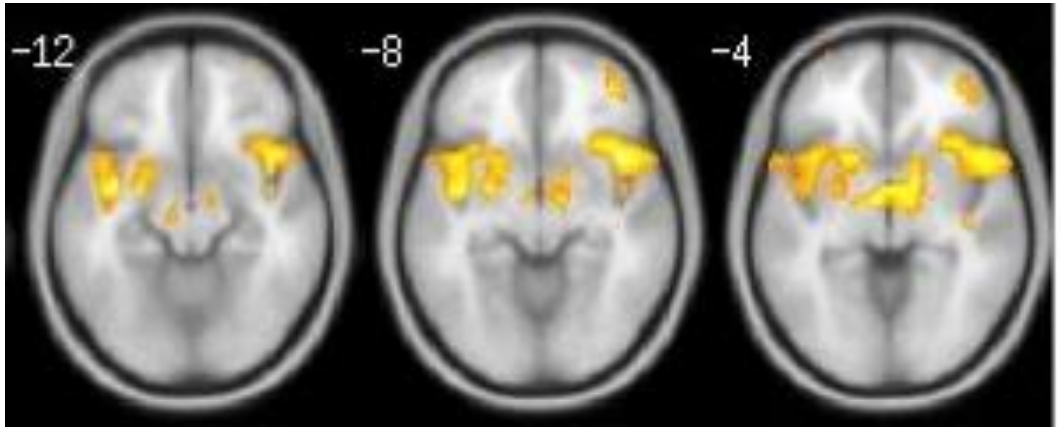
[a] Intensive Care and Department of Pediatric Surgery, Erasmus University Medical Center — Sophia Children's Hospital, PO Box 2040, 3000 CA Rotterdam, The Netherlands
[b] Pain Expertise Center, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands



Functional MRI

Brain activation during thermal pain stimuli in adults

Brain morphology



van den Bosch et al, European Journal of Pain 2013

Secondary objectives

- Neuropsychological development

Hypothesis

Children with a history of neonatal pain and opioid exposure

- altered pain thresholds
- altered brain activation during pain

Different results when opioids are given in the absence or presence of pain?

Study design

Prospective cohort study

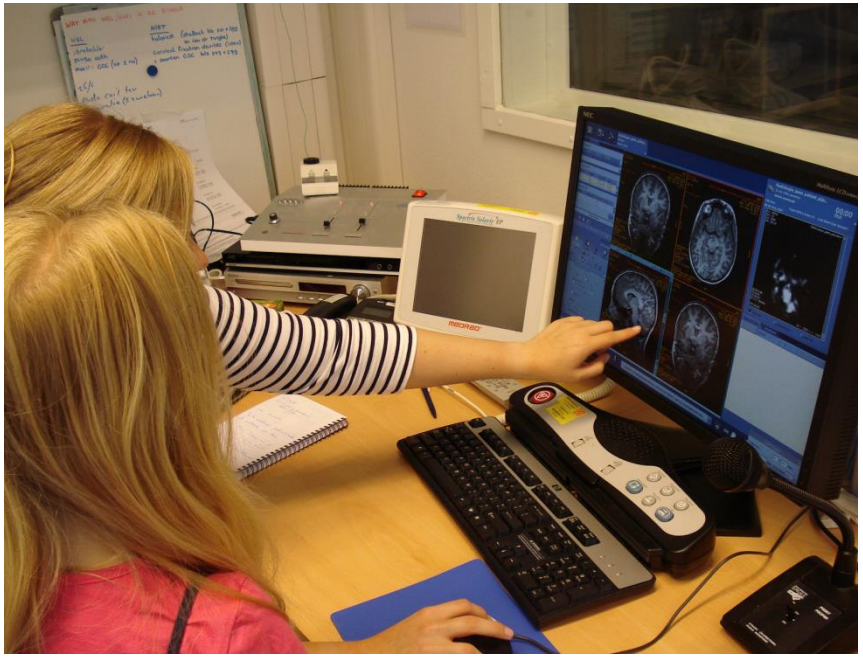
5 groups of children with different medical histories

- Age range 8 to 19 years
- Compared to healthy age- and gender matched controls

Inclusion rate

March 2011 – March 2013 (n=171)

- ECMO group 36
- Ventilated group 21
- NAS group 15
- Tierfell Naevus group 14
- Major surgery group 10
- Control group 75



Models

PAIN

Model 1a
Tierfell Naevus

Model 1b
Major surgery

Model 3
Preterm born

Model 2
ECMO

Healthy
controls

Model 4
NAS

Opioids

Preterm born children

9-10 years old

Correlations between gestational age, number of painful procedures, morphine exposure

and brain volumes

No effects on thermal sensitivity or cognitive functioning

Routine Morphine Infusion in Preterm Newborns Who Received Ventilatory Support

A Randomized Controlled Trial

Sinno H. P. Simons, MSc
Monique van Dijk, PhD
Richard A. van Lingen, MD, PhD
Daniella Roofthooft, MD
Hugo J Duivenvoorden, PhD
Niesje Jongeneel, RN
Carin Bunkers, RN
Enna Smink, RN
K. J. S. Anand, MBBS, DPhil
John N. van den Anker, MD, PhD
Dick Tibboel, MD, PhD

Context Newborns admitted to neonatal intensive care units (NICUs) undergo a variety of painful procedures and stressful events. Because the effect of continuous morphine infusion in preterm neonates has not been investigated systematically, there is confusion regarding whether morphine should be used routinely in this setting.

Objective To evaluate the effects of continuous intravenous morphine infusion on pain responses, incidence of intraventricular hemorrhage (IVH), and poor neurologic outcome (severe IVH, periventricular leukomalacia, or death).

Design, Setting, and Patients A randomized, double-blind, placebo-controlled trial conducted between December 2000 and October 2002 in 2 level III NICUs in the Netherlands of 150 newborns who had received ventilatory support (inclusion criteria: postnatal age younger than 3 days and ventilation for less than 8 hours; exclusion criteria: severe asphyxia, severe IVH, major congenital malformations, and administration of neuromuscular blockers).

Interventions Intravenous morphine (100 μg/kg and 10 μg/kg per hour) or placebo infusion was given for 7 days (or less because of clinical necessity in several cases).

Main Outcome Measures The analgesic effect of morphine, as assessed using validated scales; the effect of morphine on the incidence of IVH; and poor neurologic outcome.

Results The analgesic effect did not differ between the morphine and placebo groups, judging from the following median (interquartile range) pain scores: Premature Infant Pain Profile, 10.1 (8.2-11.6) vs 10.0 (8.2-12.0) (P=.94); Neonatal Infant Pain Scale, 4.8 (3.7-6.0) vs 4.8 (3.2-6.0) (P=.58); and visual analog scale, 2.8 (2.0-3.9) vs 2.6 (1.8-4.3) (P=.14), respectively. Routine morphine infusion decreased the incidence of IVH (23% vs 40%, P=.04) but did not influence poor neurologic outcome (10% vs 16%, P=.66). In addition, analyses were adjusted for the use of additional open-label morphine (27% of morphine group vs 40% of placebo group, P=.10).

Conclusions Lack of a measurable analgesic effect and absence of a beneficial effect on poor neurologic outcome do not support the routine use of morphine infusions as a standard of care in preterm newborns who have received ventilatory support. Follow-up is needed to evaluate the long-term effects of morphine infusions on the neurobehavioral outcomes of prematurity.

JAMA. 2003;290:2419-2427 www.jama.com

MORPHINE HAS BEEN ONE OF the most frequently used drugs to relieve pain in many age groups. Nevertheless, debate continues about whether morphine and analgesic therapy should serve as standard of care for preterm newborns who have received ventilatory support,[1] despite the recognition that all preterm neonates feel pain.

Lack of a gold standard to assess neonatal pain, fear of adverse effects, and uncertainty about the long-term effects of opioids in the neurodevelopmental outcome of newborns contribute to this clinical conundrum. Although numerous neonatal pain instruments are available, they have been based and validated on models of acute pain.[2] It is difficult, therefore, to measure the analgesic effect of morphine in neonates. Suggested adverse effects of morphine are hypotension,[3-6] sei-

Author Affiliations: Departments of Pediatric Surgery (Drs van Dijk and Tibboel and Mr Simons) and Pediatrics (Dr van den Anker), and Division of Neonatology (Dr Roofthooft, Mr Simons, and Ms Jongeneel), Erasmus MC-Sophia, and Department of Medical Psychology, Erasmus-MC (Dr Duivenvoorden), Rotterdam, the Netherlands; Department of Pediatrics, Division of Neonatology, Isala Clinics, Zwolle, the Netherlands (Dr van Lingen and Mss Bunkers and Smink); Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock (Dr Anand); and Division of Pediatric Clinical Pharmacology, Departments of Pediatrics and Pharmacology, George Washington University, Washington, DC (Dr van den Anker).
Corresponding Author and Reprints: Dick Tibboel, MD, PhD, Department of Pediatric Surgery/Pediatrics, Erasmus MC-Sophia, Dr Molewaterplein 60, 3015 GJ Rotterdam, the Netherlands (e-mail: j.illsley@erasmusmc.nl).

Long-term effects of routine morphine infusion in mechanically ventilated neonates on children's functioning: Five-year follow-up of a randomized controlled trial

Joke de Graaf [a], Richard A. van Lingen [b], Sinno H.P. Simons [c], Kanwaljeet J.S. Anand [d], Hugo J. Duivenvoorden [e], Nynke Weisglas-Kuperus [f], Daniella W.E. Roofthooft [f], Liesbeth J.M. Groot Jebbink [b], Ravian R. Veenstra [g], Dick Tibboel [a], Monique van Dijk [a,*]

[a] *Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*
[b] *Princess Amalia Department of Pediatrics, Department of Neonatology, Isala Clinics, Zwolle, The Netherlands*
[c] *Department of Pediatrics, VUMC, Amsterdam, The Netherlands*
[d] *Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA*
[e] *Departments of Medical Psychology and Psychotherapy, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*
[f] *Department of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*
[g] *Department of Medical Psychology, Isala Clinics, Zwolle, The Netherlands*

Conclusion:

The finding of a significant effect of morphine on the "visual analysis "IQ subtest calls for follow-up at a larger age focusing on the higher-order neurocognitive functions.

Pain 152(2011)1391-1397

PAIN® xxx (2013) xxx–xxx

PAIN®

www.elsevier.com/locate/pain

Does neonatal morphine use affect neuropsychological outcomes at 8 to 9 years of age?

Joke de Graaf [a], Richard A. van Lingen [b], Abraham J. Valkenburg [a], Nynke Weisglas-Kuperus [c], Liesbeth Groot Jebbink [b], Barbara Wijnberg-Williams [d], Kanwaljeet J.S. Anand [e], Dick Tibboel [a], Monique van Dijk [a,c,*]

[a] *Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*
[b] *Princess Amalia Department of Pediatrics, Department of Neonatology, Isala Clinics, Zwolle, The Netherlands*
[c] *Department of Pediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*
[d] *Department of Medical Psychology, Isala Clinics, Zwolle, The Netherlands*
[e] *Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA*

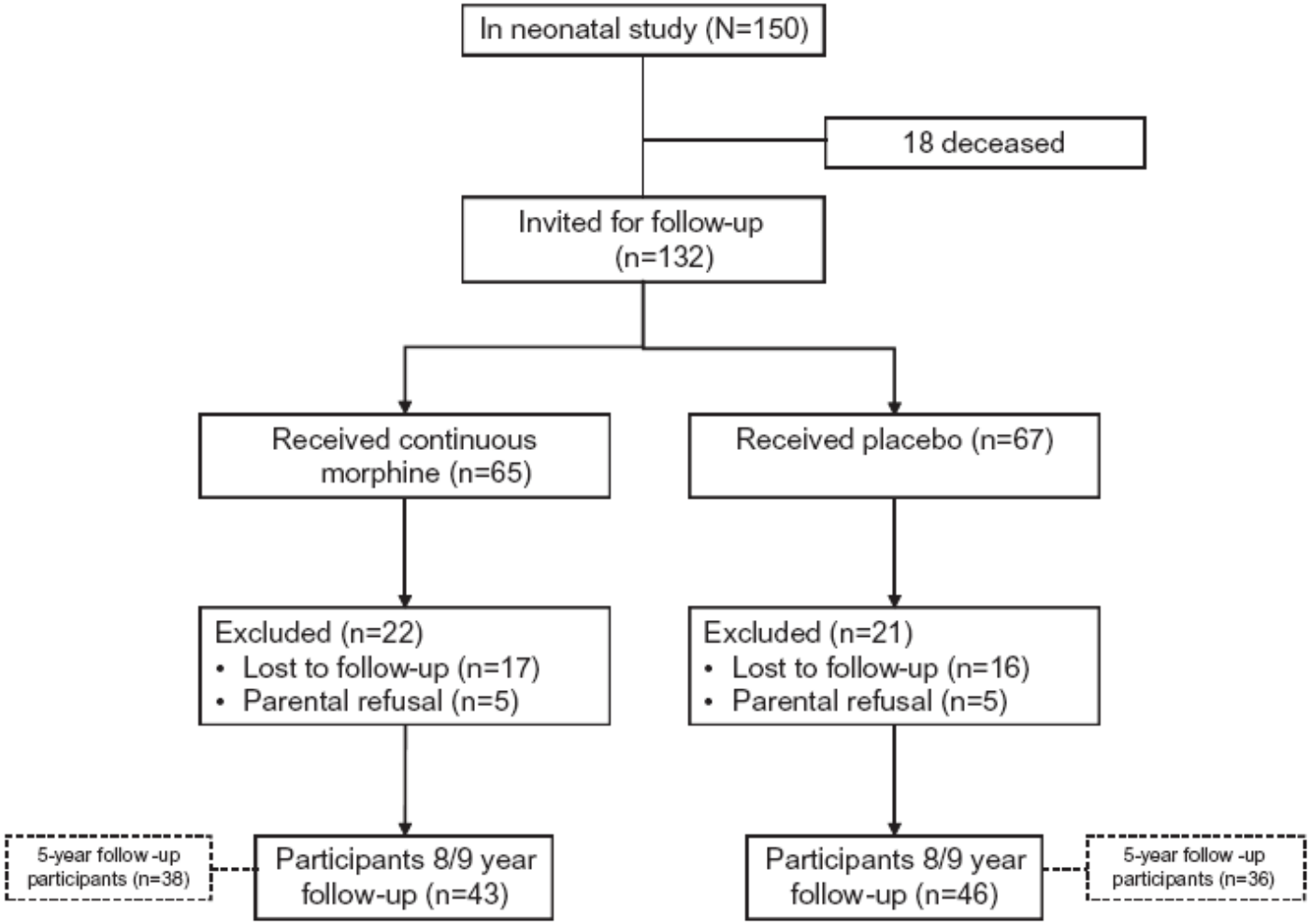


Fig. 1. Flowchart of participation.

Table 3
Neuropsychological assessments.

		Morphine cohort	Placebo cohort	*P*
Wechsler Intelligence Scale for Children III				
Intelligence score		[n = 38]	[n = 41]	
	Mean (SD)	99 (19)	101 (18)	.63
Beery-Buktenica Developmental Test of Visual Motor Integration				
		[n = 38]	[n = 41]	
	Mean (SD)	95 (12)	98 (12)	.18
Cambridge Neuropsychological Test Automated Battery				
Reaction time (ms)		[n = 34]	[n = 38]	
RTI-1	Median (IQR)	357 (302 to 458)	345 (291 to 401)	.32
RTI-5	Median (IQR)	406 (340 to 470)	396 (321 to 465)	.60
Spatial Span (SSP)		[n = 36]	[n = 40]	
SSP-forward	Median (IQR)	5 (4 to 5)	5 (4 to 5)	.60
		[n = 35]	[n = 40]	
SSP-backward	Median (IQR)	4 (4 to 5)	4 (4 to 5)	.36
Rapid Visual Information Processing (RVP)		[n = 37]	[n = 41]	
RVP-A	Median (IQR)	.95 (.92 to .96)	.93 (.90 to .97)	.77
Stockings of Cambridge				
Problems solved in minimum moves	Median (SD)	[n = 36] 7 (6 to 8)	[n = 40] 7 (5 to 8)	.74
Intra/extra dimensional set Shift		[n = 35]	[n = 40]	
Stages completed	Median (IQR)	9 (9 to 9)	9 (8 to 9)	.63
Total trials (adjusted)	Median (IQR)	86 (77 to 122)	96 (84 to 127)	.35
Stop Signal test		[n = 32]	[n = 38]	
Stop Signal Delay (SSD)	Median (IQR)	428 (320 to 498)	380 (290 to 467)	.40
Stop-Signal Reaction Time (SSRT)	Median (IQR)	246 (199 to 313)	226 (188 to 287)	.31

IQR, interquartile range.

PAIN® xxx (2013) xxx–xxx

PAIN®

www.elsevier.com/locate/pain

Does neonatal morphine use affect neuropsychological outcomes at 8 to 9 years of age?

Joke de Graaf [a], Richard A. van Lingen [b], Abraham J. Valkenburg [a], Nynke Weisglas-Kuperus [c], Liesbeth Groot Jebbink [b], Barbara Wijnberg-Williams [d], Kanwaljeet J.S. Anand [e], Dick Tibboel [a], Monique van Dijk [a,c,*]

[a] Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands
[b] Princess Amalia Department of Pediatrics, Department of Neonatology, Isala Clinics, Zwolle, The Netherlands
[c] Department of Pediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands
[d] Department of Medical Psychology, Isala Clinics, Zwolle, The Netherlands
[e] Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA

Morphine-treated children showed significantly fewer problems with executive functions in daily life as rated by parents for the subscales inhibition and organization of materials and for planning/organizing as rated by the teachers.

Overall, the present study demonstrates that continuous morphine infusion of 10 microgram/kg/h during the neonatal period does not harm general functioning and may even have a positive influence on executive functions at 8 to 9 years

Conclusion

No differences in

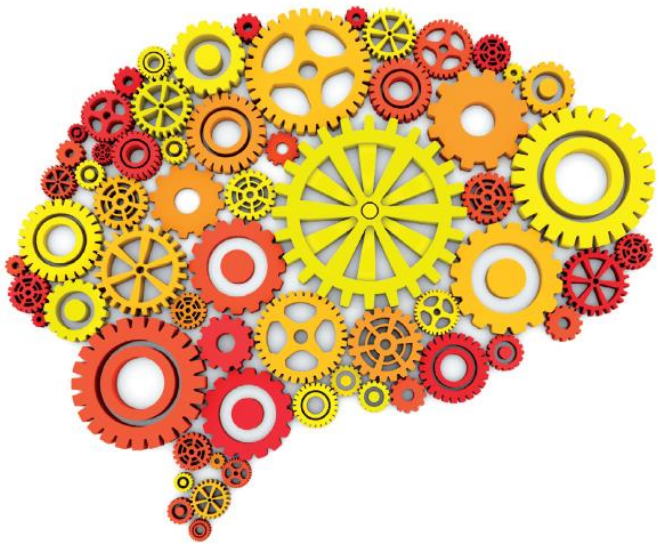
- Detection- or pain thresholds
- NRS pain scores

Minor differences in

- Brain morphology
- Brain activation during pain (parietal lobe)

The dramatic differences expected from animal studies appear not to occur

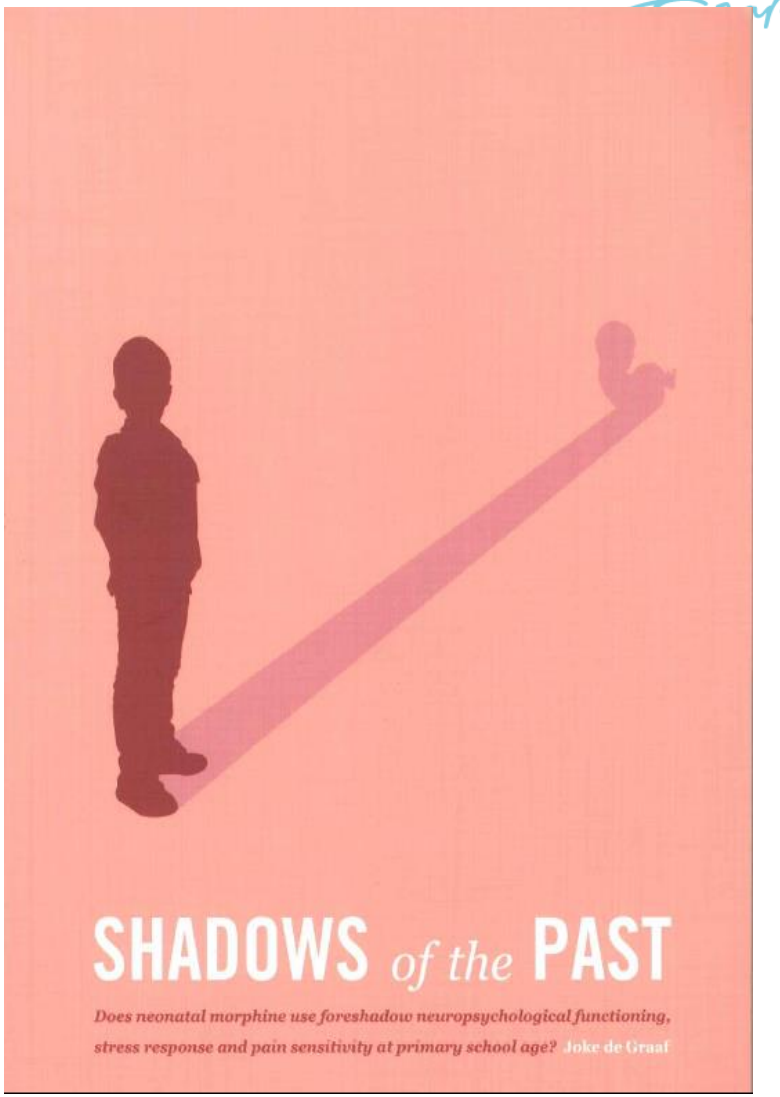
Erasmus MC



Projections of Pain

Neonatal pain in children, what remains in the brain after the wheels of time

Gerbrich E. van den Bosch



The next steps

- Implementation of the new analgesic algorithm and evaluation of its efficacy and compliance

- International survey of post cardiac analgesic regimen in the pediatric age group around the world

- RCT of iv paracetamol versus iv morphine in post cardiac patients in the 4 pediatric centers in the Netherlands

- RCT of wound catheter versus iv placebo in non-cardiac major surgery in newborns and infants < 1 year of age

Implementation

Paracetamol has replaced morphine as the drug of first choice for postoperative pain in young infants and newborns

Proof of principle in daily clinical practice (n=77)

This regimen is included in the official guideline of the Dutch Association of Anaesthesiology for postoperative pain(2014)

In humans no negative effect is shown of neonatal pain and /or the use of opioids

Future studies

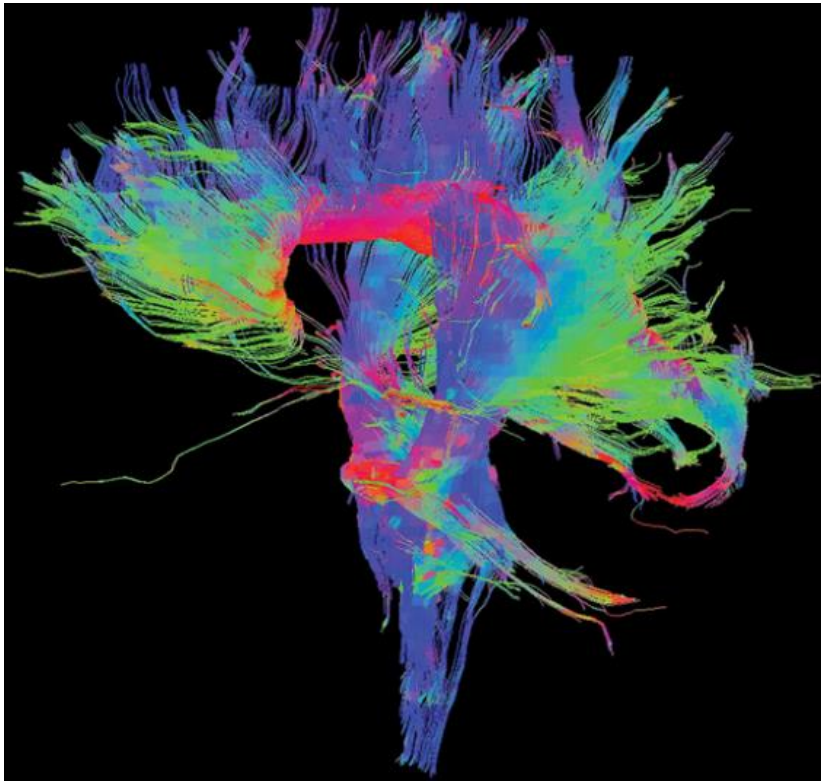
- Missing models

- Closing the gap between animal and human studies

Future studies

- Relation between genetic variations and pain sensitivity

- Resting state MRI, DTI



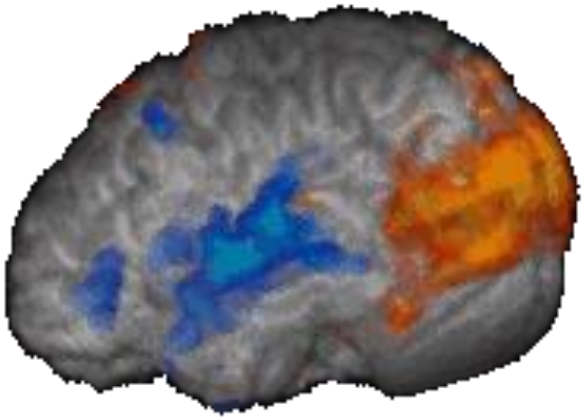
Acknowledgements

- Principal Investigators
- Catherijne Knibbe Elke Krekels; Leiden
- Sinno Simons, John van den Anker; Rotterdam
- Richard van Lingen; Zwolle
- Karel Allegaert; Leuven
- Ron Mathot; Amsterdam

Promovendi:

- Gerbrich van der Bosch;Joke de Graaf;
- Daniela Roofthooft;Ilse Ceelie en Maja Matic

Thank you for your attention

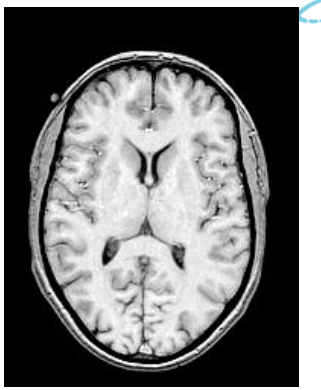


Dr. M. van Dijk Prof. Dr. D. Tibboel Dr. T.J.H. White

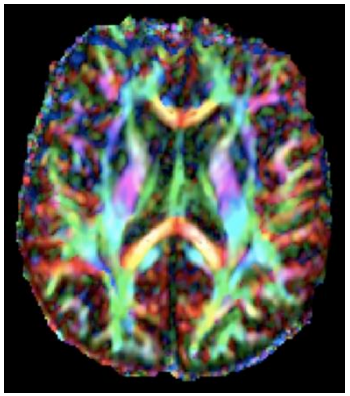
This study was supported by ZonMw Priority Medicines for Children grant 40-41500-98.9020 and the Stichting Erasmus Fonds Pijnbestrijding

MRI scans

- Structural scan (T1)

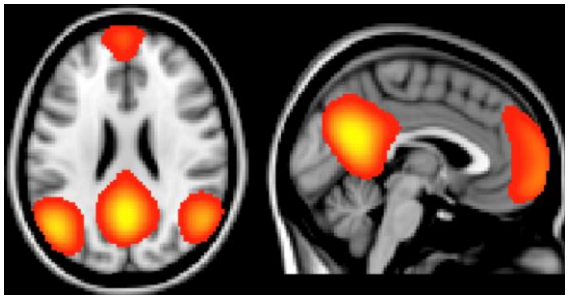


- DTI



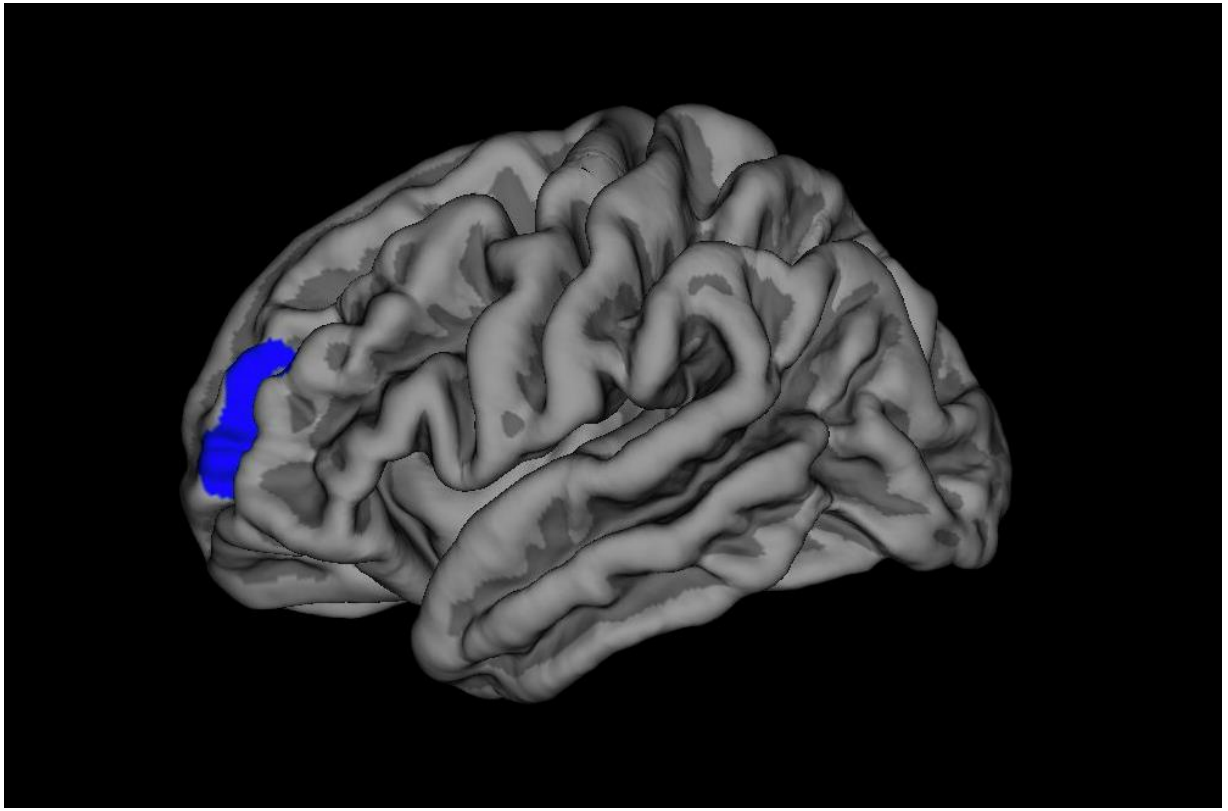
- fMRI Resting state

- 2 fMRI runs (with the TSA)



Structural MRI

Only a significantly thicker left middle-frontal cortex



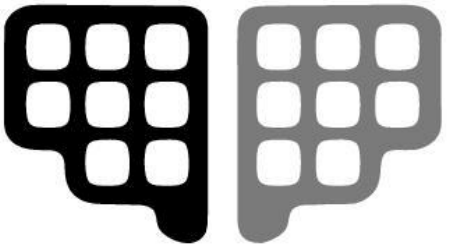
Conclusion

- Specific neuropsychological effects that warrant further investigation

- No major clinical relevant effects of pain, analgesia or sedation

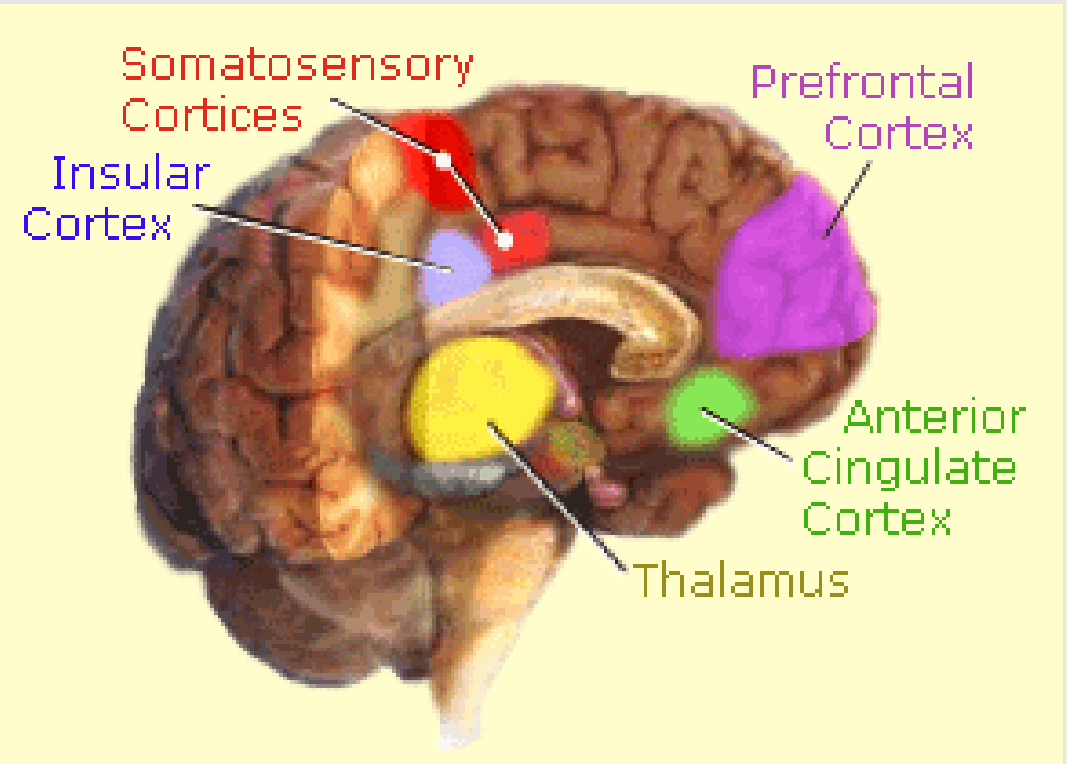
Conclusion

Poorer outcome specific memory task



Working Memory Training

Pain



Apkarian et al, European Journal of Pain 2005


Infinity C700
Geschikt voor
NO gebruik.
IC-Kinderen 22
Flow
2.1
Speed
6500
Pressure
Temp
iLA active
novalung

Pharmacotherapy and ECMO

Erasmus MC

Figure 1. Correlation between log P and the increase in volume of distribution (ΔV) for the drugs from table 2, with a parabolic nonlinear curve fit.

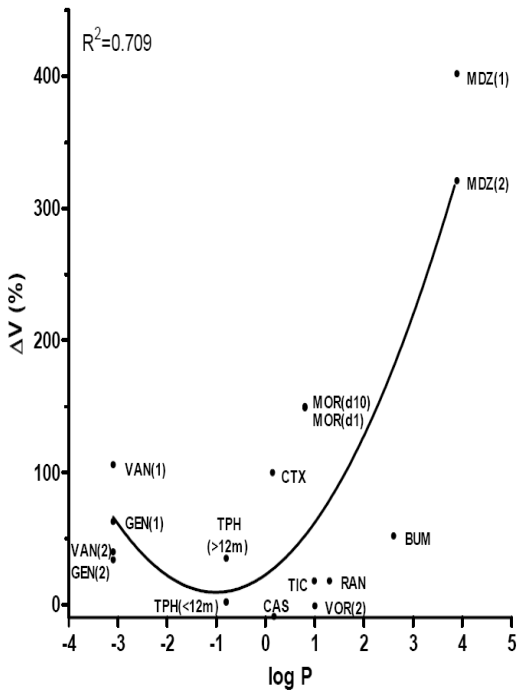
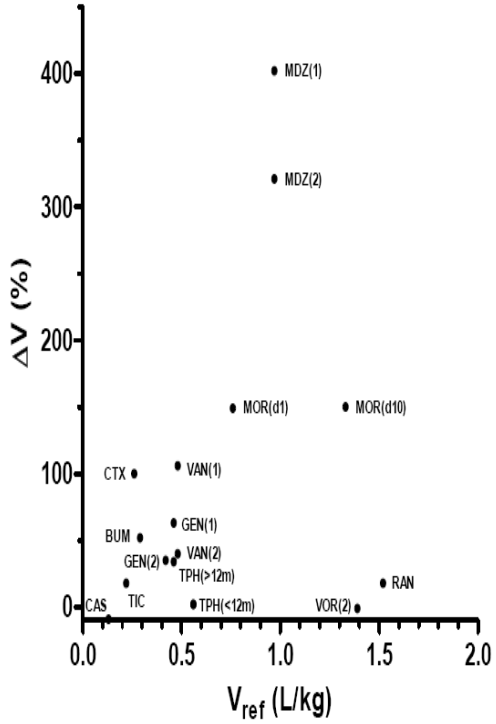


Figure 2. Increase in volume of distribution (ΔV) during ECMO vs. the median value in non-ECMO patients.



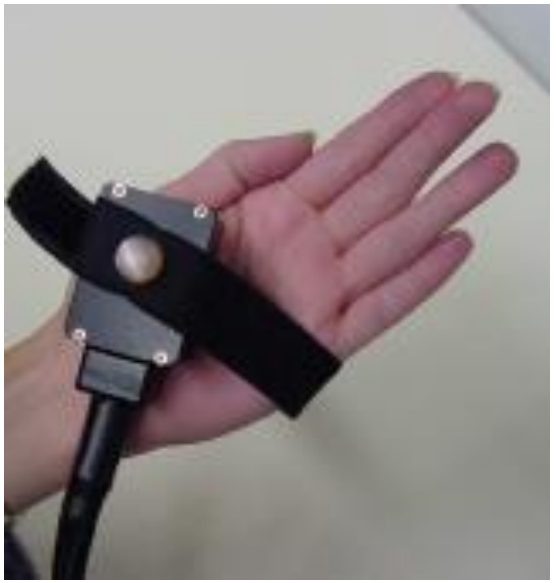
Pediatr Clin N Am 59 (2012) 1183–1204

The Impact of Extracorporeal Life Support and Hypothermia on Drug Disposition in Critically Ill Infants and Children

Enno D. Wildschut, MD, PhD[a,*], Annewil van Saet, MD, PhD[a,b], Pavla Pokorna, MD[a,c], Maurice J. Ahsman, PharmD, PhD[d], John N. Van den Anker, MD, PhD[a,e,f,g], Dick Tibboel, MD, PhD[a]

TSA

- fMRI study with thermal pain stimuli
- Thermal Sensory Analyzer (TSA)



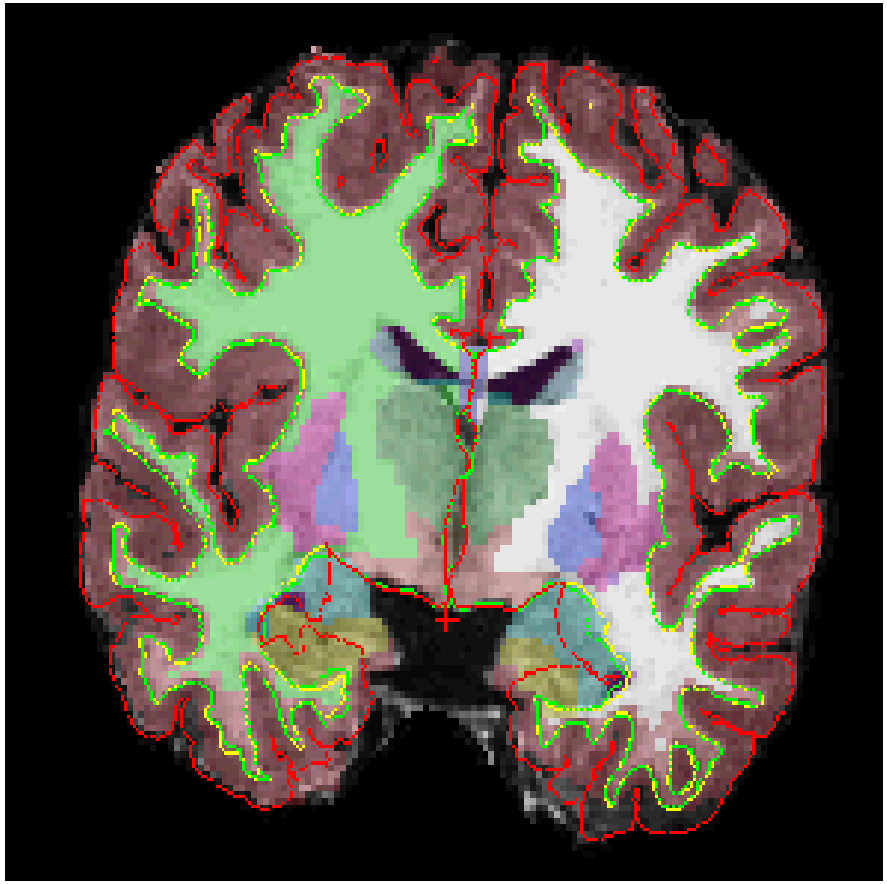
Primary objectives

- Detection and pain thresholds

Primary objectives

- Brain activation during pain

Structural MRI

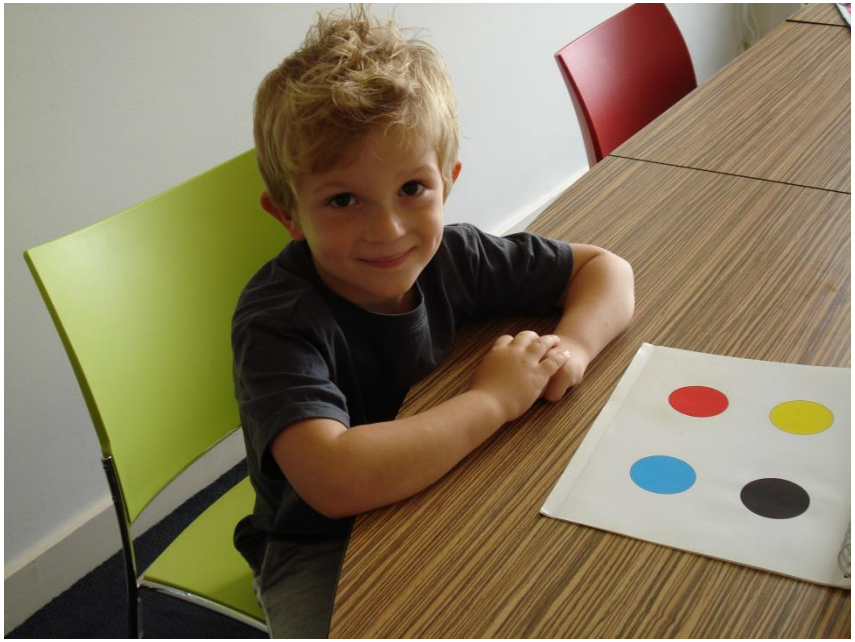


Limitations

- Relatively small sample size and selection bias
- High risk for confounding
- Missing models

NEPSY

Significantly worse performance on a narrative memory task



van den Bosch et al, PCCM 2015

Control group

- Matched on gender and age

- No history of neonatal pain or Intensive Care admission

Primary objectives

Does neonatal pain and the use of morphine alter detection and pain threshold?

Does neonatal pain and the us of morphine influence the activation of the brain during thermail pain stimuli at the age of 8-18 years old?

Secondary objectives

- **Are there any other differences in brain structures?**

Does neonatal pain and treatment influence a child's neuropsychological development?

- **Are there any other differences in brain structures?**

- **Does neonatal pain and treatment influence a child's neuropsychological development?**

- **Does neonatal pain and the use of morphine influence stress reactivity at later age?**

Long-term effects of routine morphine infusion in mechanically ventilated neonates on children's functioning: Five-year follow-up of a randomized controlled trial

Joke de Graaf [a], Richard A. van Lingen [b], Sinno H.P. Simons [c], Kanwaljeet J.S. Anand [d], Hugo J. Duivenvoorden [e], Nynke Weisglas-Kuperus [f], Daniella W.E. Roofthooft [f], Liesbeth J.M. Groot Jebbink [b], Ravian R. Veenstra [g], Dick Tibboel [a], Monique van Dijk [a,*]

[a] *Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*
[b] *Princess Amalia Department of Pediatrics, Department of Neonatology, Isala Clinics, Zwolle, The Netherlands*
[c] *Department of Pediatrics, VUMC, Amsterdam, The Netherlands*
[d] *Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA*
[e] *Departments of Medical Psychology and Psychotherapy, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*
[f] *Department of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*
[g] *Department of Medical Psychology, Isala Clinics, Zwolle, The Netherlands*

We conducted a follow-up study among 5-year-olds who, as mechanically ventilated neonates, had participated in a placebo-controlled trial on effect on morphine administration on pain and neurologic outcome. They were now tested in intelligence, visual motor integration, behavior, chronic pain, and health-related quality of life.

Pain 152(2011)1391-1397