SEDATION FOR SMALL PROCEDURES

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Universitair Medisch Centrum Rotterdam

SEDATION in newborns

- How and when
- How to evaluate
- How to dose

Health

CHILDREN'S HEALTH

Pain in babies may cause later harm

Photodisc file

Study in newborn rats suggests early trauma rewires nervous system

Debate has been raging in the medical community over how newborns experience pain and the impact later on.

REUTERS

July 27 — Newborns who have painful, but often life-saving, medical procedures in the early weeks of life may have a lower pain threshold in later years, according to a new animal study released Thursday.

Long term effects of pain

Taddio *et al.* Lancet 1995

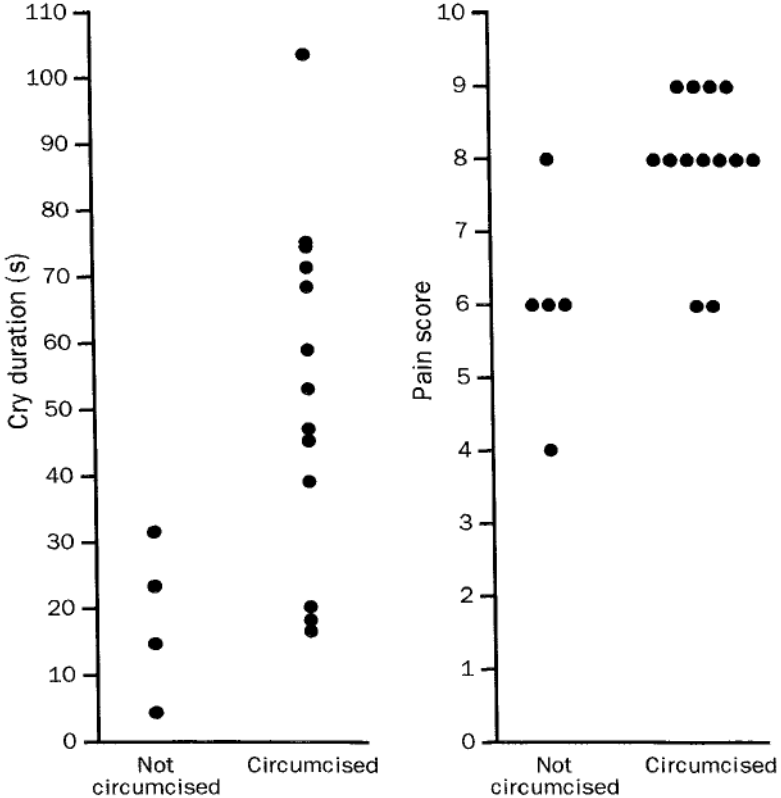


Figure: **Pain response during HIB injection in circumcised and uncircumcised boys**

Why use sedation:

Pain or distress?

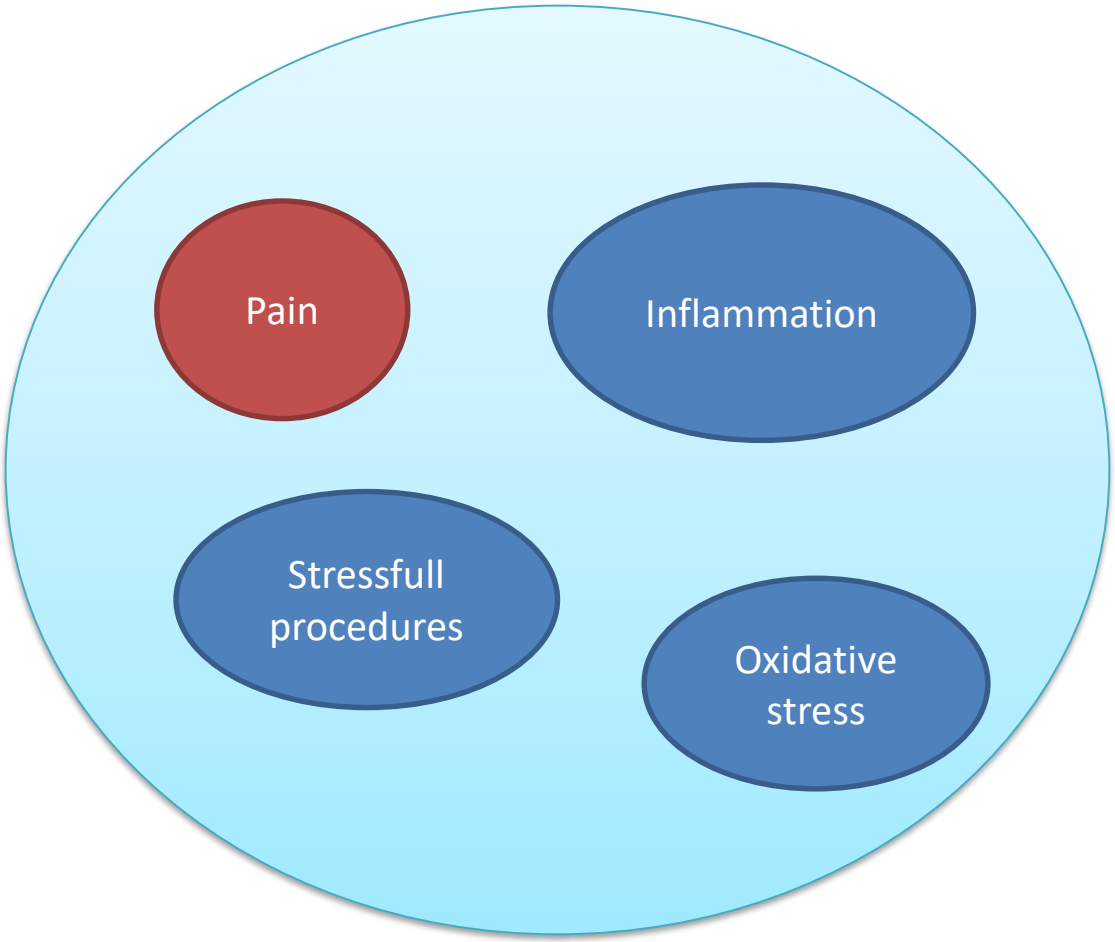
Both need to be prevented and treated

Discussion about short and long term effects of pain and distress is more important

Stress

Analgesia

Sedation



What do we know?

1987 2005 2018 2023

Neonatal distress / pain:

Decrease in white and grey matter Brummelte, 2012
Epigenetic changes (SLC6A4) Provenzi, 2015

Worse cognitive and motor development Grunau, 2009

Less visual/perceptive skills Doesburg, 2013
Thinner cortex and decrease in cerebellar volume Ranger, 2013 & 2015
Changed reaction to stress Grunau, 2013
More internalising behavior Ranger, 2014

Neonatal pain/distress experience does have negative long term effects

But what about the negative effects of sedative and analgesic drugs?

How to use sedation?

Examples:

- Intubation
- INtubation SUrfactant Extubation (INSURE)
- Mininally Invasive Surfactant Therapy (MIST)

Premedication for Endotracheal Intubation in (premature) Neonates

POLAND:
no consensus about medication

Survey all 30 tertiary NICUs

10% always use premedication,

40% use premedication before intubation only sometimes, in case of technical difficulties of active term newborns.

15,5% never use any sedation or analgesia before intubation.

Used drugs:
- midazolam (11 units, 35%),
- analgesics (10 units, 33,3%) (morphine, fentanyl, or pethidine)
- phenobarbitone (4 units, 13,3%),
- muslce relaxants (6,6%)

Premedication for endotracheal intubation in NICU in Poland.
E. Adamska, Pediatria polska 82(12):935-940 · January 2007

Endotracheal intubation: evidence

Neonatal elective intubation more successful if pre-treated

Evidence for morphine, atropine and suxamethonium vs placebo
(Oei et al 2002)

Untreated intubation probably harmful for the newborn infant

Premedication prevents acute physiological changes
(VanLooy et al 2008)
Endotracheal intubation seriously painful intervention
(Simons et al 2003)

No consensus about treatment regimen

Wide variability in treatment protocols among centres
(Kumar et al 2008 / Simon et al 2004)

Use of premedication increases; no consensus about medication

Country	Year	Routine medication	Protocol	Reference
UK	1998	37%	14 %	Whyte et al. 2000, Arch Dis Child Fetal Neonatal Ed.
UK	1999	34 %	?	Hancock et al. 2000, Arch Dis Child Fetal Neonatal Ed.
Australia	1999	67 %	?	Hanock et al. 2000, Arch Dis Child Fetal Neonatal Ed.
France	2004	37 %	?	Simon et al. 2004, Crit Care Med.
Ireland	2005		15%	O'Gorman et al. 2005, Ir Med J
Italy	2005	13 %	?	Lago et al. 2005, Paediatr Anesth
USA	2006	44 %	24 %	Sarkar et al. 2005, J of Perinatology
France	2007	74 %	60 %	Walter-Nicolet et al. 2007, Archives de Pediatrie
UK	2007	90 %	76 %	Chaudary et al. 2009, Pediatric Anesth
UK	2007	93 %	82 %	Kelleher et al. 2009, Arch Dis Child Fetal Neonatal Ed.

What do we need?

Adequate ways to measure the level of sedation

Adequate drugs and dosages

How to evaluate sedation

Intubation Readiness Score

Score	Motor reaction to stimulus
1	Spontaneous movement
2	Movement in reaction to slight touch
3	Movement in reaction to firm stimulus
4	No movement

How to evaluate sedation

	0	1	2
FACIAL EXPRESSION	Peaceful	Distressed expression May grimace slightly	Distressed expression, may cry Chin drop
BREATHING PATTERN	Calm effortless breathing	Slightly strained breathing Breathing pauses	Strained breathing Fast breathing Apneas
TONE OF EXTREMITIES	Normal tone	Varied tone	Tense or flacid
HAND/FOOT ACTIVITY	Relaxed	Slightly clenched May try to grasp Hand on face	Tightly clenched Fingers/toes spread Flaccid
LEVEL OF ACTIVITY	Calmly awake Calmly asleep	Occasional motor restlessness	Persistent motor restlessness Exhausted

Kleberg Agneta, Astrid Lindgren Children's Hospital, Stockholm, Sweden
Larsson Björn A, Astrid Lindgren Children's Hospital, Stockholm, Sweden
Lundqvist Pia, Department of Health Sciences, Lund University, Sweden

Adequate drugs?

Opioids

Morphine
Fentanyl
Remifentanil
Sufentanil

Muscle relaxants / neuromuscular blockers

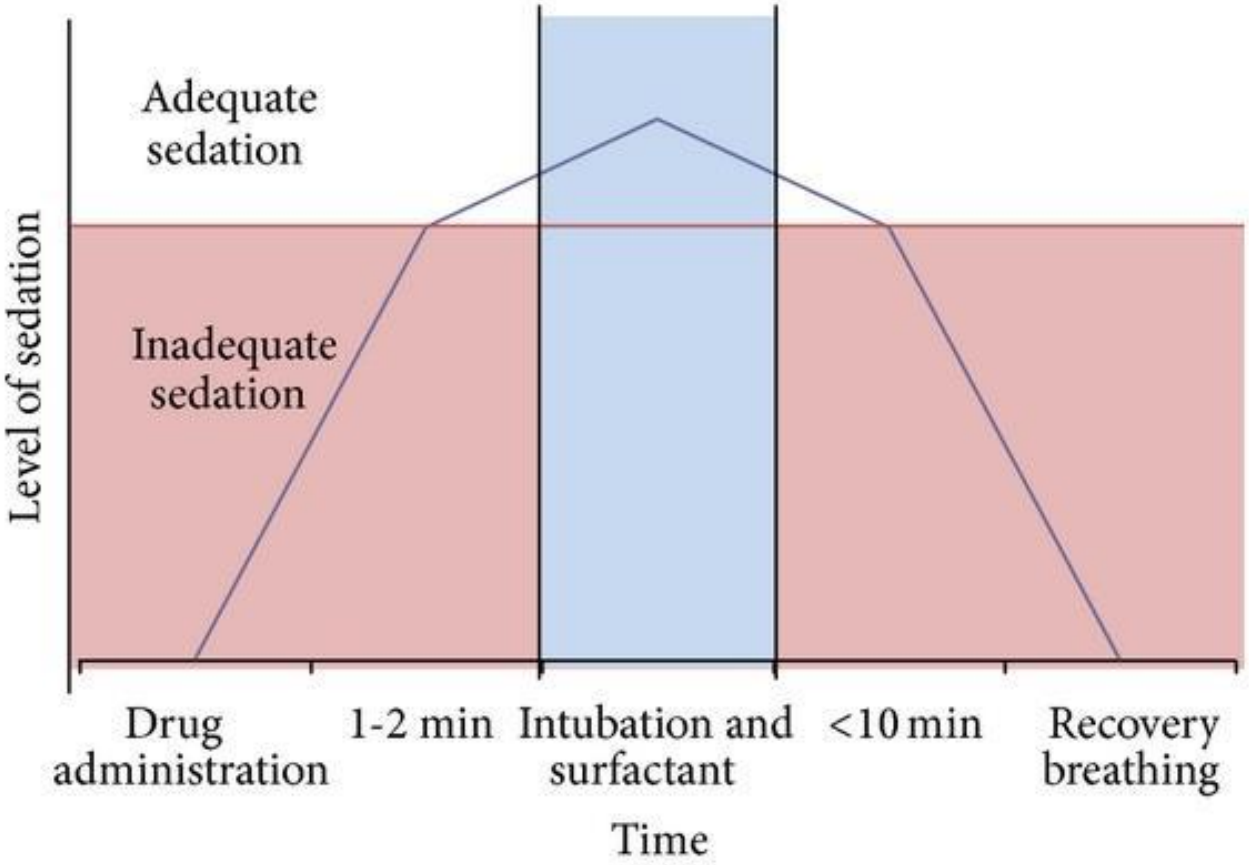
Rocuronium
(Cis)atracurium
Succinylcholine

+/- Atropine

Hypnotic / sedative drugs

Propofol
Ketamine
Midazolam
Clonidine
Phenobarbital
Thiopental

INSURE


Adequate sedation
Inadequate sedation
Level of sedation
Drug administration
1-2 min
Intubation and surfactant
<10 min
Recovery breathing
Time

Adequate drugs?

Short onset of action: (semi) urgent intubation

Fast recovery: INSURE to enable extubation

Persistent breathing of newborn : MIST

... without any negative effects on the developing newborn!

Traditional drugs

Opioid + muscle relaxant (+ atropine)

Morphine + vecuronium

- 'Gold-standard' therapy
- Extensive experience
- Unwarranted Pk/Pd properties (relatively long T_{max} and $T_{1/2}$)

Fentanyl + rocuronium / succinylcholine

- Sedation?
- Preferable Pk/Pd properties (relatively long Tmax and T1/2)

Midazolam

Benzodiazepine

Short acting

Sleep inducing

Easy to use (even nasal route directly after birth)

On-label for sedation in the NICU

No loading dose

Maintenance dose: <32 weeks: 0.03 mg/kg/hr

>32 weeks: 0.06 mg/kg/hr

Disadvantages

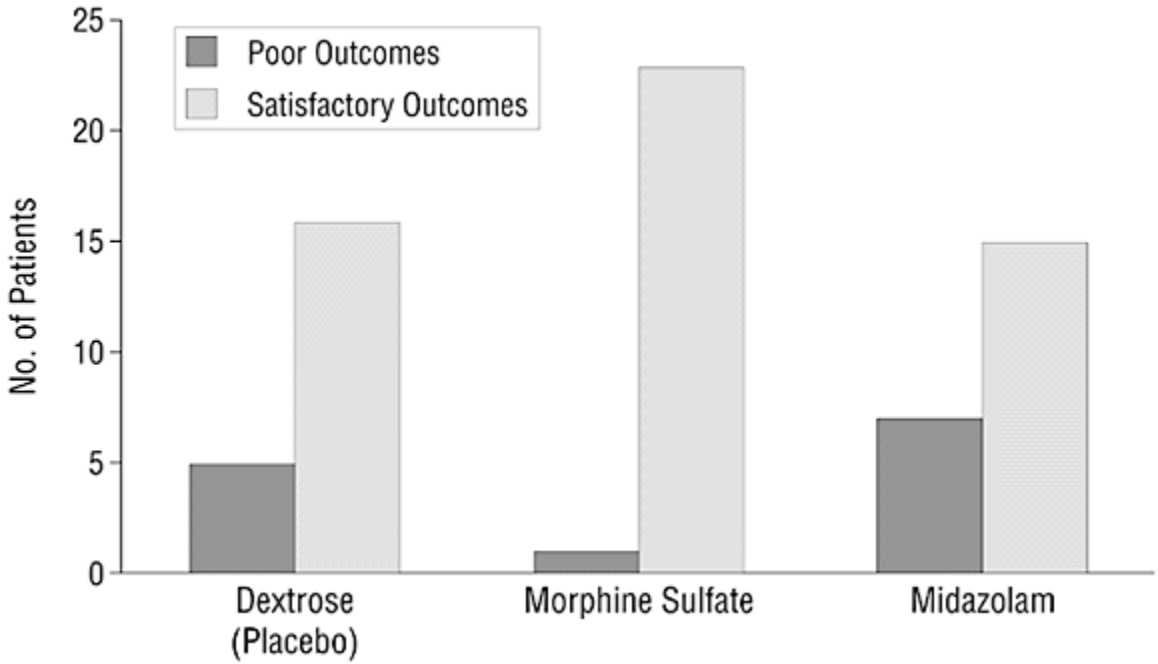
?

Midazolam

Disadvantages

Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates.

Anand KJ[1], Barton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, Vasa R.

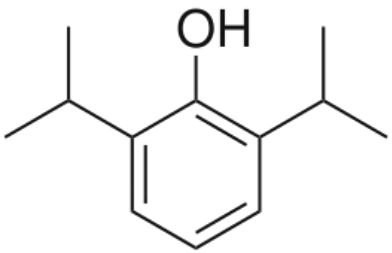


Propofol

Relatively new drug in neonatal care

Lipid soluable sedative / hypnotic agent

Extensively used in older children and adults



Advantages

Easy to use

Rapidly acting

Disadvantages

Lack of extensive knowledge in preterm newborns

Safety unknown (propofol infusion syndrome?)

Probable hypotensive side effect

No analgesic effect

Propofol

Propofol Compared With the Morphine, Atropine, and Suxamethonium Regimen as Induction Agents for Neonatal Endotracheal Intubation: A Randomized, Controlled Trial

Satish Ghanta, MBBS, MD[a], Mohamed E. Abdel-Latif, MBBS, MRCPCH, MPH, MScEpi[a,b], Kei Lui, MBBS, FRACP, MD[a,b], Hari Ravindranathan, MBBS, MD[a], John Awad, MBBS, FANZCA, FJFICM[c], Julee Oei, MBBS, FRACP[a,b]

Pediatrics 2007

RCT : N = 33 vs N = 30

Conclusion:
Propofol is more effective, more rapid in action and easier to use compared to morphine, atropine and suxamethonium.

INSURE

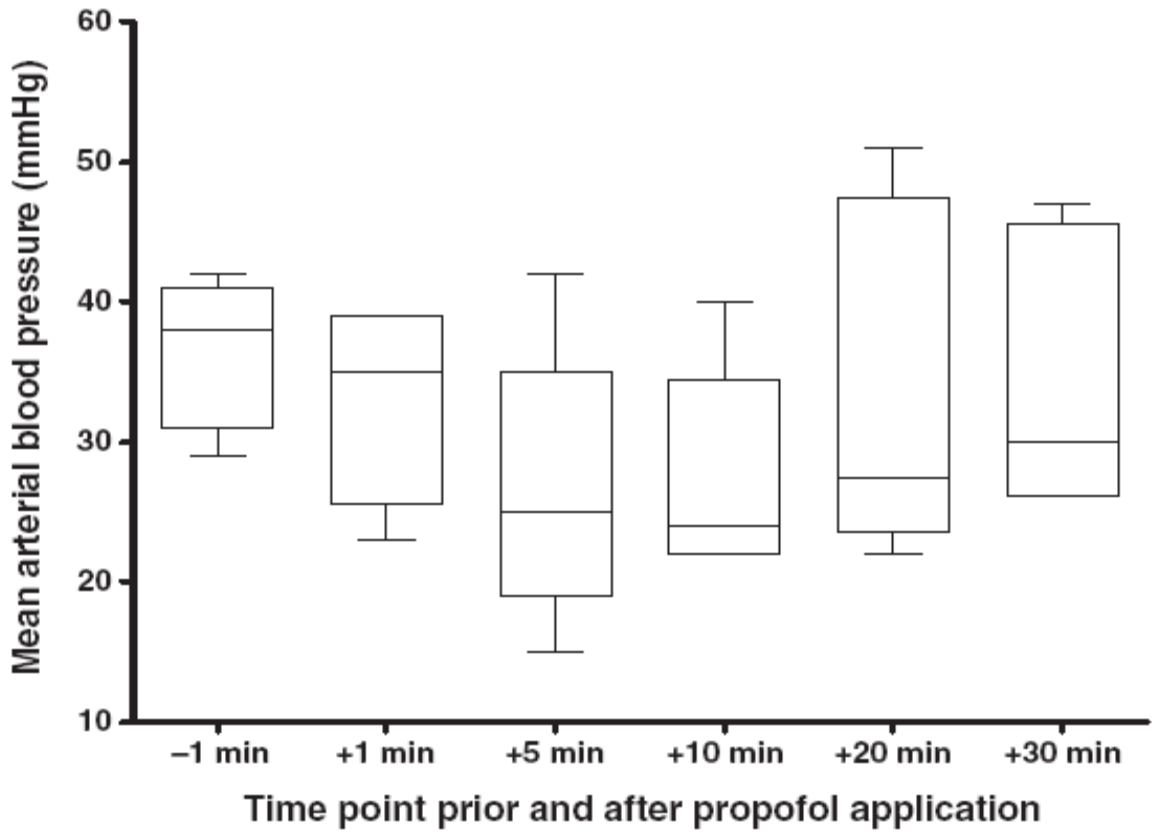
Pediatric Anesthesia

Pediatric Anesthesia 2010 **20**: 605–611 doi:10.1111/j.1460-9592.2010.03330.x

Propofol as an induction agent for endotracheal intubation can cause significant arterial hypotension in preterm neonates

LARS WELZING

Neonates received
1 mg/kg propofol before intubation for INSURE procedure



Propofol

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

Clinical evaluation of propofol as sedative for endotracheal intubation in neonates

SHP Simons (s.simons@erasmusmc.nl)[1], R van der Lee[2], Irwin KM Reiss[1], MM van Weissenbruch[3]

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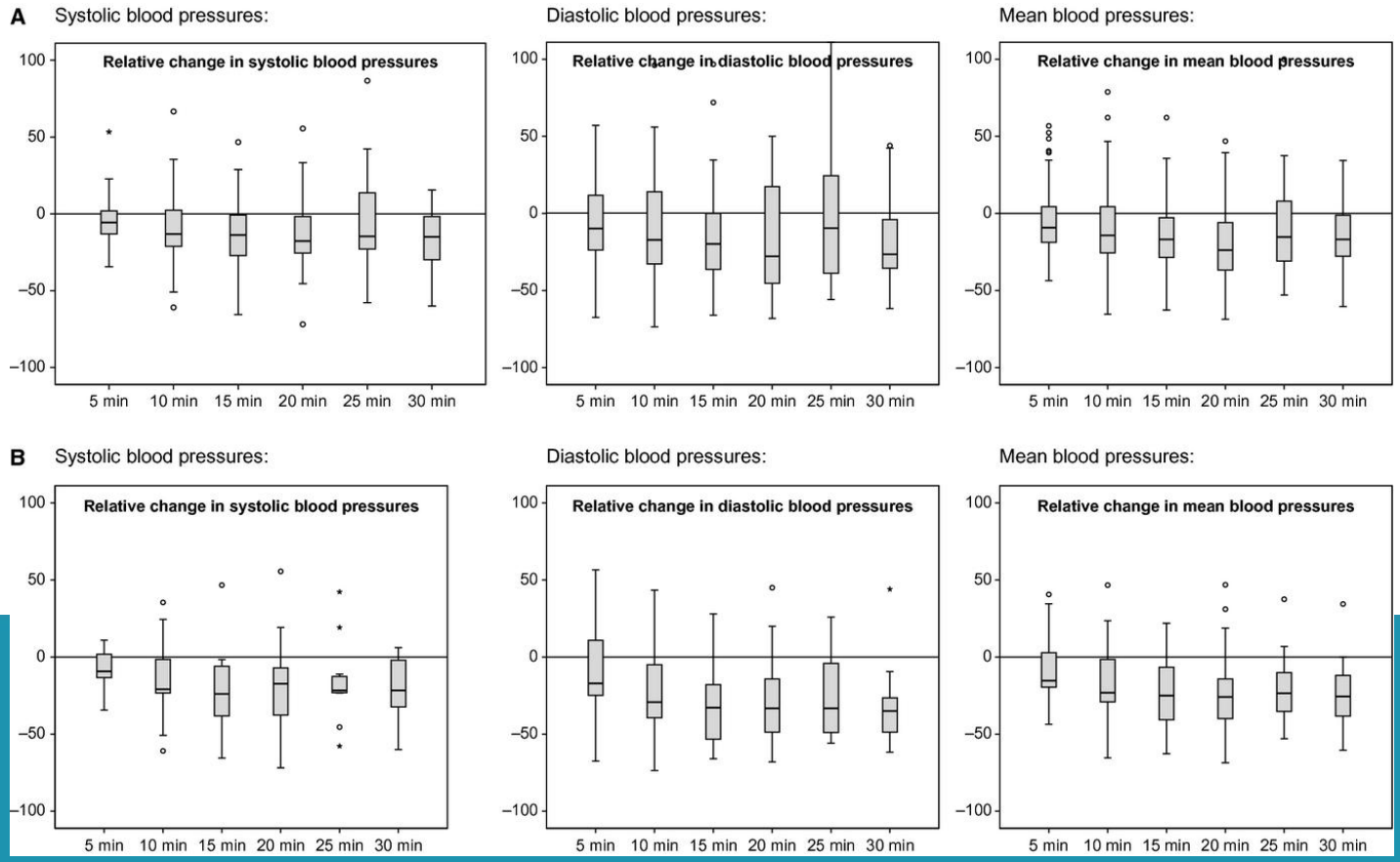
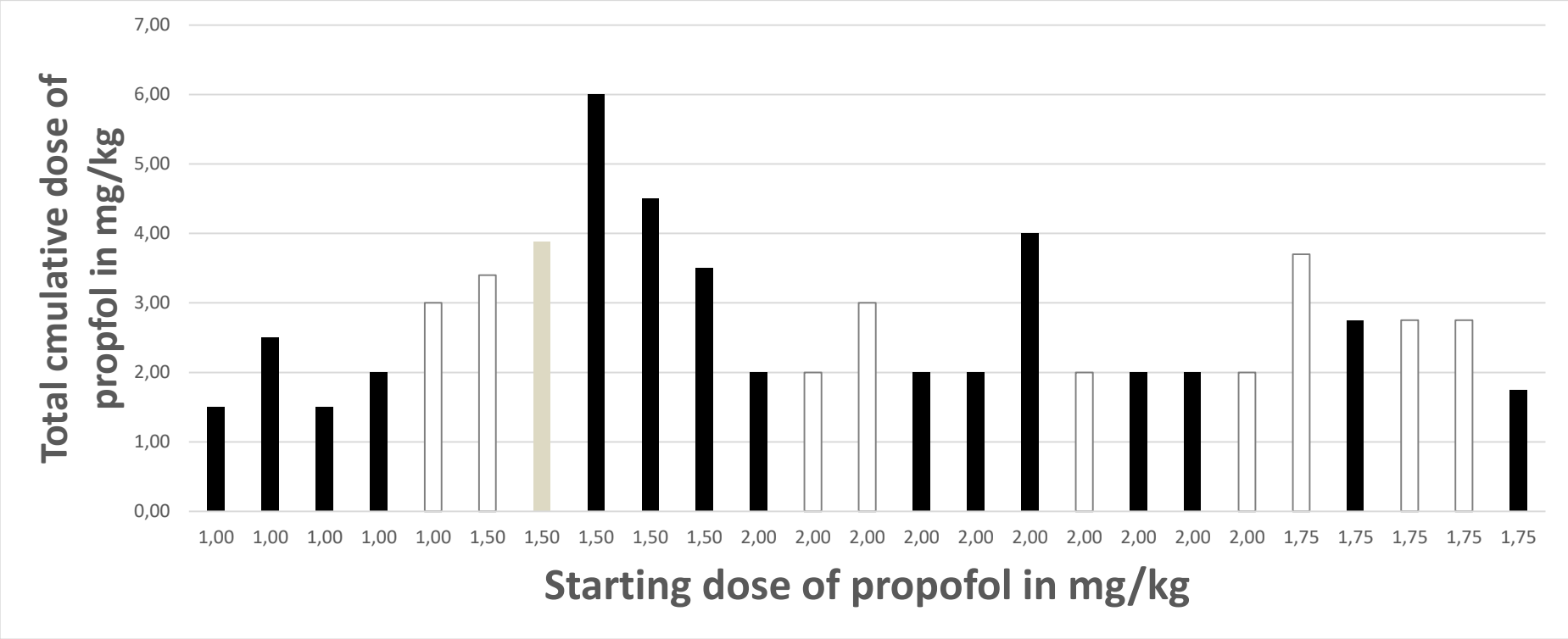
2.Department of Neonatology, AMC Emma Children's Hospital, Amsterdam, The Netherlands
3.Department of Neonatology, VU Medical Center Amsterdam, Amsterdam, The Netherlands

Hypotension in 39% of patients



Propofol dose finding



De Kort et al. PAS Toronto 2018

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Propofol dose finding

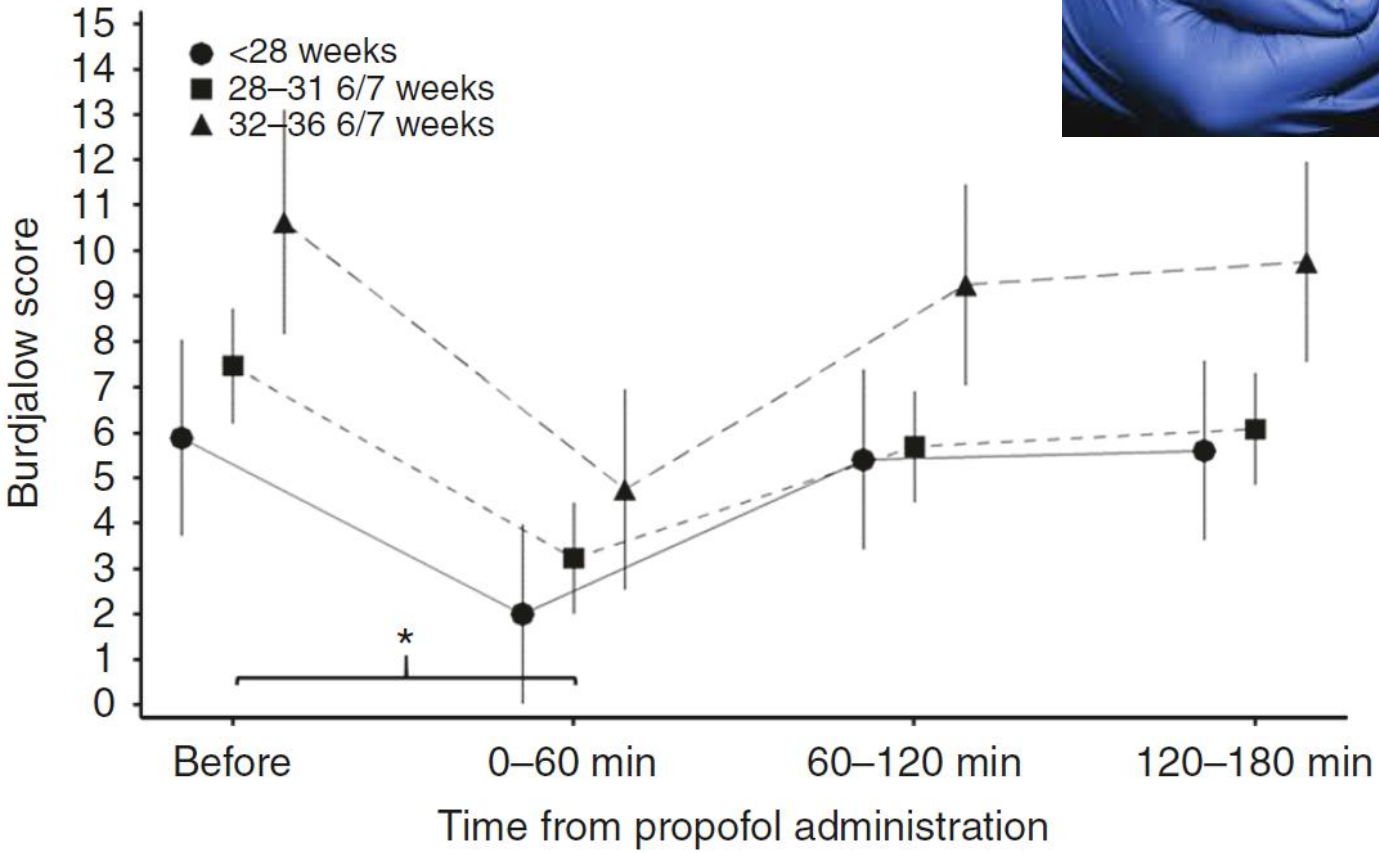
- With increasing dose (1.0 → 2.5 mg/kg), sedation improves

- But also higher risk for side-effects

- Adequate dose in individual patient can not be predicted

De Kort et al. PAS Toronto 2018

Propofol



Thewissen et al. Pediatr Res. 2018

Ketamine

NMDA receptor antagonist

Often used in pediatric anesthesia

Short duration of action

Studies on safety are lacking

Potential adverse effects on the developing central nervous system

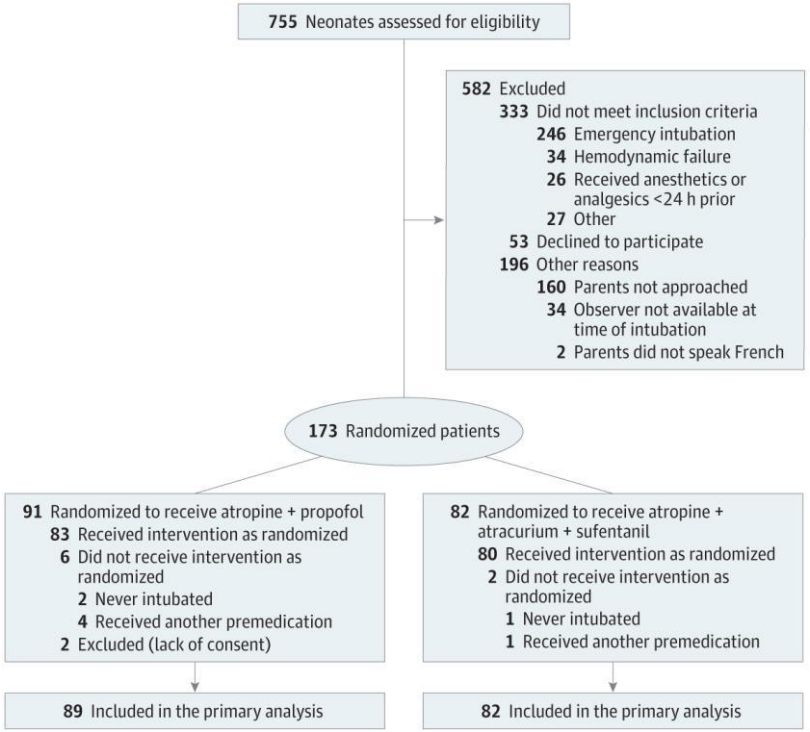
Induction of neuronal cell death

If used in painful situations it might be neuroprotective(!?)

Comparative trials...

Comparative trials...

Propofol (+ atropine) vs Atracurium + Sufentanil (+ atropine)



N=173

Prolonged desaturation =

Underpowered for other conclusions

Durrmeyer et al . JAMA 2018

MIST

Sedation during minimal invasive surfactant therapy: a randomised controlled trial

RCT

Newborns 26-36 weeks

MIST

Propofol vs no-premedication

Dekker et al . ADC 2018

MIST

Sedation during minimal invasive surfactant therapy: a randomised controlled trial

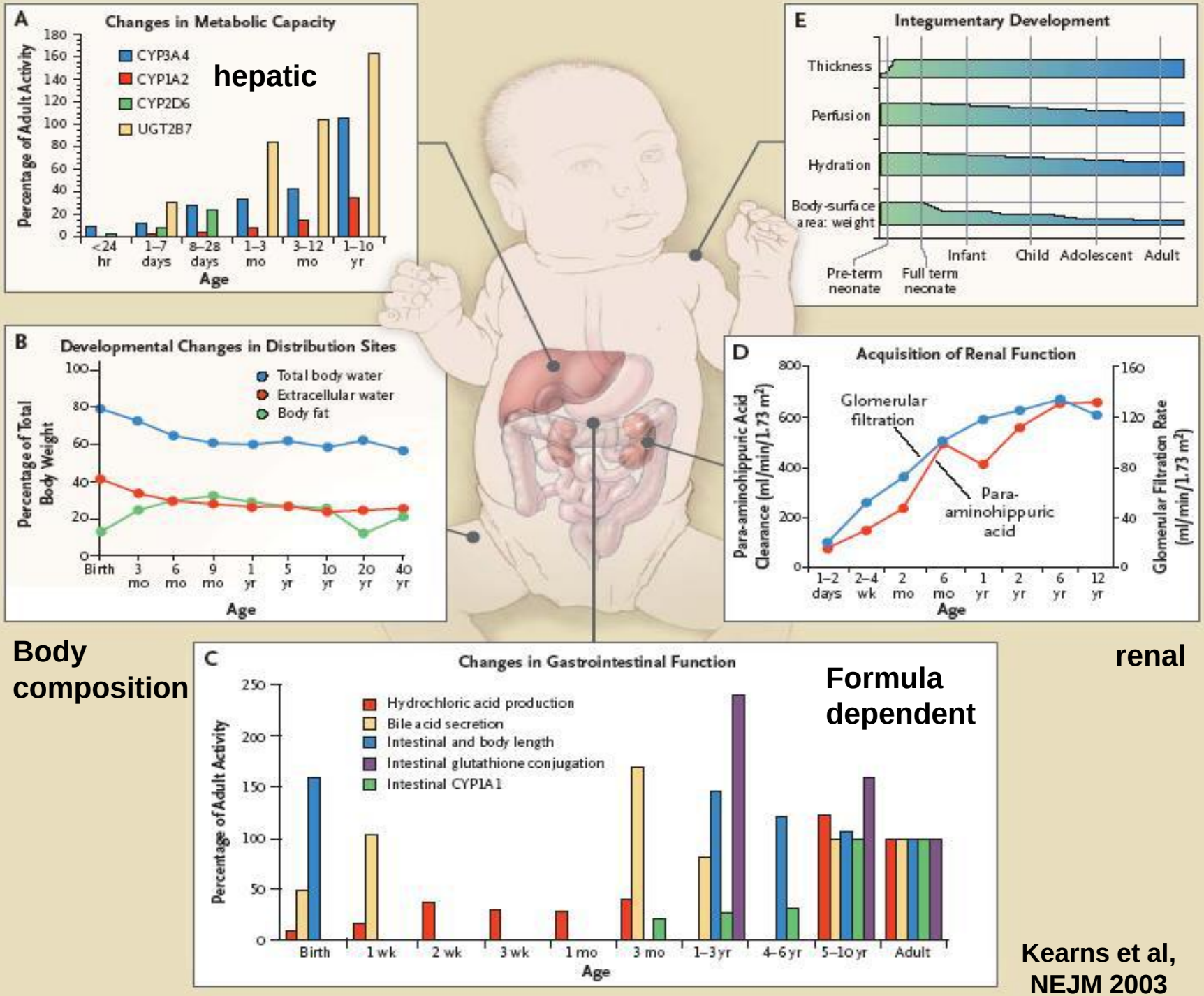
	Propofol	vs	no-premedication
Comfort scores <14	**76%**		**22%**
Desaturation < 85%	**91%**		**69%**
Nasal ventilation	**93%**		**47%**

Dekker et al . ADC 2018

sedatives in neonates ?

Use guidelines +

Think about the basics ....

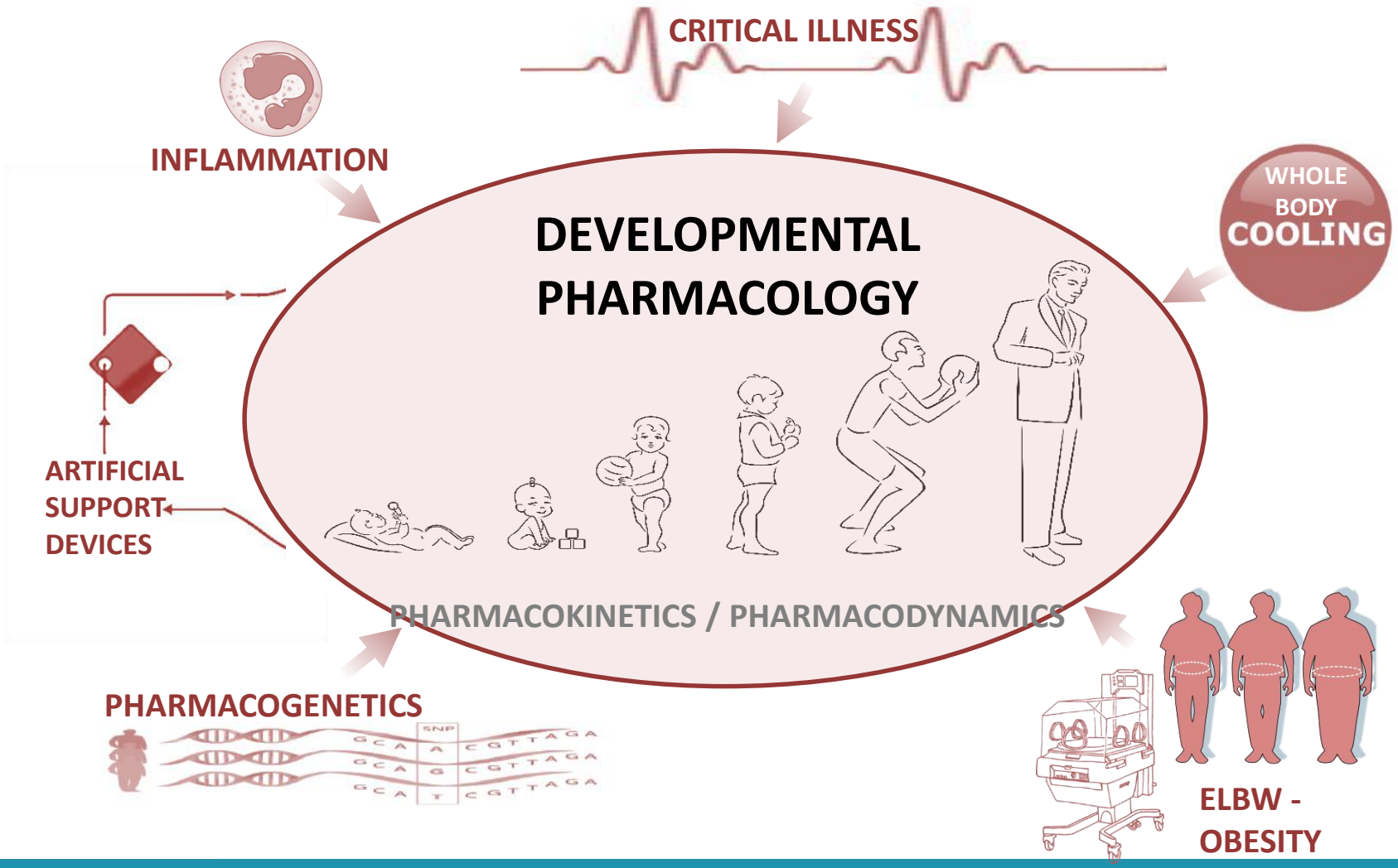


Body composition

Formula dependent

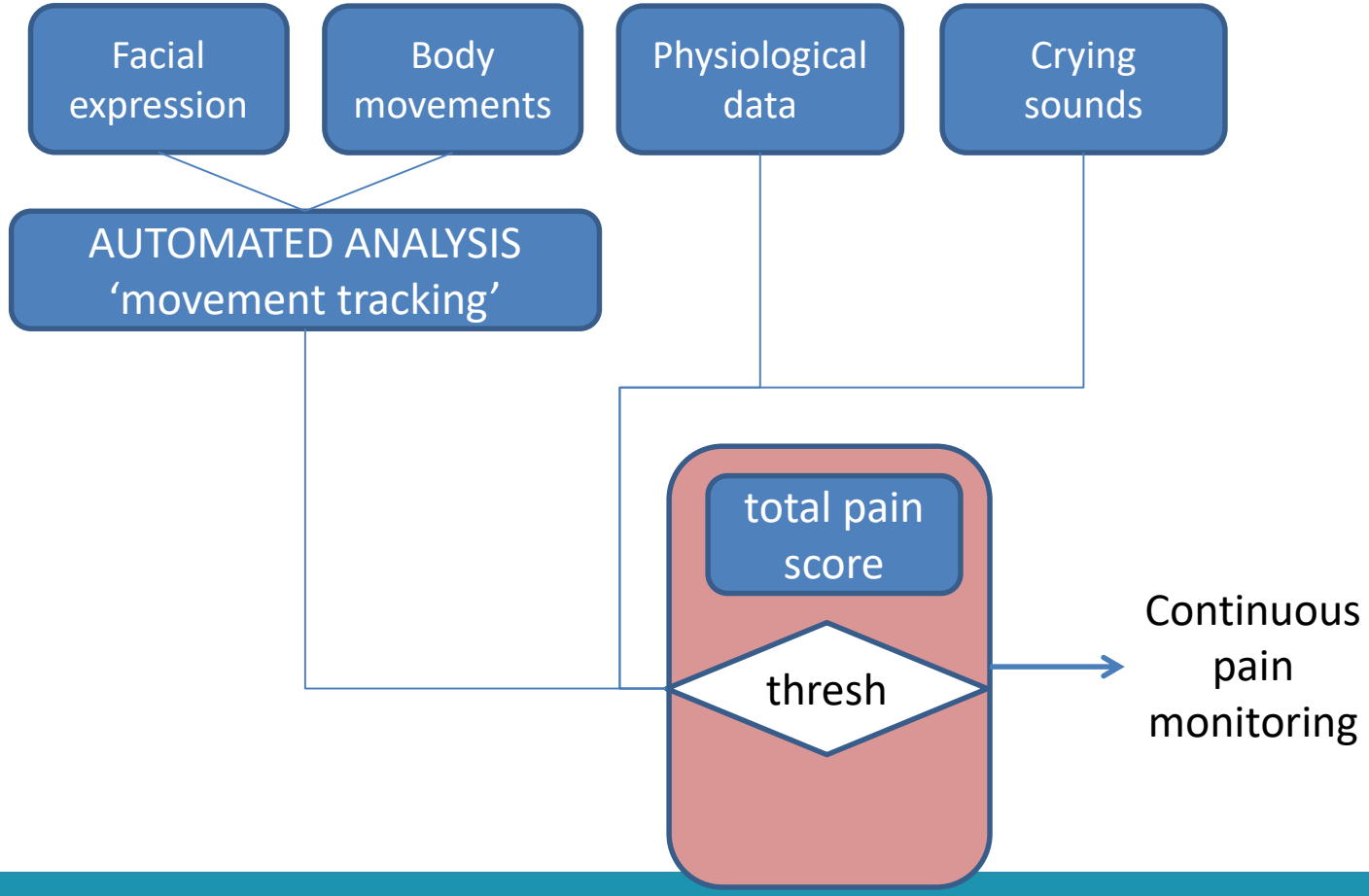
renal

Kearns et al, NEJM 2003



Allegaert, Simons. et al. Eur J Pharmaceutical sciences 2017

AUTOMATED MULTIMODAL ASSESSMENT OF INFANTS PAIN / DISTRESS



UNIVERSITY OF SOUTH FLORIDA

Abstract, PAS meeting San Fransisco 2017

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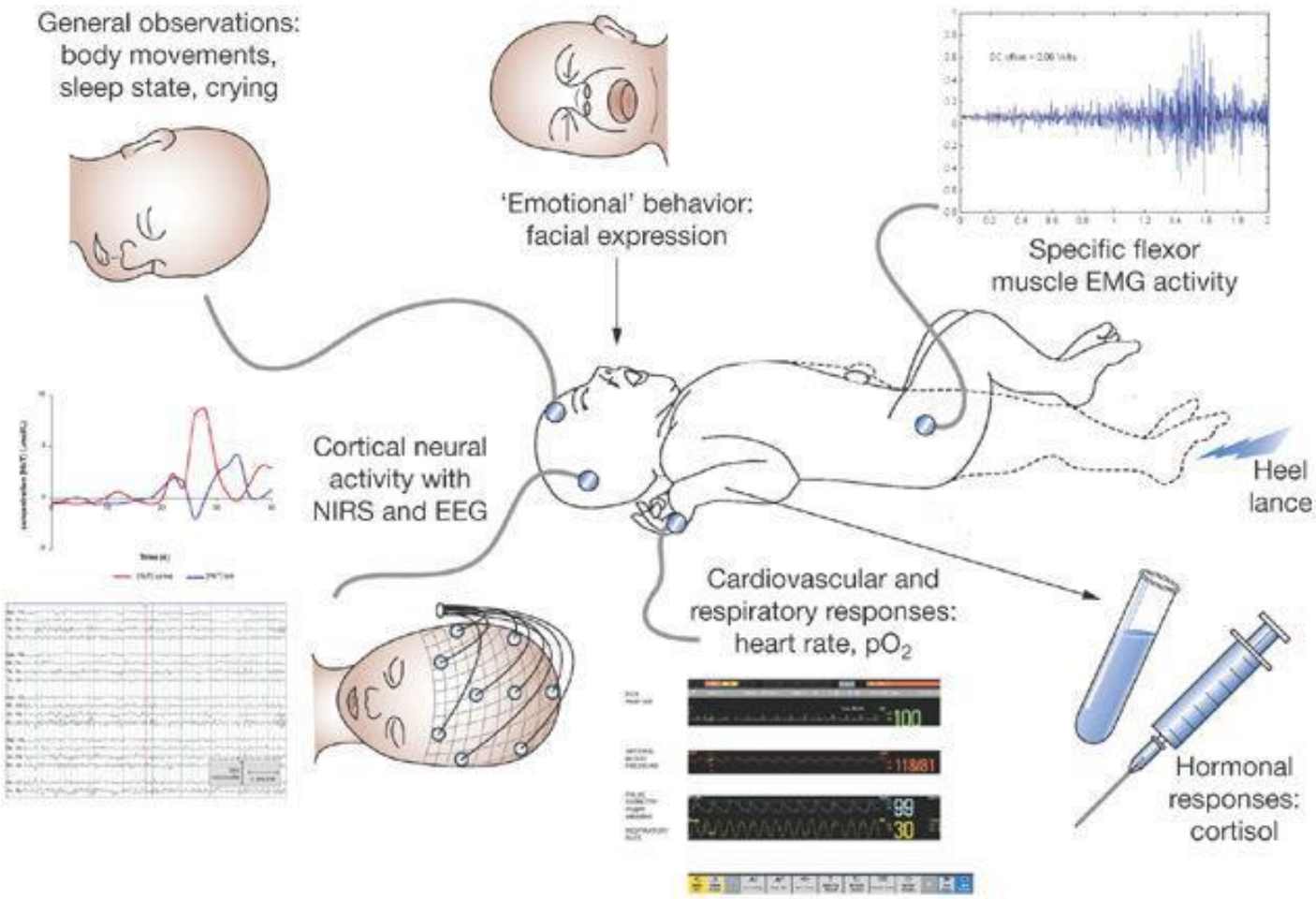
Multi model assessment



Sedation: personalized medicine!

In general for all sedation and analgesia:

The amount and intensity of treatment depends on the specific patient and the specific condition

It needs to be titrated to the individuals needs

With the Child

Analgesic treatment should be individualized according to:

- The child's pain
- Response to treatment
- Frequent reassessment
- Modification of plan as required

Thank you very much for your attention!

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