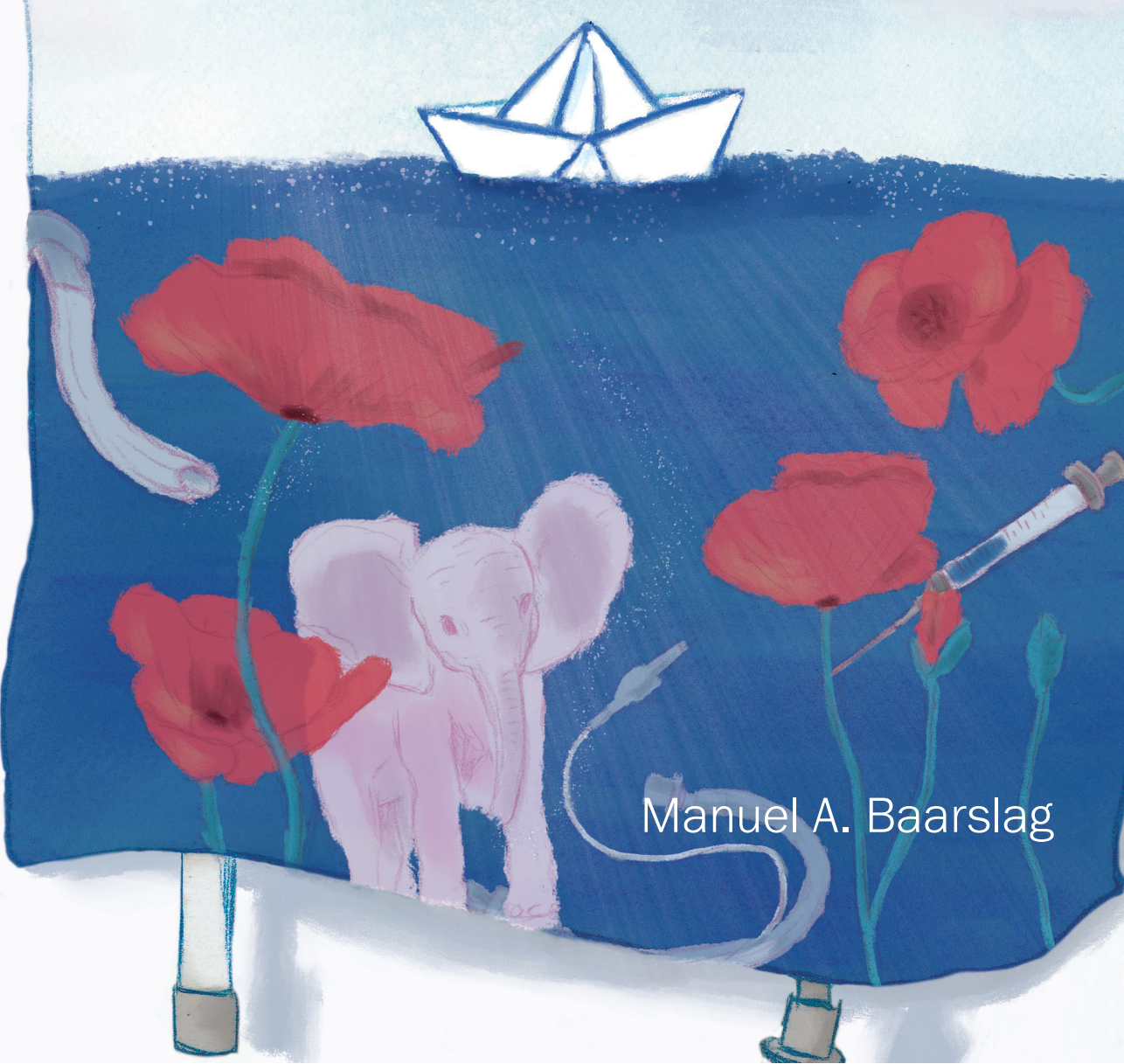
All Quiet on the Bedside Front?

Pain and sedation management in the PICU



Manuel A. Baarslag

ALL QUIET ON THE BEDSIDE FRONT?

Pain and sedation management in the PICU

Van het beddelijk front geen nieuws?
Pijnbehandeling en sedatie op de kinder-IC

Manuel Alberto Baarslag

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Prof.dr. M. van Dijk

Overige leden: Prof.dr. M. de Hoog
Prof.dr. T. van Gelder
Prof.dr. J.B.M. van Woensel

Auxilium nostrum in nomine Domini

CONTENTS

PROLOOG

Isn't it ironic…

8 december 2016. Het moet ergens begin van de avond geweest zijn. Ik ontwaakte na de heroperatie, maar de verlichting van het plafond zag er anders uit dan twee dagen eerder op de recovery. 'Je ligt op de Intensive Care' hoorde ik zeggen. De IC! Wat was er gebeurd? Enerzijds was ik geschrokken, maar anderzijds was ik blij op een afdeling te liggen waar er écht op je wordt gelet (mijn vertrouwen in de reguliere afdeling had een aardige deuk opgelopen).

Hoe wakkerder ik werd, hoe meer ik me bewust werd van de situatie. Ik kon amper bewegen want mijn armen waren gefixeerd, en ik kon niet praten want ik had een tube in mijn keel. Ik kreeg te horen dat de tube diende om mijn bedreigde ademweg veilig te stellen de komende dagen. 'Logische keuze', dacht ik. Gelukkig kon ik al gauw duidelijk maken dat ik die tube écht niet eigenhandig zou verwijderen, en kregen mijn handen weer hun bewegingsvrijheid terug.

Ik kreeg een letterbord, waarmee ik kon communiceren. De eerste vraag die ik stelde bracht mijn vrouw en de verpleging meteen in verlegenheid. 'T-R-I-G-G-E-R I-K Z-E-L-F?' Een tikje beroepsgedeformeerd, maar kennelijk zat de ABC-systematiek er zó ingebakken dat ik deze vraag reflexmatig stelde. En het geeft aan dat als je op de IC aan de beademing ligt, je de regie over je eigen lichaam even kwijt bent. En die wilde ik zo snel mogelijk terug. Weten of je zelfstandig ademt, is daarvan de eerste stap. De daarop volgende vragen hadden allemaal betrekking op mijn eigen vitale functies en medicatie.

In hoofdstuk 6 laten we zien dat endotracheaal uitzuigen de meest voorkomende pijnlijke/stressvolle handeling op de kinder-IC is. Of dit pijnlijk was of niet? Mijn antwoord is 'nee'. Ik heb het een aantal keer per dag aan den lijve ondervonden, maar ik vond er geen pijn aan te pas komen. Het was wel des te stressvoller…

10 december 2016. Na anderhalve dag genoten te hebben van een snufje propofol, een heerlijk narcosemiddel, vond de verpleging me kalm genoeg om het zonder te proberen. Hoewel ik aan de buitenkant kalm bleef, vond mijn lichaam de situatie toch niet zo kalm wat zich uitte in torenhoge bloeddrukken (tot 210 systolisch). Daarop besloot de intensivist me een ander kalmerend en bloeddrukverlagend middel te geven: clonidine. Hoera! Clonidine! Daar doe ik onderzoek naar! Isn't it ironic… Enerzijds voelde ik me bevoorrecht om als onderzoeker zelf aan de medicatie te raken waar ik mijn baan en dus uiteindelijk dit proefschrift aan te danken had, anderzijds voelde het als ironie ten top.

Desalniettemin, deze 5 dagen hebben me minstens zoveel geleerd als 3,5 jaar promotie en kan ik daar met minstens zoveel dankbaarheid op terugkijken als op het promotietraject!

1

General introduction

GENERAL INTRODUCTION

In The Netherlands, around 5000 children with the age of 1 day to 18 years old, are admitted to a PICU annually. Half of these patients are being mechanically ventilated at least once during their PICU stay.[1] During mechanical ventilation, it is essential to provide patients with adequate analgesia and sedation in order to provide maximal comfort by reducing anxiety, pain and distress. Also, adequate sedation provides more optimal ventilator conditions by improving patient-ventilator synchronicity and avoidance of unwanted adverse events such as autoextubations.[2] Pharmacologic treatment is key to provide adequate analgesia and sedation, however, this is currently far from ideal. The available agents have an identifiable side effect profile and children still suffer from iatrogenic withdrawal syndrome (IWS) or pediatric delirium (PD)[3] with a prevalence of 17-57% for IWS[4] and 5-47% for PD.[5-9] Apart from pharmacological interventions, non-pharmacologic measures such as noise reduction, parental presence, pacifiers and oral sucrose solution administration support sedation and analgesia.

Unlicensed drug use in children

The major issue in the pharmacologic treatment of children in general is the lack of available evidence. Even more so for the critically ill child, as 80-90% of patients in a PICU or NICU receive off-label drug therapy.[10] To overcome this problem, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have prioritized pediatric pharmacological research efforts with financial and regulatory measures, such as the Best Pharmaceuticals for Children's Act in 2004 by the FDA[11] and the introduction of the Pediatric Regulation in 2007 by the EMA including financial support from the Seventh Framework Programme.[12] In the pediatric ICU, off-label drug use has the highest rate along with the NICU.[10,13] The PICU has its own challenges for researchers: it is a very heterogeneous group of patients with regard to age, co-morbidities and diseases, and patient numbers for individual diagnoses are low.[14]

Pain management

It has long been believed that neonates do not feel pain. Even major cardiac surgery procedures were performed in neonates without analgesia. Since 1987, when Anand and colleagues found a huge stress response in these non-anesthesized patients,[15] a paradigm shift took place and opioids obtained a key position in neonatal pain management. However, two new questions arose: 1. do these agents cause harm to the developing brain with adverse outcomes in the long term?[16] and 2. what is the optimal dose of these opioids in neonates? We do unfortunately not have clear answers yet, but nevertheless some important steps have been made towards optimal dosing. Population pharmacokinetics allow us to predict the optimal dose for an individual patient based on a Bayesian approach to population-wide obtained data. This allows for sparse sampling and provides insight in the maturation process of drug metabolism during early life.

Also, some alternatives for opioids have been proposed. IV paracetamol proved an effective alternative to IV morphine for very young children after major surgery.[17] This led to the development and implementation of a new postoperative pain protocol in our PICU. However, this transition from opioids to IV paracetamol might herald a new paradigm shift and we wondered whether this implementation would be successful and lead to the same outcome as in the RCT.

Sedation management

In the PICU, benzodiazepines are the first-choice agents for sedation[18,19] with midazolam used most frequently in The Netherlands. Although midazolam has certain advantages, like anxiolysis, anterograde amnesia and muscle relaxation,[20] it is far from ideal. Disadvantages are that it may result in tolerance, iatrogenic withdrawal syndrome, and an increased risk of delirium.[21] Therefore, in adults, a shift has taken place towards analgosedation with an opioid as first-choice agent.[22] Non-benzodiazepine agents like propofol or α2-receptor agonists are preferred above benzodiazepines in adults. However, there is no evidence for the use of other agents in children although they are being used off-label increasingly. Over the last years, increased use of dexmedetomidine is advocated as the new magic bullet but convincing evidence of its superiority is still lacking. One of the aims of this thesis is therefore to investigate whether other agents than benzodiazepines are suitable for the sedation of patients in the PICU.

The big interplay

A major challenge in pediatric drug research is the lack of gold standard end points.[23] This holds especially true for pain and sedation research, because young children are unable to speak about their pain or discomfort, at least in a way that physicians and caregivers understand it. Therefore, we rely on behavioral indicators to estimate their level of pain and discomfort.[24] However, these indicators have their limitations as patients can be too ill to show behavior indicating pain.[25] Moreover, delirium and withdrawal symptoms resemble signs of pain, although these phenomena require a different treatment strategy.[26] It is therefore necessary to find discriminating items between pain, discomfort, withdrawal and delirium and to identify other factors contributing to 'pain-like' behavior. For instance, drugs with anticholinergic activity may precipitate the development of an anticholinergic toxidrome, a combination of manifestations classically taught as 'dry as a bone, blind as a bat, red as a beet, hot as a hare and mad as a hatter'. Restlessness, tachycardia, ataxia, picking movements and agitation are other symptoms of the toxidrome, which are similar to delirium and withdrawal symptoms. We investigated the anticholinergic burden, i.e. a sum of anticholinergic acting drugs, in patients diagnosed with pediatric delirium and/or iatrogenic withdrawal syndrome.

AIMS AND OUTLINE

In this thesis, we aim for providing answers on three key research questions:

- What is the anticholinergic burden in patients diagnosed with pediatric delirium, iatrogenic withdrawal syndrome or both?
- Is there a role for non-benzodiazepine agents for the sedation of patients in the PICU?
- Does the implementation of IV paracetamol in daily clinical practice as primary analgesic for infants achieve comparable results as in a RCT?

In **part I** of this thesis we describe the current pharmacological treatment for pain and sedation management in the pediatric and neonatal intensive care unit, as well as current sedation research. **Chapter 2** describes the pharmacokinetic and pharmacodynamic properties of the most commonly used sedatives on the PICU, with the aim of identifying pediatric-specific knowledge gaps. **Chapter 3** describes the evidence for the current treatment of pain in neonates and infants, along with challenging aspects of pain research in this population.

In **part II** we look further into these challenging aspects. **Chapter 4** describes the clinical study protocol of a multi-center, double-blind randomized controlled trial of clonidine versus midazolam for the sedation of mechanically ventilated children. In this trial, we faced several new challenges which we addressed. **Chapter 5** describes the so-called anticholinergic burden in patients with delirium and withdrawal symptoms.

Part III takes the journey further from trial to clinical practice. In **chapter 6**, we counted procedural pain and distress in the PICU in order to explore the extent of this problem. **Chapter 7** illustrates the successful implementation of a new pain management protocol for postoperative infants.

In **chapter 8**, our research findings are discussed in the broader perspective along with recommendations for future research. **Chapter 9** summarizes the most important findings of this thesis.

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PART I

CURRENT PAIN AND SEDATION MANAGEMENT IN THE PICU

2

Pharmacological sedation management in the paediatric intensive care unit

Manuel A. Baarslag, Karel M. Allegaert, Catherijne A. Knibbe,
Monique van Dijk and Dick Tibboel.

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ABSTRACT

Objective: This review addresses sedation management on paediatric intensive care units and possible gaps in the knowledge of optimal sedation strategies. We present an overview of the commonly used sedatives and their pharmacokinetic and pharmacodynamic considerations in children, as well as the ongoing studies in this field. Also, sedation guidelines and current sedation strategies and assessment methods are addressed.

Key findings: This review shows that evidence and pharmacokinetic data are scarce, but fortunately, there is an active research scene with promising new PK and PD data of sedatives in children using new study designs with application of advanced laboratory methods and modelling. The lack of evidence is increasingly being recognized by authorities and legislative offices such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Conclusion: The population in question is very heterogeneous and this overview can aid clinicians and researchers in moving from practice-based sedation management towards more evidence- or model-based practice. Still, paediatric sedation management can be improved in other ways than pharmacology only, so future research should aim on sedation assessment and implementation strategies of protocolized sedation as well.

INTRODUCTION

Sedation management is a crucial element of paediatric critical care medicine, aiming at reducing children's anxiety, distress and oxygen demand. Adequate sedation improves patient–ventilator synchrony and prevents autoextubation in ventilated children.[1] Moreover, it allows tolerance to diagnostic or therapeutic procedures. However, sedation induced by pharmacological agents often leads to adverse events including prolonged mechanical ventilation, tolerance, withdrawal syndrome and even paediatric delirium. Dosing regimens are not always based on PK data or paediatric pharmacological research findings, and even today, more than 80% of drugs used in the paediatric intensive care unit (PICU) are off-label or unlicensed.[2] Still, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have prioritized paediatric pharmacological research efforts to achieve more evidence-based pharmacotherapy.[3]

To date, there is no consensus on sedation management for children.[4,5] This review provides an overview of evidence for the commonly used drugs in paediatric sedation management and inventories ongoing and future research. Table 1 presents an overview of prospective observational studies and randomized controlled trials performed so far.

Sedation Assessment

A 'gold standard' tool to assess the sedation state of children on intensive care units has not yet been identified.[6] Assessment is difficult because signs such as motor restlessness, agitation and increased muscle tone that may point at undersedation are also signs of pain. It is generally accepted that preverbal children are not able to express their pain or discomfort in a way caregivers understand or interpret as such. Furthermore, children may suffer from separation anxiety and fear for strangers and thus show behaviour indicating undersedation.

Roughly, two types of sedation assessment scales are available[6,7]: those that score a number of behavioural indicators of distress and those that consist of one item describing the level of consciousness. Examples of the latter type validated for children are the University of Michigan Sedation Scale (UMSS)[8] and the State Behavioral Scale (SBS).[9] The UMSS assesses level of consciousness from 0 (awake and alert) to 4 (unarousable). The SBS has six levels from -3 (unresponsive) to +2 (agitated). Another one-item scale, the Ramsay scale, has been used mainly for adults and is not applicable to preverbal children as it includes an item 'responds to commands only'.[10,11] To date, the Richmond Agitation–Sedation Scale (RASS)[12] is more often used in adults, but it has not been validated for children as this includes the item 'overtly combative or violent; immediate danger to staff'.

Table 1. An overview of performed pharmacological studies in paediatric intensive care sedation.

Study	Sample size and age	Design	Outcome
Booker et al.[149]	N=50, 6 months-9 years	Observational cohort study (midazolam bolus 200 mcg/kg followed by CI 120-360 mcg/kg/h)	Adequate sedation, no major adverse events
Shelly et al.[150]	N=50, 0-18 years	Prospective observational cohort study of midazolam CI	Adequate sedation, delayed awakening especially in renal failure patients
Macnab et al. [151]	N=23, 6 months-6 years	Prospective observational cohort study of a midazolam loading dose after cardiothoracic surgery	Termination of study after severe hypotension, other participants showed no hemodynamic changes
De Wildt et al.[62]	N=21, 0-17 years	Observational cohort PK-PD study with protocolized sedation strategy: start dose midazolam 0.1 mg/kg bolus, followed by 100 mcg/kg/h	No clear PK-PD relationship, adequate sedation reached with protocol No report on toxicity
Rigby-Jones et al.[152]	N=26, 0-10 years	Observational cohort PK study, remifentanil and midazolam	Adequate sedation, 1 patient showed hypotension
Ambrose et al.[153]	N=30, 0-10 years	Three-step: IV clonidine: low-dose vs. high-dose (variable dose together with midazolam), 3rd group fixed dose	No adverse effects on hemodynamics, sufficient sedation in combination with midazolam
Arenas-Lopez et al.[83]	N=24, 0-5 years	Prospective cohort study, oral clonidine as additive to morphine/lorazepam	Opioid- and benzodiazepine sparing, safe and effective
Wolf et al.[81]	N=129, 0-15 years	Double-blind, randomized controlled trial of IV clonidine vs. midazolam	No difference in effectivity, underpowered due to recruitment problems
Hünseler et al.[82]	N=219, 0-2 years	Double-blind, randomized controlled trial of IV clonidine vs. midazolam	Opioid- and benzodiazepine-sparing in neonatal age group
Duffett et al.[84]	N=50, 0-18 years	Double-blind, randomized controlled trial of oral clonidine vs. placebo in addition to physician-driven sedation	No significant difference in effectivity, study with clonidine clinically feasible
Su et al.[154]	N=36, 1-24 months	Open-label dose-response study of dexmedetomidine	Reduction of supplementary sedatives, no cardiovascular adverse effects

Table 1. *Continued.*

Study	Sample size and age	Design	Outcome
Hosokawa et al.[155]	N=141, 0-15 years	Observational cohort study: dexmedetomidine vs. chlorpromazine, midazolam or fentanyl in cardiac surgery patients	Comparable efficacy, more haemodynamic adverse effects in dexmedetomidine group
Aydogan et al.[88]	N=32, 12-17 years	Double-blind, randomized controlled trial of IV dexmedetomidine vs. midazolam in adolescents after scoliosis surgery	Decreased pain score, fentanyl consumption and delirium in dexmedetomidine group, more bradycardia in dexmedetomidine group
Diaz et al.[156]	N=10, 0-8 years	Observational PK study of dexmedetomidine for postoperative sedation	Hypotension in most cardiac surgery patients
Tobias et al.[89]	N=30, 0-8 years	Randomized controlled trial: IV low-dose or high-dose, dexmedetomidine vs. midazolam	Equivalent sedation across 3 groups, lower heart rate in dexmedetomidine group: 1 patient removed from the study after bradycardia
Svensson et al.[157]	N=174, 0-16 years	Prospective observational cohort study: propofol CI in the PICU	No occurrence of PRIS in cohort group
Rigby-Jones et al.[158]	N=21, 0-12 years	Observational PK study of propofol CI	Adequate sedation in 17 of 20 scored patients, 1 case of hypotension and metabolic acidosis
Hartvig et al.[159]	N=10, 8-30 months	Observational PK study of ketamine CI after cardiac surgery	Adequate sedation, no adverse effects observed
Parkinson et al.[107]	N=44, 0-15 years	Randomized controlled trial of midazolam IV vs. chloral hydrate and promethazine PO	More optimal sedation in chloral hydrate/promethazine group, 1 patient with indication of delirium in chloral hydrate/promethazine group

Abbreviations: CI: continuous infusion; EEG: electroencephalogram; IV: intravenous; PO: oral; PICU: Paediatric Intensive Care Unit; PK: Pharmacokinetic; PK-PD: Pharmacokinetic-Pharmacodynamic; PRIS: PRopofol Infusion Syndrome;

An example of a scale that includes several behavioural indicators of distress is the COMFORT behavioural (COMFORT- B) scale.[10] The COMFORT-B scale can be used both in ventilated and spontaneously breathing patients and has proven to be valid for both pain and sedation assessment. In addition, the scale is able to detect treatment-related

changes in pain or distress intensity and therefore can reliably guide pain and sedation management.[13] Still, the COMFORT-B scale cannot be applied in patients with fluctuations in neurological status, pre-existing neurological disorders or patients receiving neuromuscular blocking agents. A limitation of behavioural assessment tools in general is the difficulty to discriminate between pain, discomfort, withdrawal symptoms or delirium. For example, the Face, Legs, Activity, Cry and Consolability (FLACC) scale, one of the most widely used pain assessment scales, was found wanting in its capacity to discriminate pain and distress.[14] For a decade, the Bispectral Index Monitor (BIS) was considered promising for objective assessment of sedation. Studies comparing BIS to the COMFORT (or COMFORT-B) scale[15–22] showed correlations ranging from weak[15] to excellent when grouped in a BIS range of 41–60.[17] This wide variation can be partially explained by different study conditions, as the weak correlation was found in patients undergoing endotracheal suctioning, and the high correlation was found during continuous sedation. Depending on the clinical indication, BIS can potentially be used, although it has not proven valid for children under the age of 1 year old as the EEG algorithm has not been validated in infants.[23]

Prolonged administration of sedatives may lead to drug tolerance and physical dependency, leading to iatrogenic withdrawal syndrome after abrupt discontinuation or (too rapidly) tapering down of these drugs. The symptoms of this syndrome overlap with signs of undersedation. The Withdrawal Assessment Tool-1 (WAT-1) and the Sophia Observation withdrawal Symptoms score (SOS) are the most valid and reliable tools to identify withdrawal in the PICU.[24,25] Furthermore, a position statement from the European Society for Paediatric and Neonatal Intensive Care (ESPNIC) provides clinical recommendations for sedation and withdrawal syndrome assessment in the paediatric age group.[26]

Sedation Guidelines

Sedation management in adults has shifted from full unconscious sedation to a more easily arousable state.[27] In this approach, the use of sedation guidelines and protocols was associated with reduced ICU and hospital length of stay (LOS) as well as reduced duration of mechanical ventilation (MV).[28] In paediatrics, however, a systematic review published in 2013[29] showed that some studies also found a reduced ICU LOS and duration of MV in protocolized sedation arms, but concluded that the overall evidence for protocolized sedation remained relatively poor due to the low quality of studies. Children's cognition and behaviour clearly require a different strategy.

One year later, Curley et al.[30] reported on the largest multicentre RCT comparing protocolized sedation with physician-driven usual care in a mixed PICU population. The protocolized sedation management had not resulted, however, in shorter MV duration or ICU and hospital LOS. Heterogeneity in outcome measures and pharmacological agents makes it difficult to

obtain sufficient evidence for the usefulness of sedation guidelines in paediatric intensive care. A systematic review of Vet et al.[31] concluded that optimal sedation is achieved in only around 60% of sedation assessments and that oversedation is more common than under-sedation. Oversedation often was not adequately managed by tapering off medication, indicating that healthcare professionals may be tolerating oversedation. This attitude may diminish the effect of protocolized sedation in trials. It would seem that 'protocolized' does not automatically mean 'uniformity' or 'one size fits all'.[32] In adults, the method of daily sedation interruption (DSI) seemed promising in reducing ICU LOS and MV duration,[33,34] but conclusive evidence has not yet been found.[35,36] A multicentre RCT comparing protocolized sedation and DSI plus protocolized sedation in the PICU showed no beneficial effects of DSI,[37] in contrast to two other RCTs in children.[38,39] Vet et al. compared to protocolized sedation management instead of physician-based sedation management, which may imply a positive effect of the protocolized sedation in the control arm.

Although an optimal level of sedation often cannot be achieved without pharmacological treatment it is also important to consider environmental factors and non-pharmacological interventions. Light and noise, for example, can be disturbing, and care should be taken to let the children wear ear plugs, ask staff to speak softly and prevent ongoing alarm sounds, etc. Non-pharmacological interventions to reduce stress, such as live or recorded music, have been primarily studied in adult critical care.[40] A meta-analysis including three RCTs of music therapy offered to paediatric surgical patients (0–18 years), although not in the intensive care setting, reported significant reduction in pain, anxiety and distress.[41] It would be worthwhile to study non-pharmacological interventions in the PICU setting.

Pharmacological Aspects

Several overviews of commonly used sedatives have already been published.[42–44] Still, the dosing regimens greatly differ. This is not surprising, as most of these sedatives are prescribed off-label.[2] Figure 1 illustrates the mechanisms of actions of the different sedatives. Table 2 provides PK and PD properties of the most common sedatives including proposed dosing strategies.

Low-volume blood collection techniques such as dry blood spot sampling[45] in combination with new analysis techniques such as LC-MS/MS, for which less blood is needed, could help establish optimal paediatric dosing strategies by enhancing pharmacokinetic research. Moreover, comparative effectiveness studies and population PK-PD studies using opportunistic and sparse sampling could further facilitate paediatric drug research.[46] However, many internal and external factors can alter the PK and PD of sedative drugs. The internal factors include critical illness itself, which has been correlated with altered PK parameters of midazolam[47,48] and other drugs,[49] decreased cardiac output, changes in liver and kidney function and altered distribution, for example, in children with burns.[50]

Table 2. *Sedative PK/PD properties.*

	Elimination half life	Metabolism
Benzodiazepines		
Midazolam	3-4 hours	CYP3A4/3A5, glucuronidation of phase I metabolite
Lorazepam	10-20 hours	Glucuronidation
Alpha-2-adrenergic receptor agonists		
Clonidine	7-17 hours	60% kidney excretion, metabolism by CYP2D6
Dexmedetomidine	2-4 hours	CYP2A6 and glucuronidation
Other sedatives		
Propofol	30-60 minutes	CYP2B6/2C9, glucuronidation
Ketamine	2-3 hours	CYP3A4/2B6/2A9
Chloral hydrate	8-35 hours (TCE)	Glucuronidation
Barbiturates		
Pentobarbital	15-50 hours	Hepatic microsomal enzyme system
Thiopental	6-15 hours	Oxidation (CYP2C19) and hydroxylation

Abbreviations: CI: continuous infusion; EEG: electroencephalogram; IV: intravenous; PO: oral; RC; rectal; TCE: trichloroethanol.

External factors include renal replacement therapy,[51] ECMO[52,53] and hypothermia.[52,54] Increasingly, physiology-based pharmacokinetic (PBPK) studies will offer the opportunity to integrate physiological and pathophysiological changes over time in the drug dosing schedules. Furthermore, weight-based infusion concentrations are often inaccurate. In a prospective study, 65% of opiate concentrations in a PICU and NICU differed >10% from the prescribed concentration.[55] This confounder should be taken into account in PK-PD studies, and it should be considered to measure the actual administered infusion concentration.

Not only PK but also PD may be affected by critical illness. An adult study[56] found a significant correlation between disease severity and level of sedation, independent of propofol clearance. It is plausible that this holds also for children.

Recommended dose	Advantages	Caveats
IV: Bolus of 0.1-0.2 mg/kg, followed by 0.1-0.6 mg/kg/h CI	Fast-acting	Accumulation in hepatic/renal failure
IV: 0.02-0.1 mg/kg q4-8h or 0.025 mg/kg/h CI	Metabolism independent of liver and kidney function	Propylene glycol toxicity
IV: Bolus of 2 mcg/kg, followed by 0.1-2 mcg/kg/h CI	Preserves respiratory drive and has analgesic properties	Bradycardia and rebound hypertension
IV: 0.2-2.5 mcg/kg/h CI	Short half-life	Rebound hypertension
3-15 mg/kg/h	Fast-acting, short half-life	Associated with PRIS at higher doses or prolonged use
IV: Bolus of 1 mg/kg followed by 16 mcg/kg/min (1 mg/kg/h) CI	Preserves respiratory drive and has analgesic properties	Hypertension, raised intracranial pressure
PO or RC: 25-75 mg/kg q4-6h	Does not interfere with EEG results	No IV solution available
IV: 0.5-5 mg/kg/h	Decreases intracranial pressure, profound sedation	Not suitable for hemodynamically unstable patients
IV: Bolus of 4-6 mg/kg followed by 5 mg/kg/h up to a maximum of 10 mg/kg/h	Decreases intracranial pressure, profound sedation	Not suitable for hemodynamically unstable patients

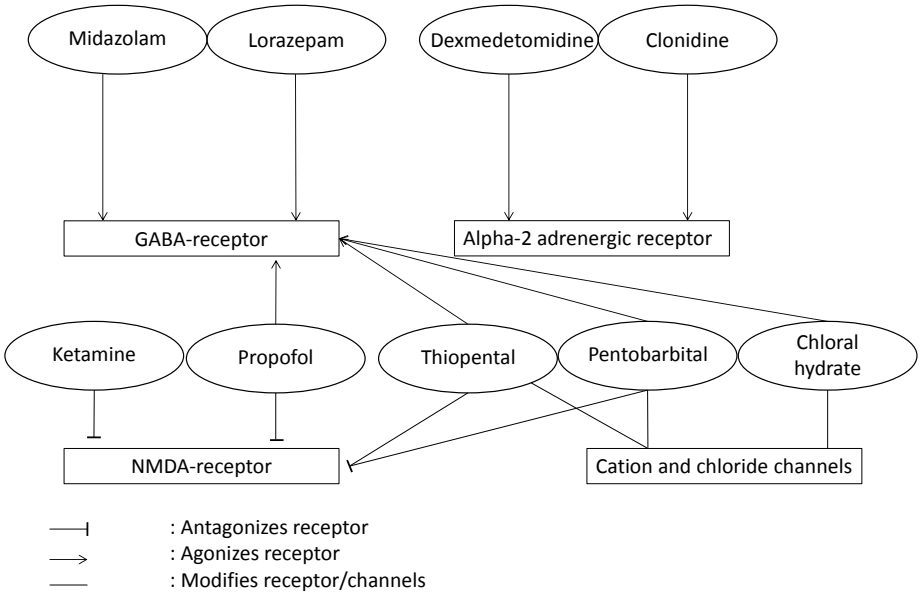
Pharmacological Agents

Benzodiazepines

Benzodiazepines are the drug class of first choice, often in combination with opioids. An exception must be made, however, for the premature population as a study showed that midazolam was associated with a higher incidence of intraventricular haemorrhage grade III or IV and periventricular leucomalacia compared to morphine.[57] Benzodiazepines have been used for sedation of mechanically ventilated children for many years. The exact mechanism of action is not yet clear, although it is known that all agents from this class share the same site of action. Binding to this site increases the frequency at which the chloride channel is opened by ɣ-amino butyric acid (GABA), thereby making the neuron more sensitive to GABA. The more chloride is allowed to enter the target neuron, the more it is hyperpolarized, resulting in a decrease in firing rate of this target neuron. This in turn leads to the pharmacological effects of benzodiazepines: sedation, anxiolysis and muscle

relaxation.[58] This inhibitory effect of the GABA system is developing during the first weeks of life; therefore, GABA-ergic agents may be less effective in prematurely born and term born neonates and may even lead to paradoxical reactions such as increased agitation and convulsions.[59]

Figure 1. *An overview of the sites of action of the most commonly used sedatives in the pediatric intensive care unit.*



Midazolam

Midazolam is recommended in UK PICU guidelines as first-choice sedative in most critically ill children. With onset of action occurring within 1–5 min after infusion, its effects last for 30–120 min after a single infusion, and even up to 48 h after one week of continuous infusion.[60] Besides sedation and anxiolysis, midazolam also provides anterograde amnesia, thus minimizing children's recall of unpleasant experiences after a PICU admission.[61] Midazolam is mainly metabolized to the equipotent metabolite 1-OH-midazolam and then glucuronidated to the renally excreted 1-OH-MDZ-glucuronide.

Although a clear PK-PD relationship was not found in a prospective study in 21 PICU patients, effective sedation was achieved within the recommended range.[62] Midazolam dosing can be effectively and simply titrated based on level of sedation. However, as 80% of conjugated 1-OH-midazolam is eliminated renally, accumulation of the metabolites

may lead to prolonged sedation in children with renal failure.[63] Furthermore, the sedation strategy for a patient with severe sepsis should take into account that critical illness reduces midazolam clearance independently of serum creatinine levels and could increase sedation depth. Critical illness thus leads to a great variability in midazolam clearance, as was confirmed in a systematic review.[64] It should be clear that this variability greatly affects correct dosing. Ongoing midazolam trials in paediatric long-term sedation or pharmacology are listed in Table 3.

Lorazepam

The longer acting benzodiazepine lorazepam is used much less than midazolam in the PICU but has been included in the Best Pharmaceuticals for Children Act (BPCA) Priority List.[30,65] Its IV formulation contains propylene glycol (PG), which at toxic amounts can lead to lactic acidosis.[43,66] Note should be taken that the PG metabolism is immature in preterm and term neonates.[67,68] It is recommended to carefully monitor the osmol gap.[69] Data on a PK-PD relationship of lorazepam for sedation are lacking. Pharmacokinetics are well-described in children with seizures and status epilepticus[70–72] and a PBPK model underscores the low elimination rate in neonates and the higher elimination rate in children around 2 years of age.[73] Still, a clear evidence-based dosing regimen for critically ill children is not yet available (see Table 3 for ongoing paediatric lorazepam studies).

Alpha-2-adrenergic receptor agonists

If benzodiazepines fail to achieve adequate sedation, adjuncts such as the α2-receptor agonists clonidine and dexmedetomidine can be used, which nevertheless are not labelled for this indication. A2-receptor agonists reduce sympathetic outflow[74] by stimulating presynaptic α2-adrenergic receptors, thereby reducing the noradrenaline release into the synapse. This provides sedation without respiratory depression. Because of its analgesic properties, clonidine is often given as spinal anaesthesia adjunct after surgical procedures.[75] Dexmedetomidine could reduce MV duration and ICU LOS[76] when compared to standard sedation practices, but there is still limited experience with this sedative. In critically ill children, both clonidine and dexmedetomidine exert effects on the cardiovascular system, the latter theoretically to a lesser extent, as this is a more α2-selective agonist. However, both seem to be well-tolerated and the cardiovascular side effects are well-manageable.[77–79]

Table 3. An overview of current trials with sedative agents in children.

Trial register number	Short title	Sedative agent
EudraCT 2014-003269-46	PedMicMida	Midazolam
NCT02302391	Morpheus	Midazolam
NCT00109395	Lorazepam Sedation for Critically Ill Children	Lorazepam
NTR5112	PK of Lorazepam Oral Liquid in PICU Patients	Midazolam
NCT02509273	CloSed	Clonidine
NCT02252848	N/A	Clonidine
NCT02249039	N/A	Clonidine
NCT01091818	Dexmedetomidine Versus Midazolam for Intensive Care Sedation of Children	Dexmedetomidine
NCT02296073	The Efficacy and the Safety of Dexmedetomidine Sedation on the Pediatric Intensive Unit(PICU) Patients.	Dexmedetomidine
NCT00875550	Study Evaluating Safety and Efficacy of Dexmedetomidine (DEX) in Intubated and Mechanically Ventilated Pediatric Intensive Care Unit (PICU) Subjects	Dexmedetomidine
NCT02375243	Use of Dexmedetomidine in Children Undergoing Cardiac Surgery	Dexmedetomidine
ACTRN12615001304527	Cardiac Baby SPICE	Dexmedetomidine
ACTRN12614000225617	Baby SPICE	Dexmedetomidine
NCT02529202	Dexmedetomidine Pharmacokinetics in Neonates During Therapeutic Hypothermia	Dexmedetomidine
NCT01266252	NEODEX	Dexmedetomidine
NCT02544854	Pharmacokinetic/Pharmacodynamic Model of Propofol in Children	Propofol
NCT01621373	NEOPROP	Propofol
NCT02040909	NEOPROP2	Propofol
ACTRN12611000451909	The pharmacokinetics and pharmacodynamics of propofol infusion in obese children	Propofol
NCT00618397	Pharmacokinetics of Low Dose Ketamine Infusion	Ketamine
EudraCT 2008-003293-18	Pharmacokinetics of ketamine in infants	Ketamine

NCT trials are found on www.clinicaltrials.gov, EudraCT trials on www.clinicaltrialsregister.eu, ACTRN trials on www.anzctr.org.au and NTR trials on www.trialregister.nl. PK=pharmacokinetics; MV=mechanically ventilated; RCT=randomized controlled trial; HIE=Hypoxic-ischemic encephalopathy

Type of study	Study population	Comparator (if applicable)	Co-medication
Microdosing PK study	Children on midazolam(0-6 years)	N/A	None
PK analysis	MV children (1 month-18 years)	N/A	Fentanyl
Double-blind RCT	MV children (0-18 years)	Midazolam	None
PK analysis of new oral formulation	Children on benzodiazepine weaning (2 weeks-12 years)	N/A	None
RCT, PK-PD analysis	MV children (0-18 years)	Midazolam	Morphine
Phase I trial	Neonates with HIE treated with hypothermia	N/A	None
Dose-finding study (phase I-II)	MV infants	N/A	None
Double-blind RCT	MV children (2-18 years)	Midazolam	None
Open-label RCT	MV children (1-16 years)	Midazolam	Fentanyl
Double-blind RCT	MV children (1-16 years)	Low dose vs. high dose	Fentanyl, morphine, midazolam
Open-label RCT	Children undergoing cardiac surgery (1 month-2 years)	Half-dose co-medication plus DEX vs. full-dose co-medication	Midazolam and morphine
Double-blind RCT	Children undergoing cardiac surgery (>6 years)	Midazolam	None
Open-label RCT	MV children (0-16 years)	Standard sedation care	None
PK analysis	Neonates with HIE treated with hypothermia	N/A	None
PK analysis	MV neonates	N/A	None
PK-PD analysis	Children (1-12 years) undergoing surgery	N/A	None
PK-PD analysis	Neonates undergoing INSURE	N/A	None
Dose-finding study	Neonates undergoing intubation	N/A	None
PK-PD analysis	Obese children (5-15 years)	N/A	None
Phase I trials with PK-analysis	MV children (3-18 years)	N/A	None
PK analysis	Infants undergoing anesthesia	N/A	None

Clonidine

Clonidine has a relatively long half-life,[80] and therefore, it is recommended to give a loading dose before a continuous infusion. Only one published trial in children, the SLEEPS study, did use a loading dose[81]; whereas in other trials, a loading dose was not applied.[82–84] This practice could lead to a later onset of action of clonidine.[80]

The SLEEPS study compared clonidine to midazolam and found no significant difference in efficacy. The study was underpowered, however, as recruitment appeared problematic, and true non-inferiority of clonidine therefore was not shown. Genuine PK-PD research has not been performed, but adequate sedation could be reached with a plasma level of 0.9–2.5 ng/ml.[83] PK-PD simulations[80] have shown that this level is reached in the majority of patients receiving 1 mcg/kg per h, but without the use of a bolus dose, it will take up to at least 24 h to reach this level. Dosing recommendations are still not evidence-based, but evidence is gained from an ongoing RCT (the CloSed trial: NCT02509273 on clinicaltrials.gov).

Dexmedetomidine

Dexmedetomidine seems to reduce cardiovascular complications after cardiac surgery.[85] A beneficial effect was found in a meta-analysis[86] of haemodynamic outcomes in children after surgery for congenital heart disease. Three RCTs on dexmedetomidine in children[87–89] showed a decrease in MV duration and an opioid-sparing effect. Many of the children in these trials had bradycardia, but this had no effect on blood pressure. Optimal dosing of dexmedetomidine is unknown. Its clearance is immature during the first 2 years of life, then increases to above adult level when expressed per kg bodyweight and returns to adult levels after 5 years of age.[90] The half-life in preterm neonates is twice that in term neonates.[91] A PK-PD model has been established only for children after cardiac surgery.[92] A target plasma level of 0.6 mcg/l is regarded effective in adults,[93] but a target plasma level for children is unknown. Simulation of doses used in trials based on a pooled population PK analysis[90] estimates the target plasma level to lie between 0.4 and 0.8 mcg/l, but this needs to be confirmed in a larger patient group. Moreover, experience with dexmedetomidine in children is relatively scarce so knowledge on safety is also lacking. Nevertheless, several paediatric studies on dexmedetomidine are underway (see Table 3).

Other sedative agents

Propofol

Propofol is a very rapid-acting and versatile sedative. It is included in the revised priority list of the EMA,[94] for procedural sedation in the neonatal age group. While often used as sedative in adult ICUs,[95] its long-term use in children is contraindicated as it may lead to a propofol infusion syndrome (PRIS), a metabolic disorder with severe metabolic acidosis, hyperkalaemia, hyperlipidemia, rhabdomyolysis and organ failure, associated with an increased risk of mortality.[60] A fatty acid oxidation disturbance may be the underlying aetiology. Risk factors are

doses >4 mg/kg per h with a duration of >48 h, but short-term high doses can be dangerous, too. Other risk factors include a young age, critical illness, high fat and low carbohydrate intake, inborn errors of mitochondrial fatty acid oxidation and concomitant catecholamine infusion or steroid therapy.[96] Wang et al.[97] pooled seven paediatric pharmacokinetic studies and evaluated the allometric exponent of 0.75, which is often used to estimate the clearance in individuals of different age. The models gave a clear insight into the PK of propofol in all age groups. Propofol PD is less well-studied. One study found a PK-PD relation[98] with a wide variability in the PD end point, for which reason the authors advise dose titration. Four propofol PK-PD trials are being performed (Table 3).

Ketamine

Ketamine is a NMDA receptor-blocking agent, which provides dissociative anaesthesia[99] 'disconnecting' the thalamocortical and limbic systems, that is disconnecting the CNS from outside stimuli.[100] Ketamine preserves the respiratory drive and the blood pressure and is thus suitable for use in haemodynamically unstable patients.[101] It stimulates the release of endogenous catecholamines, producing dose-dependent tachycardia and hypertension. This mechanism is also used in refractory bronchospastic events.[102] Ketamine is contraindicated for patients with a raised intracranial pressure as ketamine may further increase the pressure by intracerebral vasodilation. The blocking of the NMDA receptor may prevent opioid tolerance; therefore, ketamine often serves as an adjunct to sedatives and opioid analgesics, with an opioid-sparing effect.[43,103] Ketamine is available as the racemic mixture of R(-) and S(+) ketamine, but the S(+) enantiomer is twice as potent as racemic ketamine and has fewer side effects.[104] Some European countries have consequently replaced the racemic mixture with S(+) ketamine (esketamine). A PD profile of ketamine has been established in children in an emergency department setting where short-term sedation and analgesia were required for brief painful procedures.[105] The profile shows that a target serum concentration of 1 mg/l provides moderate sedation and that a concentration of 1.5 mg/l provides deep sedation. However, optimal dosing should still be confirmed by a well-designed RCT with adequate long-term sedation as end point (for ongoing PK studies, see Table 3).

Chloral hydrate

Chloral hydrate (CH) is a prodrug, rapidly converted by acetaldehyde dehydrogenase to the active metabolite trichloroethanol (TCE), which is either glucuronidated to an inactive metabolite, or oxidized to trichloroacetic acid (TCA) and then excreted by the kidneys.[106] One trial showed better sedation using chloral hydrate with promethazine compared to midazolam intravenously in critically ill children who tolerated nasogastric feeding.[107] However, enteral sedatives are not recommended primarily in this population as the enteral absorption is unpredictable.[108] Plasma levels of CH could be detected after hours in neonates, while in healthy adults, the half-life is very short.[109] A correlation was also found between CH plasma levels and sedation scores, although TCE is the presumed active metabolite. As it is unclear which

of the compounds, CH or TCE, provides sedation, pharmacokinetic data are difficult to interpret, and thus, an evidence-based dosing recommendation is lacking.[110] Moreover, neonates may be vulnerable to toxic levels of TCE and TCA because these metabolites have a longer half-life at neonatal age.[111] Chloral hydrate has been associated with a higher incidence of bradycardiac events in prematurely born neonates, which implies that cardiorespiratory monitoring is needed.[112] Future research should be aimed at the efficacy and safety of CH in long-term sedation, preferably by establishing a good PK-PD profile in different age groups. No trials involving CH have been registered yet.

Barbiturates

Pentobarbital

Pentobarbital (pentobarbitone) can provide profound sedation when other first-line therapies fail. Doses are titrated based upon a clear pharmacodynamic end point, that is burst suppression on the EEG. However, BIS monitoring, which is easier to perform, could be a valid alternative to EEG monitoring in this indication.[113] BIS monitoring is validated only for children older than 1 year and also has its limitations when used in critical care. For example, BIS is usually recorded on one side of the brain, while asymmetrical intracranial pathology may be present.[114] As the cerebral oxygen demand is reduced, the cerebral blood flow is reduced as well and consequently the intracranial pressure will fall.[115] Pentobarbital is a relatively short-acting barbiturate.[116] It is a very efficient sedative, but has been associated with adverse effects[117] such as hypotension (as it is a direct negative inotrope), oversedation, choreo-athetoid neuromuscular phenomena and withdrawal. The drug may suppress the immune system, which effect could be relevant to critically ill children with multiple accesses to the blood stream.[118] Its PK and PD have been well-established in adults, but data in children are limited. A population PK study in children after open heart surgery suggested that younger infants would need a relatively higher dose based on body weight due to increased clearance.[92] However, in this study, no link was made to a PD end point, so it remains unclear whether dosages should be adapted as there is a clear clinical titration end point.

Thiopental

Thiopental (thiopentone) is an ultra-short-acting barbiturate with an onset of action of 20–40 s after intravenous infusion.[119] It is widely used as an anaesthesia induction agent. Like pentobarbital, thiopental is a suitable agent for patients with raised intracranial pressure. PK and PD studies have been rarely performed in children, and most of them date from the 1980s.[120–123] Despite a reported double clearance compared to adults,[121] doses do not need to be doubled.[119] Thiopental dose requirement varies among individuals, and titration to the burst suppression EEG pattern should take place, along with careful therapeutic drug monitoring.[124,125] Effective plasma levels vary between 15 and 35 mg/l (see Table 2 for a proposed dosing strategy).

DISCUSSION

This review shows an increasing interest in research on PICU sedation pharmacotherapy. Still, there is a lack of well-designed studies and consequently many practices are not yet evidence based. This type of research is complicated by different methods of sedation assessment, different pharmacokinetics in different age and weight categories, patient heterogeneity with multiple factors influencing the pharmacokinetics and also by ethical and practical considerations. For ethical reasons, drug studies cannot be performed in healthy children, which implies that illness severity will always be a confounding factor. On the other hand, for PICU practice, we only need information on critically ill children, and there should be always dealt with different severities of illness.

Traditional RCTs come with limitations as well. Results often apply only to a selective study population based on strict inclusion and exclusion criteria for the sake of internal validity. External validity is compromised, however, thus, pragmatic RCTs or cohort studies and well-designed titration studies with an objective and clear PD end point should complement classical RCT designs.[126] Moreover, using a classical RCT design with placebo as comparator is unethical in sedation research as then the control group may suffer profound anxiety and agitation. When it comes to safety, children should be followed for decades after drug exposure as long-term effects are important end points as well.[127]

PK-PD modelling might overcome several practical issues in paediatric drug research. While in the standard two-stage approach, individual values play a central role in determining PK parameters, and therefore, large patient samples are needed; the nonlinear mixed-effects models (NONMEM) approach provides a Bayesian-based prediction of PK parameters using population data.[128] This approach resulted in a new dosing regimen for morphine in infants[129] with much lower dosing than generally recommended so far, suggesting that neonates have been universally overdosed.

Improvements may also be made in the field of quantifying pharmacodynamics. A study in which the item response theory was applied to the COMFORT scale and the Premature Infant Pain Profile (PIPP) score made clear that the behavioural items corresponded better with pain and discomfort than did the physiological items.[130] A previous study has already made clear that the physiological items in the COMFORT scale have no added value,[10] but the item response theory with its more advanced statistical techniques allows calculating the probability of pain for each item. Thus, when using assessment scales consisting of more than one item, it would be worthwhile to collect data on each of the items rather than the total score only.

Another form of in silico experiments are PBPK models[73,131] representing a multicompartment model applicable to multiple drugs. Pharmacodynamics can be linked to such models by adding biophase concentrations, but only a few full PBPK-PD models have been developed so far for the administration of midazolam, theophylline, lorazepam and propofol to children.[73,132,133] The validity of these models should be evaluated further. As sedatives act on the CNS, evaluation requires obtaining brain tissue concentrations, which is not possible in routine critical care. Experimental strategies include calculations based on mass balance principles using the net flux of drugs (obtained from arterial and venous concentration differences)[134] or microdialysis.[135] Both strategies are invasive and therefore subject to practical objections and ethical considerations.

FUTURE PERSPECTIVES

Apart from optimal dosing strategies, new products may also improve pharmacological sedation management. A promising example is the ultra-rapid-acting benzodiazepine remimazolam,[136] which has a pharmacokinetic profile comparable to that of remifentanil, allowing for fast titration. It has only been studied in adults so far.

Monotherapy with remifentanil was found effective for long-term ICU sedation in adults.[137] In a paediatric study, remifentanil was as effective as fentanyl for sedation and analgesia and allowed for earlier extubation.[138] However, its use carries the risk of opioid-induced hyperalgesia (OIH) that is a phenomenon seen after opioid administration,[139] notably on account of its short half-life and fast onset of action.[140,141] It has been suggested that ketamine or clonidine as adjuvants could prevent the OIH,[142] but these agents may have unwanted side effects. Gradual remifentanil withdrawal has been suggested as well, but OIH was still observed after cold pressure testing in one study.[143] Moreover, chronic pain may develop after (prolonged) surgery,[144] so more data on these issues are warranted before it is regularly used in children.

In adult intensive care, volatile agents such as sevoflurane, desflurane and isoflurane have a favourable pharmacological profile with short elimination half-lives and low toxicity and could be suitable for long-term sedation.[145] These agents have not been studied in children so far. There is some concern that they may have adverse long-term neurological effects,[146–148] so more conclusive studies on the long-term effects of these agents are needed before efficacy trials may be performed.

CONCLUSION

A variety of sedatives are used in the paediatric intensive care unit, but evidence and pharmacokinetic data are still scarce. Fortunately, there is an active research scene which yields promising new PK and PD data using new study designs combined with advanced laboratory methods and modelling. However, pharmacology is not the only way that can lead to improved paediatric sedation management. We recommend that future research focuses also on sedation assessment and implementation strategies of protocolized sedation.

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3

Paracetamol and morphine for infant and neonatal pain; still a long way to go?

Manuel A. Baarslag, Karel M. Allegaert, John N. van den Anker, Catherijne A. Knibbe, Monique van Dijk, Sinno H. Simons and Dick Tibboel.

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ABSTRACT

Introduction: Pharmacologic pain management in newborns and infants is often based on limited scientific data. To close the knowledge gap, drug-related research in this population is increasingly supported by the authorities, but remains very challenging. This review summarizes the challenges of analgesic studies in newborns and infants on morphine and paracetamol (acetaminophen).

Areas covered: Aspects such as the definition and multimodal character of pain are reflected to newborn infants. Specific problems addressed include defining pharmacodynamic end points, performing clinical trials in this population and assessing developmental changes in both pharmacokinetics and pharmacodynamics.

Expert commentary: Neonatal and infant pain management research faces two major challenges: lack of clear biomarkers and very heterogeneous pharmacokinetics and pharmacodynamics of analgesics. There is a clear call for integral research addressing the multimodality of pain in this population and further developing population pharmacokinetic models towards physiology-based models.

INTRODUCTION

Only a few years ago, doses of commonly used drugs such as morphine and paracetamol (acetaminophen) in newborns and infants were based on extrapolated data from adults or older children. Sufficient knowledge about the efficacy, appropriate dosing, and safety of these drugs derived from properly designed studies has been lacking for years. However, dose validation and the beginning of formulation of evidence-based guidelines for these drugs have now been based on a number of clinical trials, population PK/PD studies, and research on pain assessment and long-term outcomes.[1-4] To understand the challenges in designing and conducting clinical investigations with analgesic medications in newborns and infants, it is important to learn from the previous successes and failures in this area. This review will describe and discuss the challenges of analgesic research in this population on different levels. We first discuss the pain definition and next address the issue of adequate pain assessment. With paracetamol and morphine as model drugs, we provide an overview of clinical trials so far, discuss the clinical pharmacology of these drugs as well as their short- and long-term effects. Special attention will be paid to premature neonates, as research in this population is even more challenging.

Pain

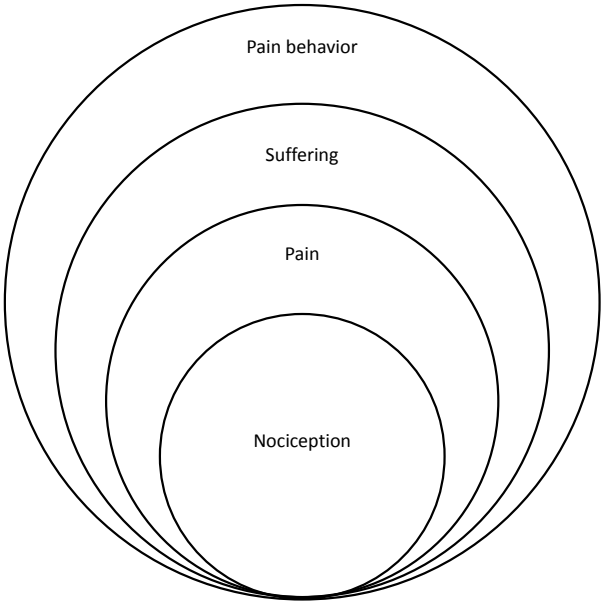
Definition of pain and its multimodality

The International Association for the Study of Pain (IASP) has provided the following definition of pain: 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.' They further state that 'pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life.' However, as this is not applicable to neonates and infants,[5] they revised this statement and added: 'The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.'

This definition aims to cover the multimodality of pain, as pain is more than nociception and/or perception of (possible) noxious stimuli alone. Loeser proposed a pain model which includes four components: nociception, pain, suffering, and pain behavior (see Figure 1).[6] Nociception refers to the detection of tissue damage by transducers connected to Aδ and C nerve fibers. The IASP defines this as 'the neural process of encoding noxious stimuli.' Pain occurs at the moment of perception, once the signal from the peripheral nerve system reaches the central nervous system (CNS). Pain can also occur without input from the peripheral nerve system, for example after CNS damage. Pain usually leads to suffering as described by Cassel[7]: a 'consequence of a physical or psychological threat to the integrity of the human being,' which has similarity with 'actual or potential tissue damage.' The fourth

component is pain behavior, which includes the whole spectrum from small moans in acute short-term pain to frequent doctor visits in cases of chronic pain. This behavior can be interpreted by others as having pain. Loeser's model makes clear that pain is a biopsychosocial phenomenon, not merely a biological one.

Figure 1. *Depiction of pain multimodality according to Loeser.*



Adapted with permission from: Loeser JD. Pain and suffering. Clin J Pain 2000; 16(2 Suppl): p. S2-6.

Types of pain

In neonatal and infant critical care, four different types of pain need to be distinguished:

- Procedural pain, acute pain caused by a short-term procedure such as venipuncture, heel lancing, or chest drain insertion/removal.
- Postoperative pain, defined as the pain experienced in the first 24–48 h after surgery.
- 'Prolonged' pain, a term increasingly used for pain with a duration >72 h and specifically for the neonatal population.[8,9]
- Chronic pain, defined as pain persisting beyond the expected tissue healing time. However, expected healing times are not clearly delineated. Thus, chronic pain was
- assumed to persist for time periods varying from 1 to 6 months,[10] but in general practice a duration >3 months is being used.

These types of pain are important when implementing pain assessment tools both in research and clinical practice. It is important to know for what type of pain a tool is validated.

Pain assessment and PD markers

Behavioral assessment tools

Taking the definition of pain into account, it follows that pain can be only reliably assessed by self-report. In preverbal infants, this is not possible and then we have to rely on the interpretation of pain behavior.

A great variety of pain assessment tools has been developed over the past decades and to date, more than 40 different tools are available just for pain assessment in neonates and infants.[11] Table 1 lists the validated observational pain assessment tools for the use in preverbal children, including their indication and age category for which it has been validated. These are recommended by several international guidelines.[12,13]

Table 1. *Validated pain assessment tools according to age and their indication.*

Pain assessment tool	Indication	Age category	Type of tool
Premature Infant Pain Profile (PIPP)[15-17]	Procedural and postoperative pain	Premature infants >24 weeks GA	Behavioral, contextual, physiologic parameters
Revised premature Infant Pain Profile (PIPP-Revised)[18,19]	Procedural pain	Premature infants >28 weeks GA	Behavioral and physiologic parameters
Neonatal Pain, Agitation and Sedation Scale(N-PASS)[20]	Procedural and prolonged pain Sedation level	Premature infants >23 weeks GA	Behavioral and physiologic parameters
COMFORTneo scale[21]	Prolonged pain Sedation level	Premature infants >24 weeks	Behavioral parameters
COMFORT scale[22,23]	Postoperative pain Sedation level	Children 0-18 years	Behavioral and physiologic parameters
COMFORT behavior scale[24]	Postoperative pain Sedation level	Children 0-3 years Children 0-18 years	Behavioral parameters
Faces, Legs, Arms, Cry, Consolability (FLACC) scale[25,26]	Postoperative pain	Children 2 months-7 years	Behavioral parameters
Multidimensional Assessment of Pain Scale (MAPS)[27]	Postoperative pain	Infants 0-31 months	Behavioral and physiologic parameters

GA: Gestational age

Physiology-based pharmacodynamic markers

As behavioral assessment tools are subjective to a certain degree, research efforts have been directed at identifying objective pharmacodynamic markers for the estimation of pain. Changes in vital signs, such as heart rate and blood pressure, do not serve as a link of pain neurobiology to pain behavior, as these autonomous responses to pain may be absent after a noxious stimulus.[23] Therefore, physiology-based markers such as near-infra-

red spectroscopy (NIRS), heart rate variability (HRV), skin conductance or pupillary reflex dilatation (PRD) have been studied but are not yet sufficiently validated. An overview is given in Table 2.

Table 2. Potential pharmacodynamic markers in neonates and infants.

Potential outcome measures	Advantages	Limitations
NIRS[28,29]	Non-invasive, continuously monitoring	Measures only cortical response;
aEEG[30]	Continuous monitoring	Not validated for pain in children <2 years
Skin conductance[31-34]	Non-invasive, continuously monitoring	Sympathetic activity may be caused by anxiety and/or distress as well
SSEP[35,36]	Non-invasive, continuously monitoring (when repetitive stimuli are being given)	Only reflects sensory response, not validated in infants
Pupillary reflex dilatation[37,38]	Promising bedside application in older children	Sympathetic activity may be caused by anxiety and/or distress, practical difficulties in infants
HRV (including ANI)[39-51]	Non-invasive, continuously monitoring	Sympathetic activity may be caused by anxiety and/or distress
fMRI[52,53]	Good overlap between findings in infants and adults, insight in pain beyond the sensory cortex	Not suitable for clinical application
Salivary cortisol levels	Non-invasive collection of sample	Delay in laboratory results
Plasma cortisol levels[54-56]	Suitable for both short- and long-term pain	Delay in laboratory results, sampling restricted in neonates
Plasma adrenalin levels[54, 57]		Delay in laboratory results, sampling restricted in neonates, less sensitive than noradrenalin
Plasma noradrenalin levels[54, 57]	Significantly reduced by analgesics	Delay in laboratory results, sampling restricted in neonates

Limitations of current pain assessment methods

On a critical note, the currently available pain assessment tools have a number of limitations. First, they cannot satisfactorily distinguish pain from anxiety, stress, or other emotional states.[57] Second, application of a particular tool in different contexts and circumstances, such as severity of illness and diagnosis, can be problematic. For example, lethargy, stiff limbs, minimal movement, and grunting all predict severity of illness,[58] but may significantly affect the total score. Third, they may be subject to a certain degree of subjectivity from the observer, who may or may not know how the child usually reacts to pain and may interpret certain behavior such as less movement as reflecting being comfortable, when in fact the child holds still because of pain.

Physiology-based assessment methods such as NIRS, skin conductance, and HRV also have their limitations. Overall, they measure either the sympathetic nervous system activity or a cortical brain response to a stimulus. Sympathetic activity may reflect pain, but is also associated with stress, anxiety, and delirium. Also, vasopressor agents may influence sympathetic tone. A cortical brain response to a stimulus may be indicative of nociception, but does not tell us directly whether a stimulus is perceived as painful. For example, in a study using NIRS,[27] cortical brain responses were not altered by the administration of oral sucrose solution, whereas observational pain scores decreased significantly.

Practical aspects of performing such measurements also impede the use of physiological tools. As an example, pupillometry can only be done in subjects with eyes opened. Infants are unable to collaborate and measuring the pupil diameter could become another stressful event. Last, amplitude-integrated electroencephalography (aEEG) measurement has been used for research purposes but has not yet been shown a useful marker for pain and analgesia in newborns and young infants.[59–62]

Item Response Theory

Pain assessment tools include several behavioral and/or physiological items. However, the items may not be indicative of pain to the same extent. Item Response Theory, an advanced statistical technique, could give insight in the informativeness of each separate item: the highest grade of intensity in one item may be more indicative of pain than the highest grade of another item. A recent study applied this technique to both the COMFORT scale and the Premature Infant Pain Profile (PIPP) in term and preterm neonates.[63] The behavioral items corresponded best with pain; physiological items did less. A similar pattern was previously reported,[21] and now advanced statistics show that high ratings of some behavioral items corresponded better with high pain levels than other items. This should be taken into account when using such a scale in new clinical trials, or when developing new observational assessment tools.

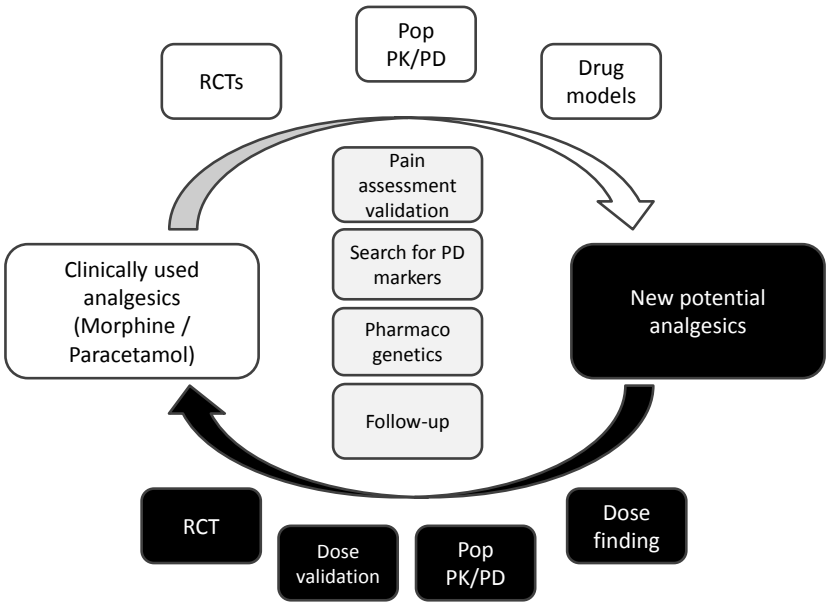
Despite numerous efforts to quantify pain, finding the optimal PD marker in infant pain studies remains a challenge.[64] We still have to rely on surrogate end points in neonatal and infant pain research. Beecher posed the problem of scientists' and clinicians' wishes to express subjective outcomes in objective measures research already 50 years ago and this problem has not yet been mitigated in infant and neonatal pain research.[65,66]

Clinical trials

Clinical trials to evaluate dosing, efficacy, and safety of paracetamol and morphine in infants and newborns have been performed rather unconventionally compared to the scientifically desired drug development process known from newly introduced drugs. Both

drugs are not new at all and were both given to newborns and young infants long before the first trials were performed. Several research groups started to evaluate the efficacy of analgesia during surgery[67] and ventilation[68] in the early 1990s. The first pharmacokinetic studies were also published.[69] Figure 2 presents a schematic overview of steps toward evidence-based pharmacotherapy (the desired way is illustrated by the black boxes) and illustrates that clinical research with morphine and paracetamol has followed the opposite way so far (as the white boxes indicate). The gray boxes indicate factors that influence the white and black boxes. These factors require further research to optimize analgesic research in neonates and infants.

Figure 2. *Schematic diagram of clinical research with morphine and paracetamol (white boxes) in practice.*



Black boxes represent new drugs to be studied. Dose finding and population PK/PD modelling with both internal and external validation into clinical practice will be possible. RCT: randomized controlled trial; pop PK/PD: population pharmacokinetics/pharmacodynamics; PCM: paracetamol.

Before those trials, it was generally believed that neonates were not capable of experiencing pain, therefore neonatal surgery often was performed without any analgesia.[70] Anand et al.[53] showed significantly lower hormonal stress responses in an analgesia group of operated newborns and better neurological outcome compared to placebo-treated neonates.

These findings raised public and scientific interest in neonatal and infant pain research.[71] Consequently, several analgesic trials were performed since. These trials compared for instance the short-term outcomes of continuous and intermittent postoperative morphine in newborns and infants,[72] postoperative rectal paracetamol vs. morphine,[73] and routine morphine with placebo during endotracheal ventilation in preterm newborns.[74] See Tables 3a and 3b for the randomized controlled trials (RCTs) performed. Studies involving neonatal abstinence syndrome or without analgesic end point (for example endotracheal intubation facilitation) were excluded.

In the earlier trials, dosing regimens were based on scarce neonatal pharmacokinetic data.[69,89] Later trials used dosages based on population PK/PD models derived from these early trials.[1,3] Besides optimizing dosing regimens in clinical practice, this evidence-based dosing improved the quality of analgesic clinical trials. In the Ceelie et al. trial[3] for example, a fairer comparison between paracetamol and morphine could be made, as morphine plasma levels across all ages were the same. In the Van der Marel et al. trial,[73] which found no beneficial effect of paracetamol, the analgesic effect of paracetamol could have been masked by relatively high morphine plasma levels as their study population was very young.

Pharmacokinetics/pharmacodynamics

One of the major challenges in neonatal and infant drug research is the rapidly changing pharmacology in this age group. Due to the rapid developmental changes in both the pharmacokinetics and the pharmacodynamics of a drug, a very heterogeneous population exists. These developmental changes will to a large extent determine the safety and efficacy of the studied drugs. Below, we will discuss the PK and PD of morphine and paracetamol as model drugs, to illustrate the importance of the changes throughout the first phase of life.

Morphine pharmacokinetics

Morphine metabolism

Drug metabolizing enzymes are classified by the reactions they catalyze: phase I reactions including oxidation, reduction, or hydrolysis and phase II reactions including glucuronidation, sulfation, methylation, or acetylation. Traditionally, phase I enzymes such as the cytochrome P450 system have received more attention in pharmacological research than phase II enzymes such as the uridine diphosphate glucuronosyltransferase (UGT) isoenzymes.[90] Morphine is glucuronidated by the UGT isoenzyme 2B7 into two active metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).[91]

Table 3a. Randomized controlled trials with morphine in the young pediatric population.

Authors	Year	Sample size	RCT study design	Outcome	Major limitation(s)
Barker et al.[76]	1995	27	Low vs. high loading dose diamorphine	Adequate analgesia in both groups, high loading dose produced greater respiratory depression	Pain was not the primary end point and assessed by hormonal stress response
Wood et al.[77]	1998	88	Morphine vs. diamorphine in ventilated preterm neonates	Reduced stress response in both groups, more hypotension in morphine group	High morphine dose: 200 mcg/kg in 2 hours and 25 mcg/kg.hr in preterm neonates Pain assessed by hormonal stress response, no placebo control group
Anand et al.[78]	1999	67	Morphine vs. midazolam vs. placebo in ventilated preterm neonates (NOPAIN pilot trial)	Morphine and midazolam reduced PIPP scores, only morphine improved neurological outcome	High midazolam loading dose and high morphine maintenance doses
Lynn et al.[79]	2000	83	Morphine continuous targeting predefined plasma level vs. intermittent bolus in infants postsurgery	Continuous morphine provided better analgesia, morphine dosing was higher	Power calculation performed on ventilatory end point
Van Dijk et al. [73]	2002	181	Morphine continuous vs. intermittent postsurgery aged 0-3 year	No difference in pain scores or morphine consumption	No power calculation performed
Simons et al.[75]	2003	150	Morphine continuous vs. placebo in ventilated preterm neonates	No beneficial effect on pain, less IVH in morphine group, comparable composite outcome	Rescue morphine not based on pain assessments
Anand et al.[80]	2004	898	Morphine continuous vs. placebo in ventilated preterm neonates (NEOPAIN trial)	No beneficial effect on neurologic outcome measures	High morphine dose, no baseline for primary composite outcome
Carbajal et al.[81]	2005	42	Morphine boluses vs. placebo for procedural pain	No adequate analgesia in morphine group	Continuous morphine used for procedure
Taddio et al.[82]	2006	132	Morphine vs. placebo vs. tetracaine for central catheter insertion in premature neonates	Beneficial effect of both morphine and tetracaine	Morphine infusion allowed during intervention

Table 3b. *Randomized controlled trials with paracetamol in the young pediatric population.*

Authors	Year	Sample size	RCT study design	Outcome	Major limitation(s)
Howard et al.[83]	1994	44	Paracetamol vs. placebo in neonates undergoing circumcision	Minimal effect of paracetamol	Sweet solutions (both PCM and placebo) may have biased the results Crying time as pain end point
Shah et al.[84]	1998	75	Paracetamol vs. placebo 90 minutes before heel lance	No effect of paracetamol	No validated pain assessment tool
Van der Marel et al.[74]	2007	54	Morphine vs. rectal paracetamol in postsurgery infants	No effect of paracetamol	High continuous morphine doses could have masked a clean paracetamol effect
Van Lingen et al.[85]	2001	122	Rectal paracetamol vs. placebo after vacuum extraction	No analgesic effect of paracetamol	No validated pain assessment tool, rectal administration unreliable in neonates
Bonetto et al.	2008	76	Oral glucose vs. oral paracetamol vs. topical EMLA vs. placebo	No effect of paracetamol	No comment on inter-observer variability of pain assessment tools
Badiee et al.[86]	2009	72	Oral paracetamol vs. placebo 90 minutes before heel lance	No effect of paracetamol	Time of administration could possibly be too early: no clear PK data on start of study
Manjunatha et al.[87]	2009	18	Oral paracetamol vs. oral morphine vs. placebo 60 minutes before ROP screening	No significant effect of morphine or paracetamol	Underpowered (calculated sample size was n=63)
Tinner et al.[88]	2013	123	Rectal paracetamol vs. placebo after forceps or vacuum extraction delivery	No effect of paracetamol	Only 2 doses of paracetamol: no steady-state
Seifi et al.[89]	2013	120	Oral acetaminophen vs. oral sucrose vs. placebo	No effect of paracetamol	Paracetamol administered 30 minutes before ROP screening
Ceelie et al.[3]	2013	71	Morphine vs. IV paracetamol in postsurgery infants	Significant reduction of morphine consumption	Single-center study

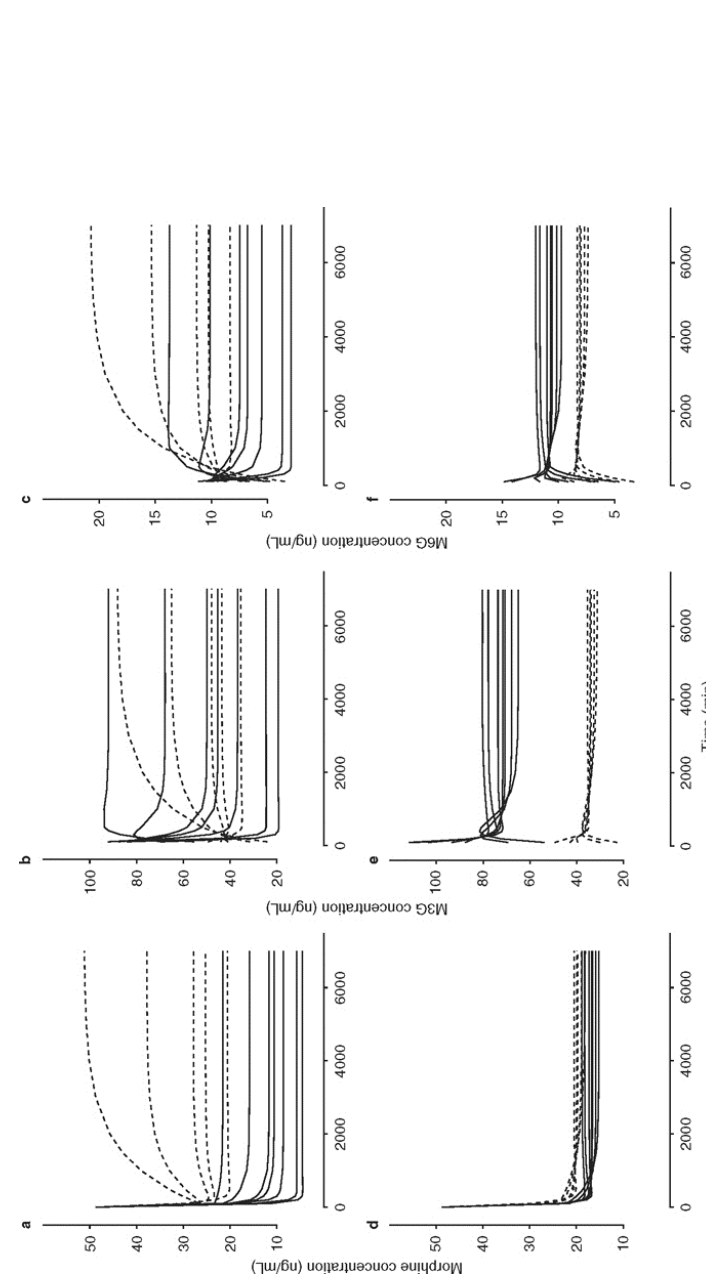
Maturation of morphine metabolism

Maturation of glucuronidation significantly influences the clearance of morphine in neonates, and most of the maturation process takes place in the first few months. A first indication came from the work of Lynn et al.[92] in a group of post-cardiac surgery newborns and infants. Morphine clearance (expressed per kg bodyweight) was reduced in the first month of life but then increased to above adult levels. This pattern has been confirmed by two models derived from nonlinear mixed-effects modeling[93] and clinical research, respectively. Bouwmeester et al.[94] described that neonates in the first week of life required less morphine and had higher morphine plasma concentrations than thereafter, at the same mg/kg dosing regimen. These findings led to the development of a pharmacokinetic model for children up to the age of 3 years, including preterm neonates.[2] This model shows that the morphine glucuronidation capacity and the clearance of the glucuronides are influenced by bodyweight in a nonlinear manner (bodyweight-based power equation with an exponential scaling factor of 1.44). Furthermore, before the postnatal age of 10 days, clearance and glucuronidation capacity was approximately 50% lower than thereafter. The resulting new model-based dosing advice recommended significantly lower doses, particularly for the youngest neonates, than the generally recommended 10–40 mcg/kg/h.[1] It is thought therefore that neonates, especially aged <10 days, frequently may have been overdosed worldwide because of their low glucuronidation capacity. Figure 3 illustrates the plasma levels of morphine, M3G and M6G with the old vs. the new dosing regimen.

Model-based dosing

As this increase in clearance at day 10 after birth may be considered an arbitrary cut-off, Wang et al. further evaluated morphine pharmacokinetics and, using a wider population, developed a bodyweight-dependent exponent (BDE) model. The BDE model predicted clearance across the entire pediatric age range better than the model with a fixed exponent of either 0.75, the 'classical' allometric scaling exponent, or the age-dependent exponent of 1.44.[95] While for neonates and infants below 1 year, the dosing schedule hardly differs between these two models, the next step in pediatric morphine research is evaluating this morphine dosing regimen based on the BDE model for other indications than postoperative pain after major noncardiac surgery.[1] An observational study, for example, showed that higher dosages for NEC are required, most likely because this is a very painful condition.[96] These studies are important because so far the model-based dosing guidelines[1,95] are only corrected for differences in PK and not for type of pain or severity of illness.

Figure 3.



(a, d) Morphine concentrations, (b,e) morphine-3-glucuronide (M3G) concentrations, and (c,f) morphine-6-glucuronide (M6G) concentrations predicted in model-based simulations in children weighing 0.5, 1, 2, 2.5 and 4 kg and a postnatal age of <10 days (dotted lines) and children weighing 0.5, 1, 2, 2.5,4, 10 and 17 kg and a postnatal age of >10 days (solid lines) based on (a–c) a dosing regimen with a loading dose of 100 mg/kg and maintenance dose of 10 mg/kg/h and (d–f) a regimen with a loading dose of 100 mg/kg followed by an infusion of 10 mg/kg1.5/h with a 50% reduction in the maintenance dose for children with a postnatal age <10 days. Reprinted with permission from: Knibbe, C.A, et al., Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. Clin Pharmacokinet, 2009. 48(6): p. 371–85.

Factors contributing to variability

Despite this progress in optimizing exposure to morphine in infants by correcting for structural pharmacokinetic differences as a result of developmental changes, there is still a large random variability in morphine clearance,[97,98] with the highest variability in critically ill neonates. This may perhaps be attributed to variability in hepatic and renal function and hepatic blood flow, which in turn are influenced by positive pressure ventilation.[99] Other factors such as therapeutic hypothermia,[100] extracorporeal membrane oxygenation (ECMO) treatment[101] or type of surgery[92] may also be influential.

Furthermore, it cannot be excluded that genetic differences play a role here. As an example, single-nucleotide polymorphisms (SNPs) in the gene encoding for UGT2B7 have been shown to alter the pharmacokinetic parameters in adolescents.[102] The drug transporter P-glycoprotein, also known as MDR1 or ABCB1, may alter pharmacokinetics of morphine,[103] as well as organic cation transporter 1 (OCT1) and ABCC3.[104] So far, however, the effects of pharmacogenetics on pharmacokinetics in children have been rarely studied. Large sample sizes are needed to demonstrate a significant contribution of certain SNPs, because some SNPs occur only in 1–5% of the population. Sufficiently large sample sizes can most likely be achieved only in (international) multicenter studies.

Plasma concentrations vs. CNS concentrations

While to date most developmental changes in plasma pharmacokinetics of morphine have been characterized, another source of variability could be the distribution into the CNS. As the blood–brain barrier (BBB) prevents a 1:1 concentration ratio of many substances between brain interstitial fluid and plasma, targeting certain plasma concentrations may not adequately reflect desired CNS concentrations. Therefore, insight in the transport of morphine and its active metabolites across the BBB will contribute to individualized dosing. So far, only a few pharmacokinetic studies have considered concentrations in the cerebrospinal fluid (CSF) in humans, and such studies in children are rare, and completely missing in preterm newborns.

One of the studies in adults showed an increase of the CSF:plasma morphine concentration ratio from 0.2 to 0.6 over a two-hour period.[105] Another study in patients with chronic use of oral morphine reported a ratio of 0.9,[106] suggesting that reaching a steady-state balance between both compartments takes some time. In children, only one study so far has linked serum and CSF concentrations of morphine[107] after a single infusion. The plasma:CSF concentration ratio was nearly 1:1 after 2 h. For M6G, this ratio remained about 10:1, as this metabolite is less lipophilic. This finding could be relevant, as it is being debated whether morphine itself or M6G is the most important pain relieving substance.[108,109] M3G, which circulates in substantially higher concentrations than morphine and M6G, is thought

to lead to adverse effects such as hyperalgesia, particularly upon prolonged use when this metabolite accumulates.[110,111] Studies have shown that M3G accumulates in critically ill patients, even after a 33% dose reduction.[111,112] Morphine plasma levels decreased, but M3G levels remained the same after this dose reduction, indicating that M3G could be highly responsible for side effects in this specific population. This is an important finding and the role of M3G in morphine safety should be studied further.

Even though attempts have been made to describe the CNS pharmacokinetics of morphine, the full picture is not yet clear. The BBB is changing throughout childhood, and the fact that the P-glycoprotein drug transporter is less readily available in the neonatal brain could mean an increase in diffusion of morphine into the brain.[103,113] Unfortunately, no human data are available to confirm this. Animal models using microdialysis have shown a higher morphine influx in premature sheep than in adult sheep.[114] Also, morphine efflux out of the brain is reduced in premature rats compared to adult rats.[115] In pigs, the plasma:CSF transfer ratio decreased from 0.7 to 0.5 during the first 6 weeks of life, which was not statistically significant.[116] Nevertheless, data of animal models cannot easily be extrapolated to humans, notably in view of the considerable differences in BBBs across species.[117] Moreover, it is very likely that the BBB and related morphine diffusion have undergone changes in CNS disorders such as meningitis and encephalitis.

Morphine pharmacodynamics

PK–PD relationship

The pharmacokinetic research described above centralized the plasma concentrations of morphine, but unfortunately the pharmacodynamic effects of morphine greatly vary between infants, even at similar plasma concentrations. It is known that analgesic needs in general depend on the type, severity and duration of pain. In relation to postoperative pain, morphine requirements depend on duration and severity of surgery but also on the type of surgery, such as cardiac or abdominal surgery.[3] Newborns operated for NEC need much higher morphine dosages postoperatively than newborns operated on for other conditions.[96]

Efforts to establish a minimal effective plasma concentration or a therapeutic window have not led to a clear target[118] and a concentration–response curve is lacking.[119] Future research should aim for specific plasma targets for different types of pain or procedures.

Development of morphine sensitivity

Postmenstrual age may play a role in morphine sensitivity, due to maturation of nociceptive pathways. Morphine exerts its effects mainly on the mu-opioid receptor and to a lesser extent on the kappa and delta opioid receptors.[120] Sensitivity to morphine seems to be higher at neonatal age, although this has been suggested merely in rat models.[121] However,

human neonates[3] below the age of 10 days needed significantly less rescue morphine than older neonates despite similar morphine plasma levels.[1] This could be due to less capability of pain expression, or to a higher BBB permeability for morphine. Another explanation may lie in the postnatal reorganization of opioid receptor expression. In rats,[121] during the first 3 weeks of rat life, the mu-opioid receptor expression is downregulated in the A fibers, but remains unchanged in the C fibers. Also, in this period, the central terminals of the A fibers are found in the superficial dorsal horn, whereas at adult age only C fibers project into the superficial dorsal horn and the A fibers project in the deeper lamina, suggesting a higher morphine sensitivity in the early weeks of life.

Pharmacogenetics

Pharmacogenetics may also play a role in morphine sensitivity. In human neonates, a combination of SNPs in two different genes, OPRM1 and COMT, was found associated with postoperative morphine consumption.[122] The same polymorphisms are associated with the severity of neonatal abstinence syndrome.[123] While OPRM1 is the coding gene for the mu-opioid receptor, COMT is a regulatory gene of mu-opioid receptor expression.[124] If both expression and function of the mu-opioid receptor are being disrupted by gene mutations, this could diminish the response to opioids.

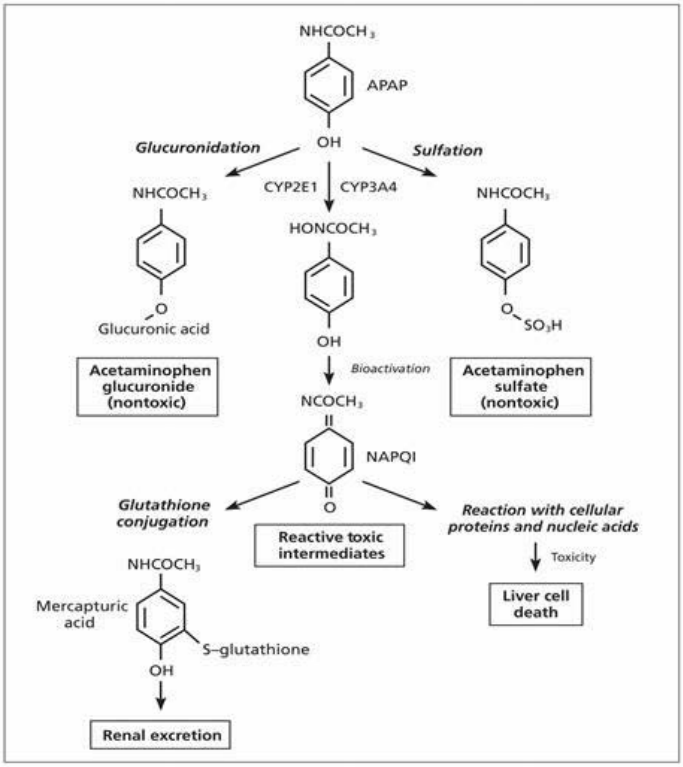
Paracetamol pharmacokinetics

Paracetamol is different from morphine with respect to safety and efficacy aspects. Paracetamol is a weaker analgesic, but on the other hand has a more favorable side effect profile. Still, the only side effect to take into account is probably more lethal than the opioid-induced respiratory depression, namely acute liver failure. In Western countries, paracetamol overdose is the most common cause of acute liver failure in adults and children.[125,126] However, when kept within the therapeutic range, paracetamol provides analgesia as well as antipyrexia.

Paracetamol metabolism

Paracetamol is mainly metabolized by phase II enzymes to paracetamol-glucuronide and paracetamol-sulfate. Only a small fraction (1–4%) is excreted unchanged by the kidneys. The remainder is being metabolized to the hepatotoxic metabolite NAPQI through the action of cytochrome P450 (CYP) enzymes such as CYP2E1, CYP1A2, CYP3A4, and CYP2A6.[127] Under normal circumstances, reduced glutathione (GSH) neutralizes NAPQI very rapidly and the inactive cysteine and mercaptopuric metabolites are being formed and excreted renally. See Figure 4 for the metabolic pathways of paracetamol.

Figure 4. *Metabolic pathways of paracetamol.*



Reprinted with permission from: Roofthooft, D.M.E., Paracetamol and Preterm Infants: a painless liaison? PhD thesis, 2015, Erasmus University.

Maturation of paracetamol metabolism

Glucuronidation of paracetamol is very low in preterm infants and matures during early childhood, thus simultaneously increasing the relative contribution to paracetamol elimination[128] whereas the sulfation route remains fairly constant.[129] CYP enzymes mature during early infancy as well, but data on NAPQI formation in neonates are lacking. One modeling study in 47 patients could not attribute any clearance to oxidative pathways.[128] However, as renal clearance is lower in neonates compared to adults, renal metabolite clearance may be reduced.[130] Expression of CYP2E1, the main isoenzyme responsible for NAPQI formation, increases during the first three postnatal months.[131] Whether NAPQI formation is reduced in this period remains unclear, but clinically there are no clues of NAPQI formation in neonates leading to hepatotoxicity, even at higher doses.[132]

The pharmacokinetics of paracetamol in children for different administration routes is well described.[133–138] Population PK studies showed that weight is the most important predictor of paracetamol clearance in neonates.[130,139] In a BDE model, this relationship was found to be nonlinear between children within the neonatal range and adults.[4]

Factors contributing to variability

There is, however, a great interpatient variability in paracetamol clearance.[129] For instance, clearance is lower in preterm neonates than in term neonates.[140] Paracetamol is being metabolized by many enzymes, thus the current role of pharmacogenetics is small. SNPs and mutations in metabolizing enzymes have been described, but often have not been studied in relationship to paracetamol.[141] Whether genetic variability influences the PK of paracetamol is hard to tell. If one or two metabolizing enzymes lose function due to genetic polymorphisms, other enzymes may take over. Differences in activity of transporters, epigenetic phenomena, and organ-specific activity of metabolizing enzymes probably all play a role. System biology-based modeling strategies may contribute to insight in the complex interactions between ontogeny, metabolic functions, and genetics.[142]

Paracetamol pharmacodynamics

Unknown site of action

While the pharmacokinetic basis for an evidence-based paracetamol dosing regimen has been established,[133–138] much groundwork remains to be done on the pharmacodynamics. For one thing, the exact mechanism of action remains unclear, even after comprehensive research.[127, 143] Its primary target has been suggested to lie within the CNS, as CSF concentrations corresponded better with analgesic response than did plasma concentrations.[144] In contrast, another study showed that analgesic response occurred earlier than changes in CSF plasma level.[145] A delay of the onset of action of the drug, a phenomenon called hysteresis, could perhaps explain why it is difficult to relate actual plasma and/or CSF levels to a pharmacodynamics end point such as temperature or pain score. Therefore, Gibb and Anderson recommend to use indirect-response models to describe paracetamol PK and PD.[146]

PK–PD relationship

As the mechanism of action is unclear, factors influencing the pharmacodynamic effects of paracetamol in children are hard to establish. The administration route, though, certainly has an impact on its effectiveness[3,73,137,147] because of more favorable pharmacokinetics of the oral and intravenous routes compared to the rectal route.

A dose-dependent response in children has been suggested when paracetamol was administered as treatment for both pain and fever.[148,149] In general pediatrics, an adequate analgesic target plasma level of 10 mg/L is suggested.[147] It is unclear whether this target fits neonates

and infants. Validation of these targets using validated assessment scales is necessary. Moreover, the question remains why there is a great variability in response. Whether this can be attributed fully to the action of paracetamol or to other factors such as the interpretation of the pain assessment tool needs to be studied further, especially as most trials studying the morphine-sparing effect of acetaminophen have been performed in older children.[150–152] Pharmacogenetics also does not help explain variability in response. This is mainly due to the lack of knowledge on the mechanism of action, impairing the search for relevant genes.

Short-term and long-term side effects

Morphine

Short-term effects

Morphine has several side effects, observed not only in adults but even more so in children and in neonates, such as respiratory depression, nausea, vomiting, constipation, urinary retention, and hypotension. Hypotension in neonates, who are more vulnerable to changes in blood pressure,[79] may have severe consequences such as intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL). On the other hand, pain leads to an increased blood pressure which could also contribute to these sequelae. In a large RCT, the incidences of PVL and IVH were significantly higher in the placebo group compared to the morphine group.[79] In another RCT using lower morphine doses, IVH was also less frequent.[74] These data implicate that adequate analgesia may protect the brain on the short term. Both clinical trials concluded, however, that routine administration of morphine in ventilated newborns should not be recommended.

An important challenge is detecting side effects of analgesics in neonates and infants, as these can overlap with symptoms of their underlying disease. Structural proactive screening for side effects should take place in analgesic trials in the neonatal and infant population.

Long-term effects

Drugs administered when the child's brain is still developing possibly interfere with neurodevelopment.[153–155] This may especially be applicable to opioids, which directly act on the CNS. Moreover, in premature neonates, this interference may be even larger as the third trimester of gestation is important in CNS maturation. The current literature is not consistent regarding the long-term outcome of neonates receiving opioids. Some studies suggest alterations in neurological anatomy or structure,[153,154,156] but neuropsychological outcomes seem to be not affected by morphine exposure at neonatal age.[154, 157,158] Follow-up trials cannot include a control group, as adequate analgesia is ethically obligatory and keeping neonates without opioids is highly undesirable. In the vulnerable preterms admitted to NICU who still receive a large amount of morphine,[159] morphine should not be considered the only causative factor for abnormal neurodevelopmental outcome.[156,160]

Schuurmans et al. suggest a more standardized approach with large patient samples to detect small outcome differences.[161] Data about analgesics and long-term effects from such large studies are not yet available. Standardization of long-term follow-up should include clinically relevant end points, preferably neuropsychological outcomes, especially executive function skills, as they determine a person's functioning in daily life.[158,162]

Paracetamol

Short-term effects

Paracetamol is regarded very safe on the short term. The major short-term side effect is acute liver failure, but no major hepatotoxic events have been reported so far in neonates.[132]

Long-term effects

Recent studies on atopy development associated with paracetamol exposure in early childhood are reason for concern[163–165] although they have important methodological limitations.[166,167] Prospective studies should be performed to establish this potential causal link.[168] Such trials should at least incorporate pharmacogenetic assessment,[169,170] although fundamental research on the mechanism(s) of action should pave the way for targeted pharmacogenetic research.

Long-term effects of pain

An important other challenge regarding the long-term effects of analgesics, is the long-term effect of pain itself. Pain exposure during early infancy also leads to alterations in brain structure[171,172] and affects pain sensitivity in later life.[173] Finding an optimal balance between accepting long-term opioid effects, on which the literature is still divided,[154,174,175] and the long-term effects of pain itself, is not yet feasible. Finding this balance could be supported by either more optimal dosing strategies, such as always starting with the lowest dose possible and up-titrate on the effect, taking into account inter-individual variability, or introducing alternative analgesics. This should be the aim of neonatal pain research in the near future, including larger sample size studies.

Premature neonates

Special attention should be paid to (extreme) premature neonates when it comes to both pain and developmental clinical pharmacology. In the vulnerable premature neonate, pain is not only 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage,' but is harmful on both the short and long term.[171–173] These children daily undergo many potentially painful procedures,[176–178] while it is still unclear how to prevent or treat this pain optimally. What is more, the developing brain of the preterm infant is probably extremely vulnerable for the toxic effects of pharmacological agents, such as morphine.[153]

Evidence from animal and human studies suggests an inverse relationship between postconceptional age and pain sensitivity, as measured by the reflex withdrawal test using von Frey hairs. However, whether this also means an increased pain sensation is doubtful as cortical pain responses seem to increase with increasing gestational age.[179] Nevertheless, little is known about the premature cortical pain processing and consequently the statement that (extreme) premature neonates feel more pain than their term peers is hardly based on solid methodological evaluation. At present, the techniques to investigate these phenomena are far from ideal. Therefore, investigators developed pain assessment tools based on the heel lance as a standardized painful procedure. Heel lancing is associated with an acute pain response that differs from more prolonged continuous distress and pain responses that are associated with preterm neonatal care.

The pain experienced by neonates should be treated with adequate analgesics and preferably be prevented using the concept of preemptive analgesia. Morphine is recommended in several guidelines for the treatment of severe pain in premature neonates.[12,180] The question arises whether the clearance of morphine differs between premature neonates and term neonates and if recommended doses can be used in extreme premature neonates. A recent study in extreme low birth weight neonates[181] compared five population PK models applied to their own prospective dataset of PK samples. The model based on data from extreme low birth weight infants[182] fitted best with their own dataset. The authors concluded that not only bodyweight but also maturation (including hepatic and renal function) contributes significantly to clearance, independently of bodyweight.

For paracetamol, clearance changes nonlinearly with bodyweight.[4] In premature neonates, the paracetamol clearance matures more slowly than morphine clearance, and this could be attributed to the complex metabolism of paracetamol.[139] However, robust PK data in extreme preterm neonates are scarce[183] and in this population, more research is warranted on PK and its relation with both the analgesic effects and short- and long-term neurodevelopmental outcomes.

EXPERT COMMENTARY

Neonatal and infant pain management and research have taken an extensive scientific journey so far. However, there is still a long way to go. The complex multimodality of pain comes along with major challenges in research. The first challenge is the assessment of pain. While current pain assessment tools merely reflect the outer circle of Loeser's pain model, i.e. pain behavior, opioids and paracetamol act mainly on the nociception circle or the pain circle. This means that end points in pain research in children can only be surrogate end points. To measure analgesic effectivity, we should aim at biomarkers reflecting the direct effect of analgesics in the CNS. Attempts have been made with pupillometry, skin conductance, and HRV. These physiological, objective markers reflect sympathetic nervous system activity and are closer to the CNS. NIRS and somatosensory evoked potentials reflect the perception of a stimulus by the CNS, and are therefore promising in pain research. Multimodal studies, such as performed by Slater et al.[27] and Hartley et al.[184] demonstrate lack of correlation between nociceptive brain activity and behavior at least in an experimental procedural pain study, which is a clear call for more clinical research.

The other major challenge is optimal pharmacological pain treatment. Healthcare professionals need to take two important steps: choosing the right drug and defining the right dose. In order to choose the right drug, it is necessary to define type of pain first. From the clinical trials performed so far in neonates and infants, it seems that morphine is not the best choice for procedural and chronic pain, but has proven effectiveness for postoperative pain. Many clinics use fentanyl as an alternative to morphine and fentanyl or alternatively one of the synthetic derivatives is proven effective for procedural pain. Paracetamol (Table 3b) seems to have no effect on procedural pain and a slight effect on postoperative pain. It is unknown whether it is effective for chronic pain. However, again it should be taken into account that these trials all have used surrogate end points and there is still a long way to go to determine true effectivity for each type of pain.

The choice of drugs is also heavily influenced by the safety profile, and both morphine and paracetamol have been ascribed long-term negative effects without convincing evidence.[156,160] These speculations call for well-designed trials with long-term outcomes as primary end points. Studies have been performed in different patient groups but with relatively small sample sizes and therefore underpowered to detect small differences in neurological outcome.[154,185,186]

Dosing is also a major challenge due to both the rapid changing pharmacokinetics and pharmacodynamics in neonates and infants. Many population-based pharmacokinetic models have been developed for this population and have provided important data on the maturation of drug clearance. Still, there is no clear PK–PD relationship for morphine. PK is mainly focused on plasma levels, but PD effects are the result of morphine levels in the CNS. Further insight in the plasma–CNS relationship is necessary to define target plasma levels. The same holds for paracetamol, for which the PK is well described for term neonates and infants but a PK–PD relationship also has great variability.

FIVE-YEAR VIEW

Pain assessment could possibly be improved by techniques reflecting CNS activity such as NIRS[27,28] or aEEG,[29] although the analyses and interpretations of these techniques are yet far from optimal to recommend their clinical use as pain measurement instruments. Functional MRI seems a promising method to look for specific brain areas involved in pain processing and the role of analgesics on these pain areas. Still, it should be kept in mind that activity in these areas does not always reflect pain, as these areas are also responding to stimuli in patients not capable of experiencing pain.[187] This technique should be further developed and applied in order to compare the 'true' effect of different analgesics, and comparative studies with both behavioral assessment tools, fMRI and/or NIRS/SSEP/aEEG may provide further insight in how to optimize pain assessment. Meanwhile, behavioral pain assessment tools are not to be forgotten. Application of the Item Response Theory[63] may identify the most pain-specific items of pain assessment scales and further improve bedside pain assessment.

Furthermore, interactions between analgesics, for example paracetamol and opioids, deserve attention. A study already found that the use of paracetamol could reduce infants' opioid consumption by 66% after major noncardiac surgery.[3] In our center, a similar trial is ongoing in cardiac surgery patients (the PACS trial; Dutch Trial Registry ID NTR5448). Trials like these could be a great opportunity to address the issue of long-term effects of both analgesics.

The increasing knowledge of the ontogeny of drug metabolizing enzymes and drug transporters provides a good basis for a system-based approach of pediatric pharmacokinetics. This approach enhances the development of both individualized evidence-based pharmacotherapy of currently existing drugs and new analgesic drugs for children. Knowledge gained in the pharmacokinetic modeling of one drug could be applicable to other drugs as well. When specific properties such as logP and pKa of other drugs are applied to such models, clearance of these drugs can be predicted. Building such physiologically based pharmacokinetic models may save the tremendous effort of describing PK of all drugs separately.[188]

Other analgesics are also being introduced to neonatal and infant pain management. This review focused on morphine and paracetamol as model drugs, but fentanyl is also often used in the NICU.[12,189,190] Current use of fentanyl is based on little evidence, and its PK is highly variable in preterm neonates.[191] Studies performed with fentanyl are small.[192–194] This is a problem in most clinical trials involving neonates, especially in the NICU population. Therefore, to improve clinical research in this population, multicenter studies, if possible in established international consortia, could increase sample sizes. If this is not feasible, the required sample size may be reduced with the use of comparative effectiveness studies rather than superiority trials.[195]

Another opioid which seems promising, especially for application in procedural pain, is remifentanil.[196–198] This very-short-acting opioid is being metabolized by plasma esterases, independent of organ function or age. However, it does not automatically 'do away with' the dosing problem as its side effects such as chest wall rigidity can be age dependent.[197] Caution is required with the clinical application of remifentanil.

Last, the focus should be set on long-term effects. We do not know yet which analgesic is most harmful in the long term, but must not forget pain is harmful anyway. Finding the optimal balance remains challenging[199] and calls for standardized long-term follow-up in neonatal pain trials.

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PART II

CHALLENGES IN PEDIATRIC PAIN AND SEDATION RESEARCH

4

The CLOSED trial; CLOnidine compared with midazolam for SEDation of paediatric patients in the intensive care unit: study protocol for a multicentre randomised controlled trial

Antje Neubert, Manuel A. Baarslag, Monique van Dijk, Joost van Rosmalen, Joseph F Standing, Yucheng Sheng, Wolfgang Rascher, Deborah Roberts, Jackie Winslade, Louise Rawcliffe, Sara M. Hanning, Tuuli Metsvaht, Viviana Giannuzzi, Peter Larsson, Pavlá Pokorná, Alessandra Simonetti and Dick Tibboel; on behalf of the CloSed Consortium.

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ABSTRACT

Introduction: Sedation is an essential part of paediatric critical care. Midazolam, often in combination with opioids, is the current gold standard drug. However, as it is a far-from-ideal agent, clonidine is increasingly being used in children. This drug is prescribed off-label for this indication, as many drugs in paediatrics are. Therefore, the CLOSED trial aims to provide data on the pharmacokinetics, safety and efficacy of clonidine for the sedation of mechanically ventilated patients in order to obtain a paediatric-use marketing authorisation.

Methods and analysis: The CLOSED study is a multicentre, double-blind, randomised, active-controlled non-inferiority trial with a 1:1 randomisation between clonidine and midazolam. Both treatment groups are stratified according to age in three groups with the same size: <28 days (n=100), 28 days to <2 years (n=100) and 2–18 years (n=100). The primary end point is defined as the occurrence of sedation failure within the study period. Secondary end points include a pharmacokinetic/pharmacodynamic relationship, pharmacogenetics, occurrence of delirium and withdrawal syndrome, opioid consumption and neurodevelopment in the neonatal age group. Logistic regression will be used for the primary end point, appropriate statistics will be used for the secondary end points.

Ethics: Written informed consent will be obtained from the parents/caregivers. Verbal or deferred consent will be used in the sites where national legislation allows. The study has institutional review board approval at recruiting sites. The results will be published in a peer-reviewed journal and shared with the worldwide medical community.

INTRODUCTION

Unlicensed and off-label drug use

In Europe, <30% of marketed drugs include results from paediatric clinical trials and other information on paediatric use in their documentation (Summary of Product Characteristics (SPC) or Product Leaflet).[1] This results in widespread off-label use in paediatrics, especially in the case of old drugs that have never received a paediatric authorisation. Off-label paediatric use (including all the uses not listed in the SPC[2]) in Europe accounts for 45%–60% of the total number of prescriptions, with rates of up to 90% in patients admitted to neonatal (NICU) or paediatric intensive care units (PICU).[3]

The entry into force of the Paediatric Regulation in 2007[4] gave an important stimulus to support the development of medicines for children by introducing a specific measure to favour work on off-patent medicines, the so-called Paediatric Use Marketing Authorisation (PUMA). A PUMA application should include the submission of paediatric data in accordance with an agreed Paediatric Investigation Plan (PIP).

According to article 40 of the Regulation, the European Commission (EC) reserved funds 'to develop off-patent medicinal products with recognised therapeutic interest for children and included in a 'Priority List' adopted by the European Medicines Agency (EMA) through its Paediatric Committee (Seventh Framework Programme for Research HEALTH—(2007–2013) Programme area—topic 4.2–1). Among 20 projects approved,[5] the CLOSED project was granted with the aim to develop an age-appropriate formulation of clonidine for sedation in PICU, in line with the EMA 'Revised Priority List for Studies into Off-Patent Paediatric Medicinal Products' 2012.[6] In order to specifically meet this therapeutic need, a comprehensive development plan in the form of a PIP was submitted to the EMA Paediatric Committee (PDCO) in July 2012 and approved in January 2013. In March 2015, a modification of the PIP was proposed after the finalisation of the clinical study protocol. This modification was approved by the PDCO in August 2015.

Analgosedation in PICU

Approximately 2% of all paediatric patients admitted to hospital require treatment in PICU.[7] Most PICU admissions are unplanned emergencies, mainly in the context of congenital heart diseases (40%), respiratory diseases (20%), major trauma (15%) and neurological problems other than trauma (<10%).[8]

Often, mechanical ventilation is required for facilitating recovery after major surgery or for treating respiratory failure. In most of these cases, analgosedation using potent opioids and sedatives is mandatory to reduce metabolic rate and oxygen demand, assist mechanical

ventilation, avoid inadvertent self-extubation and lower anxiety and distress.[9,10] To this effect, a variety of agents are used in NICU and PICU, such as opioids, GABA-receptor agonists, N-methyl-d-aspartate receptor (NMDA)-receptor antagonists and α2-receptor agonists.[11]

Opioids

The main opioids used in PICU and NICU are morphine, fentanyl and remifentanil. Opioids bind to the μ-receptor in the central nervous system (CNS), and provide analgesia as well as sedation.

GABA-receptor agonists

GABA receptors have an inhibitory effect on the CNS. Benzodiazepines agonise these receptors and therefore have sedative, anxiolytic and anticonvulsant properties. Disadvantages are paradoxal reactions (agitation and confusion) and tolerance and withdrawal after prolonged use.

Propofol is a unique agent with GABA-ergic properties as well as anti-NMDA and sodium channel blocking effects. Propofol is not suitable for long-term sedation, due to the perceived risk of propofol infusion syndrome, a metabolic derangement accompanied by severe metabolic acidosis, hyperkalaemia, hyperlipidaemia, rhabdomyolysis and organ failure, associated with an increased risk of mortality.[12]

Midazolam

Midazolam is the most widely used sedative agent in PICU. It is a short-acting benzodiazepine (Tmax of 5–10 min after intravenous injection) with a half-life of 1–3 hours (up to 12 hours in neonates). Besides sedation and anxiolysis, midazolam also provides anterograde amnesia, thus minimising children's recall of unpleasant experiences after a PICU admission.[13] Midazolam is mainly metabolised to the equipotent metabolite 1-OH-midazolam (1-OH-MDZ), and then glucuronidated to the renally excreted 1-OH-MDZ-glucuronide. Its main adverse effects include tolerance, dependence and withdrawal syndrome following discontinuation.

Clonidine

Clonidine agonises the α2-adrenergic receptor. The reduced sympathetic outflow[14] in the CNS results in sedation, anxiolysis and analgesia.[15,16] Because of its analgesic properties, it has been used as an adjunct in surgical procedures as premedication or as a supplementary agent in regional anaesthesia.[17] The reduction of sympathetic outflow associated with clonidine may have specific benefits in critically ill children. A2 agonists can improve neurological outcome associated with ischaemic cerebral injury,[18–20] the mechanism of action

of which is unclear but may be due to suppression of extracellular glutamate and aspartate release during energy failure.[21] Recent data have also demonstrated that preconditioning before the insult can both reduce infarct size and improve neurological outcome after the insult.[22] Surgery and critical illness are associated with a variety of stress responses, which can result in organ dysfunction[23]: renal function deteriorates after both adult and paediatric cardiac surgery, and this effect is due in part to the increase in sympathetic outflow and the rise in circulating vasoconstrictors such as norepinephrine, vasopressin and angiotensin.[24,25] Clonidine has been demonstrated to suppress these responses and prevent the associated decline in renal function after adult cardiac surgery.[26] In addition, clonidine has independent local effects on tubular function which promote both diuresis and natriuresis.[27] In terms of cardiovascular responses, reduction in stress responses by α2-agonists have been shown to reduce perioperative myocardial ischaemia in adults undergoing cardiac and non-cardiac surgery.[28] As the mechanism of action of clonidine is very different from the GABA-agonist midazolam, the hypothesis is postulated that it may be less associated with paediatric delirium and withdrawal syndrome. Moreover, clonidine is one of the agents used for the treatment of withdrawal syndrome.[29]

Previous clinical trials

Clonidine is commonly used off-label in paediatric anaesthesia and intensive care medicine. Its use is recommended for the sedation of critically ill children in PICUs by the UK and German consensus guidelines[12,30] and local hospital guidelines across Europe. Unfortunately, despite this widespread use of clonidine, there are limited data on efficacy, dose requirement and safety when used for sedation on PICUs. A number of studies have been performed,[31–35] however, to overcome this knowledge gap (see table 1 for a short overview).

Study aims

For the purpose of sedation of intubated and mechanically ventilated paediatric patients, this clinical study sets out to provide the data needed for a PUMA application for the use of clonidine in PICU patients: Data on efficacy and safety of clonidine compared with midazolam.

Pharmacokinetic (PK) data on both clonidine and midazolam in critically ill children and adolescents, using a population-based approach. Together with the development of age-adapted and weight-adapted formulations of clonidine, as part of this study, data on quality and stability of these new formulations will also be generated.

Table 1. An overview of paediatric studies involving clonidine for sedation in the intensive care unit.

Study	Sample size and age	Design	Outcome
Ambrose et al.[31]	N=30, 0-10 years	Three-step: IV low-dose vs. high-dose (variable dose together with midazolam), 3rd group fixed dose	No adverse effects on haemodynamics, sufficient sedation in combination with midazolam
Arenas-Lopez et al.[32]	N=24, 0-5 years	Prospective cohort study, oral clonidine as additive to morphine/lorazepam	Opioid- and benzodiazepine sparing, safe and effective
Wolf et al.[33]	N=129, 0-15 years	Double-blind, randomised controlled trial of IV clonidine vs. midazolam	No difference in effectivity, underpowered due to recruitment problems
Hünseler et al.[34]	N=219, 0-2 years	Double-blind, randomised controlled trial of IV clonidine vs. midazolam	Opioid- and benzodiazepine-sparing in neonatal age group
Duffett et al.[35]	N=50, 0-18 years	Double-blind, randomised controlled trial of oral clonidine vs. placebo in addition to physician-driven sedation	No significant difference in effectivity, study with clonidine clinically feasible

METHODS/DESIGN

Study design

The CLOSED study is a multicentre, double-blind, randomised, active-controlled non-inferiority trial with a 1:1 randomisation between clonidine and midazolam. Both treatment groups are stratified according to age in three groups with the same size: <28 days (n=100), 28 days to <2 years (n=100) and 2–18 years (n=100). The primary end point is defined as sedation failure within the study period.

Patient recruitment

Patients in five different European Union (EU) member states (Czech Republic, Germany, Italy, The Netherlands and Sweden) will be recruited. Patients (neonates ≥34 gestational weeks and children <18 years) eligible for inclusion in the trial, according to inclusion and exclusion criteria, will be screened for possible enrolment (see table 2 for inclusion and exclusion criteria).

Surgery schedules will be screened on a daily basis for possible patients expected to be admitted to the intensive care unit (ICU). These patients and parents will be identified, approached, informed and enrolled prior to surgery by study responsible doctors and/or nurses. Patients eligible for inclusion transferred to the centres will be identified by the transport team. Patients admitted to the PICUs will continuously be screened by PICU medical staff to identify patients possible for enrolment. Parents of these eligible patients will be approached, informed and enrolled by study-responsible doctors and/or nurses.

Table 2. *Inclusion- and exclusion criteria for the CLOSED trial.*

Inclusion criteria	**Exclusion criteria**
Aged from birth (GA ≥34 weeks) to <17 years, 11 months and one week	Body weight <1200 g or GA <34 weeks
(Expected) admission to the PICU	Body weight ≤3 kg AND age ≥28 days Body weight <10 kg AND age ≥2 years Body weight >85 kg
(Expected) indication for mechanical ventilation (both invasive and non-invasive)	Clonidine within last 7 days prior to admission* Sedation >72 hours prior to screening
Anticipated need for continuous sedation ≥24 hours	Known hypersensitivity to clonidine, midazolam, morphine or propofol or any of their formulation ingredients and their rescue medication
Informed consent (or deferred consent if applicable)	Administration of continuous muscle relaxants or other contra-indicated drugs
Informed assent if applicable	Post-resuscitation within 24 hours or therapeutic whole-body hypothermia
	CPAP or ECMO treatment
	Severe organ insufficiencies: • Renal failure according to pRIFLE[63] or nRIFLE[64] criteria • Cardiac failure as defined by modified Ross class 3 or 4 • Arterial hypotension according to guidelines[62] • Circulatory failure as defined by Goldstein criteria[59]**
	Traumatic brain injury or other intracranial pathology including mental retardation and status epilepticus
	Phaeochromocytoma, acute asthma or paralytic ileus***
	Severe bradyarrhythmia
	Pregnancy
	Known arterial hypertension in medical history
	Previous participation in this trial at any time or previous participation in drug trial within last 3 weeks
	Declined informed consent from parent(s)/legal guardian(s)

CPAP: continuous positive airway pressure; ECMO: extracorporeal membrane oxygenation; GA: gestational age.

**) This exclusion criteria has been removed in the second protocol amendment*

***) These criteria have been modified in the second protocol amendment and allow for use of inotropes/vasopressor drugs*

****) The exclusion criteria acute asthma and paralytic ileus have been removed in the second protocol amendment*

Children are often admitted to PICU/ NICU in an emergency setting. Urgent action will most likely be required and the subject's parent(s)/legal guardian(s) may not be immediately available to give consent. An example of this is when a critically ill baby is delivered by

caesarean section, the mother may still be under anaesthesia while another parent/legal guardian of the child may not be present. Therefore, given the nature of the trial, especially considering that ICU patients are often admitted as a result of emergency, deferred consent/assent, as described in Article 35 of the new European Regulation on clinical trials (EU) No 536/2014 of the European Parliament and of the Council,[36] is foreseen if allowed by local legislation, as described in section 'Ethical considerations'. This allows for the child to be enrolled in the trial before the parent(s)/legal guardian(s) are able to give consent, which is then sought once they are available. If, subsequently, deferred consent is withheld, the subject is removed from the study but a record will remain in the subject's medical notes.

Study treatments

First, it was necessary to define the dosing scheme so that appropriate drug concentrations could be used to maintain double blinding. A plasma clonidine concentration of around 2 μg/L gave adequate sedation combined with morphine infusion in ventilated PICU patients,[32] and 2 μg/L clonidine concentration also drops the Bispectral Index to 71 in adults.[37] Clonidine has a long elimination half-life (16.9 hours in neonates, 11.4 hours in infants and 7.4 hours in children[38]), so loading doses are proposed. It was therefore decided that loading and maintenance doses aimed at achieving steady-state concentrations of around 2 μg/L would be aimed for, and this scheme was designed by a PK/pharmacodynamic (PD) expert working group within the CLOSED consortium. Based on these doses, a similar dose scheme of midazolam was designed that would maintain double blinding.

The agreed dosing scheme consists of 15 min loading doses followed by a maintenance infusion rate. Increases or decreases, based on the evaluation of COMFORT-B and Nurses Interpretation of Sedation Score (NISS) score, in infusion rate are permitted, and preceding any increase, a loading dose over 15 min is specified. There are also compulsory lock-out times between each dose escalation or de-escalation to allow for new steady-state conditions to be approached. Participants will follow the dosing regimen, with 1 unit meaning 1 μg for clonidine, or 100 μg for midazolam:

First bolus (T=0). Initial loading dose is 2 units/kg over 15 min and the following continuous infusion 1 unit/kg/hour will be administrated to all patients followed by 15 min lock-out period.

Second bolus. If insufficient sedation after the first lock-out period, the second loading dose is 2 units/kg over 15 min and the following continuous infusion 1 unit/kg/hour will be administrated with a 15 min lock-out period.

Third bolus. If insufficient sedation after the second lock-out period, the third loading dose is 2 units/kg over 15 min and the following continuous infusion 1.5 units/kg/hour will be administered with a minimum of 105 min lock-out period.

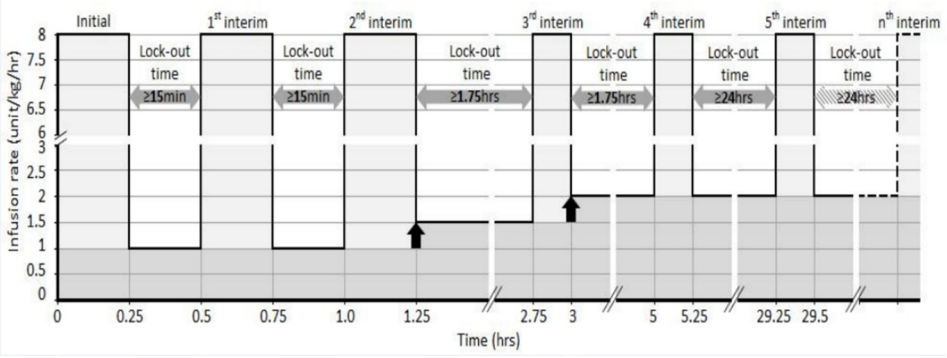
Fourth bolus. If insufficient sedation after the third lock-out period, the fourth loading dose is 2 units/kg over 15 min and the following continuous infusion 2 units/kg/hour will be administered followed by a 105 min lock-out period.

Fifth bolus. If insufficient sedation after the fourth lock-out period, the fourth loading dose is 2 units/kg over 15 min and the following continuous infusion 2 units/kg/hour will be administered with 24 hours lock-out period.

Sixth to 11th bolus. If insufficient sedation after 24 hours lock-out period, the 6th–11th loading dose of 2 units/kg over 15 min and the following continuous infusion 2 units/kg/hour would be administered with at least 24 hours lock-out period between.

All doses are halved in patients younger than 1 month. Figure 1 shows the scenario of all loading doses of study drug administered for subjects. Decreasing the maintenance dose will be possible in the case of oversedation (i.e., COMFORT-B >22 OR COMFORT-B=11–22 and NISS=3).

Figure 1. *Minimum time line of infusion rate increases for all loading doses of IMP administered for subjects (half doses in neonates).*



Following steps will be taken to decrease the dose (doses are halved in neonates):

- 2 units/kg/hour will be decreased to 1.5 units/kg/hour.
- 1.5 units/kg/hour will be decreased to 1 unit/kg/hour.

- 1 unit/kg/hour will be decreased to 0.75 units/kg/hour.
- 0.75 unit/kg/hour will be decreased to 0.5 units/kg/hour.

If patients are still oversedated with the minimum dose, the Investigational Medicinal Product (IMP) administration will temporarily be stopped until patients need sedation again, and they will start back at T=0.

During the preparation of the trial, the consortium faced one unknown challenge. In V.1.0 of the protocol, dose reduction should be performed when a child is oversedated. After 30 min, a new sedation assessment should be performed and acted on the same. In an oversedated child, this could lead to a child being without IMP after 90 min (three dose reductions). This is certainly not a desirable situation, but not unthinkable as the half-life of both drugs are longer than 90 min. Therefore, a 6-hour observation period has been implemented. After a dose reduction, it is recommended to wait for 6 hours before the next dose reduction.

In this same amendment, another problem has been mitigated. Version 1.0 did not provide clear information about increasing the dose again after a prior decrease. In the amendment, it has been made clear that subjects having a decrease of maintenance infusion to <1 unit/kg/hour will return to 1 unit/kg/hour, irrespective of the current infusion rate. If the decrease has been made while increases before have led to a maintenance infusion rate of ≥1 unit/kg/hour, re-increase will be following the precedent step (e.g., if a decrease has taken place from 1.5 to 1 unit/kg/hour, re-increasing will return the rate back to 1.5 unit/kg/hour).

Pharmaceutical development

To overcome the potential for administration errors associated with commercially available clonidine ampoules, three different strengths of clonidine HCl—low (250 µg/50 mL), medium (500 µg/50 mL) and high (2500 µg/50 mL)—have been developed. Based on the dosing regimen described above, the concentrations of the low, medium and high strengths of midazolam (25 mg/50 mL, 50 mg/50 mL and 250 mg/50 mL) were 100-fold higher than for clonidine HCl. For study blinding purposes and to avoid dosing errors, a simple three-colour scheme based on strength will be used.

To avoid the administration of preservatives, all formulations will be stored in single-use glass phials, with any contents remaining after 24 hours to be discarded. A 50 mL volume has been selected to limit the number of children requiring more than one phial in 24 hours (only subjects weighing over 46 kg and receiving the maximum dose in 24 hours will require two phials in a 24-hour period).

Efficacy end points

Level of sedation was evaluated using the COMFORT-B score (ranging from 6 to 30), which is a validated scoring system commonly used in PICU.[39] Level of sedation was also evaluated by NISS when the COMFORT-B score fell between ≥11 and ≤22. NISS is the nurse's expert opinion of the level of sedation (1: insufficient sedation; 2: adequate sedation; 3: oversedation). A subject is considered to be undersedated in cases of COMFORT-B score of >22; or COMFORT- B score of 11–22 in combination with NISS of 1.

In addition to COMFORT-B score (and NISS where appropriate), pain was assessed using the Numerical Rating Scale (NRS) at the same time intervals. The 11-point NRS is a global pain rating scale with which the nurse rates pain intensity by number (0=no pain and 10=worst imaginable pain).[40] In this study, to simplify matters, the NRS score was addressed first, so, if the pain score was ≥4, morphine treatment was escalated while sedation treatment remained the same, regardless of the COMFORT-B score. This means that any pain score took precedence over the sedation score.

Primary objective

To assess the non-inferiority of the sedative properties of continuous intravenous clonidine compared with continuous intravenous midazolam in mechanically ventilated children and adolescents (0–18 years) admitted to a PICU.

Primary end point

The primary end point is defined as sedation failure within the study treatment period (a maximum of 7 days). Sedation failure is defined as:

When a subject's assessment results are:
NRS score <4 and COMFORT B score >22 OR
NRS score <4 and COMFORT B score ≥11 and ≤22 AND NISS score 1 at a point during the study where no further increase in IMP dose are permitted as described in the dose-escalation scheme.
In summary, there are two possible outcomes (success or failure) of the primary end point.

Secondary objectives

- To evaluate the safety and tolerability (including withdrawal effects) of clonidine compared with midazolam in ventilated children and adolescents admitted to PICU.
- To determine clonidine dose-dependent effects on sedation.
- To establish the PK/PD relationship of clonidine for sedation in PICU.
- To compare the cumulative total morphine consumption/kg between the two arms in the first 48 hours of IMP administration.

Secondary end points

Primary PK parameters estimated will be clearance (CL), volume of distribution (VD) and intercompartmental clearance (Q). PK measurements will be made using sparse opportunistic sampling.

PK/PD modelling will seek to elucidate the relationship between IMP PKs and sedation as measured by COMFORT-B score. The PK/PD covariate model will include demographics (e.g. age, weight), clinical characteristics (eg. reason for admission) and pharmacogenomics (see the 'Pharmacogenomic end points' section).

Safety and tolerability assessments

Safety and tolerability assessments include:

Extent of withdrawal effects using the Sophia Observation withdrawal Symptoms-Paediatric Delirium (SOS-PD) scale measured three times a day in subjects who receive sedatives and/or opioids for 5 days or more and after cessation of treatment in all subjects for at least 24 hours after treatment. The extent of delirium measured by the SOS-PD scale.[41]

- Rebound hypertension monitored for at least 72 hours postcessation of treatment.
- Percentage of respiratory depression per group.
- Adverse event reporting of symptoms indicative of post-ICU stress (e.g. nightmares, confusion, hallucinations).
- Neurodevelopment of subjects recruited in lower age group (from birth to 27 days) at 12 months after cessation of IMP, as measured using the Bayley II score.[42]

Effect size justification

The primary objective of this study is to evaluate the efficacy of clonidine compared with midazolam in the sedation of ventilated children and adolescents admitted to PICU, with a view to demonstrate non-inferiority of clonidine.

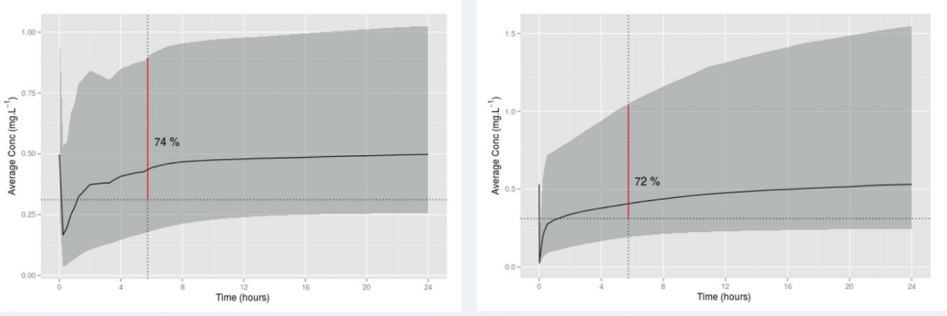
Every patient enrolled will be in need of sedation, thus a placebo cannot be considered. Intravenous midazolam is the standard treatment for long-term sedation in children. It is licensed in this population, regarded as standard of care and recommended by treatment guidelines.[12,30]

Based on clinical experience and the limited data available regarding the use of clonidine as a sedative agent in PICU, it is assumed that the sedation success rate for clonidine is higher than for midazolam. The estimated difference in success rate between the two drugs was assumed to be 5%.

The primary end point is the success or failure of the subject's sedation treatment. Failure is defined as inadequate sedation with no further dose increases allowed in the dose titration scheme. This will be assessed by a nurse or physician using the COMFORT-B sedation assessment and, if appropriate, NISS. These assessment scales are open to a degree of subjectivity and it is therefore considered essential to have a double-blind study design to minimise bias due to knowledge of treatment group by the assessor.

In order to define the effect size, the expected success rate for midazolam was needed. The target concentration for midazolam was taken from the paper by de Wildt et al. showing around 311 µg/L is required for sedation.[43] The maximum midazolam dose of 200 (100–200) µg/kg bolus followed by 200 (50–200) µg/kg/hour for all age groups (including neonates) is recommended by Dutch clinical consensus guideline.[44] According to the proposed dosing schedule, the exposure of midazolam is similar to the Dutch recommended dosing regimen from the simulation (figure 2).

Figure 2. *The proportion of average midazolam plasma concentration above the target value (0.311 mg/L) after the time of 5th bolus according to the proposed dose scheme(left) and the maximum Dutch recommended dosing regimen(right).*



Furthermore, after the fifth bolus according to the proposed dose scheme, the proportion of average midazolam plasma concentration above the target value (0.311 mg/L) is 74% and from the Dutch dose scheme is 72%. Thus, we assumed that the sedation success rate in the midazolam arm given our dosing scheme would be 75%, and in the clonidine group this would be 80%.

Sample size calculation

Given this assumed effect size of a 75% success rate for midazolam, a sample size of 258 (129 per treatment arm) provides at least 80% power to show non-inferiority of clonidine compared with midazolam. The sample size calculation is based on a logistic regression

for the primary efficacy end point of sedation success, with adjustment for study arm, age category and baseline COMFORT-B score. Non-inferiority of clonidine requires that the lower limit of the one-sided 97.5% CI for the OR of sedation success using clonidine (vs. midazolam) is at least 0.583, which is equivalent to a 10% non-inferiority margin in case of a sedation success rate of 80%. The required sample size was calculated using simulation. It is assumed that the total drop-out rate will be <13% and hence 300 subjects will be recruited, 150 in each arm and 100 in each age subgroup. The sample size of 300 subjects also provides at least 70% power to prove non-inferiority with respect to sedation success rate for each age subgroup (>90 subjects per age subgroup). Since the sample size for the age subgroup analyses is limited, a 15% non-inferiority margin at a one-sided alpha level of 0.025 is used, with an assumed sedation success rate of 80% in the midazolam group and 85% in the clonidine group. Subgroup analyses will be performed using a CI for the Mantel-Haenszel risk difference, with stratification by centre.

Statistical analysis

Analysis populations

The safety evaluation set (SES) is the subset of all subjects who were randomised into the trial and exposed to study medication (also referred to as the intention-to-treat (or ITT) population). Safety analyses will be performed in the SES.

The full analysis set (FAS) is the subset of subjects in the SES for whom the primary efficacy variable is available. Data analysis for the efficacy end points will be performed in the FAS. The per protocol set (PPS) is the subset of subjects in the FAS without major protocol deviations. Major protocol deviations will be defined during the Blinded Data Review Meeting. The PK/PD analysis set (PKS) is the subset of subjects in the SES with evaluable PK samples defined as drug concentration measurements.

Primary efficacy analysis

Logistic regression of the primary end point, sedation failure, with treatment group, baseline sedation assessment (i.e., the baseline COMFORT-B score), centre and age group as covariates, at a one-sided significance level of alpha=2.5% will be used. The statistical hypotheses are the following:

H0: $OR \leq \delta OR$ and H1: $OR > \delta OR$,

$OR = pC*(1-pM)/((1-pC)*pM)$, where pC and pM are probabilities of sedation success in the clonidine group and midazolam group, respectively; δOR is the non-inferiority margin which is predefined as 0.583.

H0 will be rejected if the lower bound of the one-sided 97.5% Wald CI for the OR of sedation success proportion will be >0.583. The primary analysis will be based on the ITT principle. The primary end point will be evaluated for FAS. An equivalent analysis for the PPS will be performed as a sensitive analysis. No interim analyses are planned for the primary end point.

Secondary efficacy analyses
All secondary efficacy analyses will be conducted on FAS. Secondary efficacy end points will be analysed in detail as follows:

The proportion of subjects with sedation success between treatments within each age group will be based on the Mantel-Haenszel risk difference, with stratification by centre.[45] A 15% non-inferiority margin at a one-sided alpha level of 0.025 will be used.

The aggregate intervals (i.e., the total time) (based on the planned assessment points) with COMFORT-B score >22 or <11 during treatment period between treatment groups were analysed using the Mann-Whitney U test.

The proportion of subjects with COMFORT-B score ≤11 between treatment groups and within each age group will be analysed using the $\chi 2$ test or Fisher's exact test.

The morphine consumption in units of µg/kg/day during the first 24 hours of IMP administration and for the remaining study period between treatment groups will be analysed using linear regression analysis, with adjustment for centre and age group. An appropriate transformation of morphine consumption may be used to ensure normality of the residuals in the linear regression model.

An age subgroup analysis will be performed for each age group, using centre as a stratification variable.

PK/PD analyses
The primary objective of PK/PD analyses in this trial is to evaluate the pattern and extent of covariates affecting the PK/PD profiles of clonidine and to provide the information of optimal dose for patients based on their particular age and other related covariates for future clinical practice. Three PK/PD interim analyses will be undertaken, whereby samples will be shipped and assayed for drug concentrations in order to ensure the systems for sample transport and analysis, along with data linkage to the electronic Case Record Form (eCRF) are fully operational, and to allow preliminary PK/PD model development. PK/PD interim analyses will be conducted after 15, 100 and 200 subjects will complete the study.

PK/PD data will be modelled using the Fortran-based non-linear mixed effects software NONMEM. Typical PK dispositional compartmental models will be tested, along with investigation of linear and non-linear elimination. Multivariate covariate analysis will be undertaken to investigate the impact of subject factors on PK model parameters. In particular, we will focus on the effect of body size with allometric models, and age (both postmenstrual and postnatal) possibly using literature prior models in order to delineate the effect of size and age from other factors. We will also look at the impact of drug metabolising enzyme genotype on interindividual variability. The link between PK and PD (COMFORT-B score) will be investigated by sequential and simultaneous modelling, possibly including an effect compartment. The Item Response Theory (IRT) will also be considered for PK/PD modelling, whereby effect is considered an unobserved normally distributed latent variable, and each item score of COMFORT-B is allowed to contribute to this through link functions.[46] Since subjects will receive other sedative agents for procedures, the concentrations of which may not be measured, a PK/PD approach will be taken to model sedation requirements in this period.

Mixed effects models will be fitted with maximum likelihood and addition of a single fixed effect will be guided by improvement of fit using the likelihood ratio test. Model evaluation will consist of goodness-of-fit (residual plots) and simulation-based diagnostics (visual predictive check), and parameter precision and robustness will be investigated with non-parametric bootstrapping.

Safety analyses

All safety analyses will be performed on the SES. Analyses will include the following end points:

- Adverse Event (AE)s, Serious Adverse Event (SAE)s and Suspected Unexpected Serious Adverse Reaction (SUSAR)s.
- Deaths.
- Clinical laboratory evaluations and vital signs. Descriptive summaries of laboratory values (including clinical chemistry, haematology, coagulation and urinalysis variables) and changes from baseline throughout the study will be generated. Shift tables will also be used for comparing changes from baseline and the proportion of subjects experiencing abnormalities between treatment groups.
- The SOS scores will be descriptively summarised and analysed with a linear mixed model (with between-arm differences at baseline constrained to be 0).
- Neurodevelopment will be evaluated using the Bayley Scales of Infant and Toddler Development. The scale will be descriptively summarised and compared between treatment groups using linear regression analysis, with adjustment for centre and age group.

Quantitative variables will be by the number of subjects analysed (N), mean, median, minimum and maximum. Categorical variables will be analysed by frequencies and percentages for each category.

Randomisation and kit assignment

Randomisation is stratified by both age subset and clinical site. Each stratum consists of 99 prerandomised numbers (randomisation numbers), assigned to either clonidine or midazolam. These randomisation lists were prepared by a statistician not otherwise involved in the study, with the use of blocked randomisation consisting of small variable block sizes, in order to maintain blinding and conceal allocation.

At each clinical site, the kits marked with the random numbers for each age subset will be assigned to subjects in the order they are enrolled into the study. Each subject kit will contain two IMP boxes of seven phials, in order to supply the subject with enough medication for the maximum 7-day study period. The contents of each subject kit is outlined in table 3.

Table 3. *Composition of the subject kit for each age group.*

Age Subset	Age group	Formulation strength	Subject bodyweight	Number of boxes
1	<28 days	Low	≤3 kg	1
		Medium	>3 to <10 kg	1
2	28 days to <2 years	Medium	>3 to <10 kg	1
		High	≥10 kg to <47 kg	1
3	≥2 years to <18 years	High	≥10 kg to 85 kg	2 (in case ≥47 kg)

Emergency unblinding will be possible as for each randomised subject kit, two complete sets of sealed emergency envelopes have been prepared (one set for safekeeping by the investigator, the other will be delivered to the group responsible for overseeing pharmacovigilance of the study). Unblinding of the treatment allocation for a subject will be performed in an emergency that, in the opinion of the investigator, is warranted for a given subject for safety reasons.

PK/PD end points

PK/PD analyses will be carried out as a secondary end point to give further information on the dose-concentration-effect relationship primarily of clonidine, and also of midazolam. The PK/PD model will be used to evaluate the dose scheme used in the study, and if necessary recommend an updated dose scheme for clinical use. PK/PD data will be modelled using non-linear mixed effects modelling. The impact of drug metabolising enzyme genotype on interindividual PK/PD variability will be considered alongside other demographics in the multivariable covariate analysis. The link between PK and PD (COMFORT-B score)

will be investigated by sequential and simultaneous modelling, possibly including an effect compartment. IRT will be explored for PK/PD modelling, whereby effect is considered an unobserved normally distributed latent variable, and each item score of COMFORT-B is allowed to contribute to this through link functions.[46]

Mixed effects models will be fitted with maximum likelihood and addition of a single fixed effect will be guided by improvement of fit using the likelihood ratio test (change in objective function of 3.84 is significant at p=0.05 level for 1 df by the $\chi 2$ distribution). Model evaluation will consist of goodness-of-fit (residual plots) and simulation-based diagnostics (visual predictive check), and parameter precision and robustness will be investigated with non-parametric bootstrapping.

Pharmacogenomic end points

Patients treated with sedatives and analgesics may respond very differently to the same dosage of medication. Several gene polymorphisms have been discovered to influence the PK and PD of clonidine, midazolam and morphine. PK data collected in this study can be interpreted more completely if data on pharmacogenomics are available.

Moreover, to study candidate polymorphisms gives further insight into the response of critically ill children to clonidine, midazolam and morphine. Most candidate genes have been established in adult subjects, this study is an opportunity to study the effects in children. The candidate genes which will be genotyped are shown in table 4.

Table 4. *Candidate genes for linking pharmacogenomics to pharmacokinetic and pharmacodynamics end points.*

Midazolam	**Clonidine**	**Morphine**
CYP3A4, CYP3A5, POR, ABCB1, GABA, MDR1, MRP1, MRP2, MRP4, BRCP.	ADRA2A, CYP2D6.	COMT, OPRM1, OCT1, UGT2B7, ABCC3, MC1R, IL-1Ra, IL-6

Ethical considerations

Ad hoc considerations and measures have been set up to ensure safe and ethical conduct of this multinational trial, including a population requiring special protection such as children. In order to guarantee the respect of ethical rules regardless of the country in which the trial is carried out, an ethical standard based on the EU ethical and legal framework has been agreed among centres. All submissions are based on the current European ethical and legal framework and on the international ethical principles and guidelines.

Based on the Council of Europe Convention on Human Rights and Biomedicine[47] and EU Ethical Recommendations 2008,[48] research involving vulnerable populations is allowed if the results of the research are expected to provide real and direct benefit to the health of

the patient, or some benefit for the population represented by the patient, and the trial will pose only minimal risk and burden to the individual concerned. The risk-benefit assessment has been carefully addressed considering IMP-related risks (including pharmacological properties and proposed dosing regimen of the IMP, information on use in target population, IMP development, IMP management) and expected benefits, the trial design (including study population inclusion and exclusion criteria), study-related procedures, qualification of the study team and host sites, rights of patients (including informed consent and assent procedures and data protection and confidentiality). Minor increase over minimal risk is anticipated for the CLOSED trial, as the study deals with a novel treatment modality in vulnerable paediatric patients and carries minor risk based on the available information about the study drug as well as randomised controlled trial (RCT)-related procedures. Important benefits for PICU population as a group are anticipated, since the study will provide clinically relevant and directly applicable results, expected to influence future standard of care.

The informed consent and assent process in this trial is in line with the applicable relevant regulatory documents, including Good Clinical Practice (GCP) guideline,[49] Directive 2001/20/EC,[50] the EC Detailed Guidance 2006,[51] Directive 95/46/EC,[52] the International Ethical Guidelines for Biomedical Research Involving Human Subjects CIOMS-WHO (2002),[53] the Additional Protocol to the Oviedo Convention (2005),[54] ICH Topic E11 and the EC 2008 Paediatric Recommendations. Accordingly, clear and appropriate information sheets and informed consent forms for parents/legal representatives, and patient information sheets and assent forms are prepared for patients and customised according to the local requirements.

Given the nature of the trial, especially considering that ICU patients are often admitted as a result of emergency, deferred consent/assent, as described in Article 35 of the new European Regulation on clinical trials (EU) No 536/2014 of the European Parliament and of the Council,[36] is foreseen if allowed by local legislation. Informed consent of the legal representative and, if feasible, the patient's assent will be sought for as soon as possible. If informed consent is not obtained, the possibility of withdrawing all collected data from the trial will be explained and appropriate measures, based on patient's decision will be taken. A record will remain in the subject's medical notes. In the Netherlands, deferred consent is permitted under national legislation ('Wet medisch-wetenschappelijk onderzoek met mensen', Paragraph 2 Article 6.4).

As the protocol includes pharmacogenetic tests, informed consent and assent to perform genetic tests will be obtained separately, in line with the most relevant provisions in the field (International Declaration on Human Genetic Data, UNESCO, 2003[55]; Ethical Guidelines CIOMS-WHO, 2002). Accordingly, the participants will have the possibility to join the trial without participating in the pharmacogenetic part.

Finally, involvement of appropriate external expertise in the form of Data Safety Monitoring Board (DSMB), Independent Scientific Advisory Board (ISAB) and Patient Advisory Board (PAB) is foreseen. In details, the DSMB will review the study's safety data and assess subject safety data throughout the study; the ISAB will input in the final protocols, monitor the progress of the project and ensure the ongoing scientific and ethical integrity of the clinical trial; the PAB will advise the Sponsor to ensure that the subjects' rights and subjects' protection will outweigh any commercial considerations and conflicts of interest that may appear in relation to the project.

In accordance with GCP, as implemented at national level, the study protocol and related documents have been approved by the competent ethics committees in Rotterdam, the Netherlands, and in Erlangen, Germany. Submission is currently being prepared for the three other centres (Stockholm, Prague and Rome).

Dissemination

The results will be published in a peer-reviewed journal and shared with the worldwide medical community.

DISCUSSION

Study design

Sedation management in PICU mainly consists of the use of intravenous midazolam by continuous infusion. Midazolam has several advantages, but is by far not the ideal agent for longer-term sedation. Other agents have made their off-label entry into PICU, mainly based on adult practice. One of these agents is clonidine, which could have some specific advantages over midazolam. It is being used increasingly, but is still off-label. This study design allows for data collection on safety, efficacy, PK, pharmacogenomics and to a lesser extent neurological outcome. This multimodal approach generates data that is very useful for licensing clonidine for sedation in children. Moreover, application of different formulation strengths, allows for easier paediatric clinical implementation as the current available formulation (Catapresan®) has only been developed for adults.

Study limitations

Despite the careful design of this trial, some limitations exist. First, we have chosen a non-inferiority design for this trial because, based on clinical experience and limited available data, we estimate the difference in sedation success rate will be very low. This would mean that showing superiority of clonidine requires a large sample size and thus compromising feasibility. This design, however, means that we cannot demonstrate possible superiority of clonidine. However, if equal efficacy is shown under safe circumstances, clonidine can be licensed for sedation in PICU.

Second, the recruitment window has been set on 72 hours. This could lead to confounding as having a large time window could increase the risk of tolerance and withdrawal symptoms. A smaller recruitment window may reduce these risks but parents need some time to consider participation and not every study site has 24/7 research nurse availability.

Third, this trial has an extensive list of exclusion criteria. This could compromise the external validity of the results and could complicate implementation of the results in new guidelines. This is a known limitation of almost any controlled trial.[56] However, these exclusion criteria are based on expected elements affecting both primary outcome and patient safety. Our primary end point is based on a validated behavioural scale. Therefore, any disease status that can cause many fluctuations in behaviour (such as neurological injury) needed to be excluded from this trial for the results to be valid. The same holds for safety end points such as cardiovascular stability. The decision to allow for inotropes/vasopressors in the second amendment is a big step towards generalisability of the results.

Role of researcher-driven studies, Seventh Framework Programme-funded projects CLOSED is one of the 20 projects approved in the framework of the Seventh Framework Programme for Research that should specifically meet both criteria for scientific excellence and regulatory standards for high-quality paediatric research, as prescribed by the Paediatric Regulation, in order to put paediatric drugs on the market. A very recent publication demonstrated that these projects face the need for overcoming the existing methodological and ethical difficulties affecting research in the paediatric population.[5]

In fact, paediatric clinical trials are often multinational and researchers need to know and apply rules from the regulatory, legal and ethical frameworks, acting both as investigators and as sponsor and/or other concerned parties. This is not simple considering the lack of harmonisation of clinical trial procedures among countries (http://www.ncbi.nlm.nih.gov/pubmed/26037896) and makes it necessary to prepare, agree and apply guidelines based on the EU rules.

Challenge to perform a trial compliant with GCP and other regulations
Clinical trials must follow the same rules, notwithstanding if sponsored by industry or non-profit organisations, from GCP to the new clinical trials regulation[49] to recommendations and guidelines.

Accordingly, the new regulation[49] recognises that a large proportion of clinical trials are conducted by non-commercial sponsors, frequently supported by public funds or charities and that these trials should be encouraged.

However, this means a heavy work from researchers and a deep knowledge of both EU and national rules. This issue is aimed to be overcome by the international public-private cooperation between different stakeholders foreseen by EU-funded projects (researchers, clinicians, regulatory and ethical experts, clinical research associates). On the other hand, it seems that the paediatric consortia generated by the FP7 paediatric projects are conducting these studies and trials using a limited amount of money in comparison with the recognised cost of paediatric trials in an approved PIP which is estimated to be three to four times higher.[5]

Challenges of maintaining double-blinding
Clonidine and midazolam have different half-lives: 1–3 hours for midazolam (up to 12 hours in neonates) and 9–17 hours for clonidine, thus maintaining double-blinding is challenging. PK/PD simulations have played a major role in the strategy to overcome this challenge. It has led to the implementation of a loading dose, which is in line with the current clinical recommendations for midazolam.[44] Target plasma levels have been achieved based on the

literature.[32,43] It should be noted, however, that the PK/PD relationship is assumed, but not formally studied. This study will contribute to the determination of a PK/PD relationship.

Risk to patients

Both clonidine and midazolam are frequently used sedatives in PICU. However, a careful assessment of possible study-related risks has been performed. In general, side effects of IMP are the major cause of study-related risk. As midazolam is the gold standard treatment, the side effects do not contribute to an increased risk in this study. For clonidine, bradycardia and hypotension are the most clinically relevant side effects and are likely to occur most often during the loading doses and the early starting phase.[33] Therefore, a loading dose will be given as a 15 min infusion instead of a direct bolus. Moreover, the setting where patients are being monitored consists of five well-equipped and experienced PICUs. Treatment of hypotension and/or bradycardia is common practice in the study population and should therefore not increase the risk to subjects dramatically.

Rebound hypertension could also be a side effect after sudden discontinuation of clonidine. In a comparable trial,[31] this was observed once in 64 patients and resolved quickly without any intervention. Monitoring of blood pressure up to 72 hours after IMP cessation has been included in the study protocol with the recommendation to treat hypertension according to local common practice.

Blood sampling is a possible risk to small children participating in drug research.[57] In this study, the amount of sampled blood will not exceed the 3% of patient's plasma volume, which is a general limit of study-related blood sampling.

In general, as most elements of this study are similar to current clinical practice, the study-related risk to patients is deemed low.

Pharmacogenetics

This study incorporates a pharmacogenetics assessment of recruited patients. Both PK and PD may be influenced by gene polymorphisms. The current proposed pharmacogenetics assessment has been based on the literature available, but a degree of flexibility has been built in when more information on these genes or medications will come available.

In accordance with the appropriate regulations,[51,53,55] separate consent and assent will be obtained from participants. This strategy enables the possibility of participating in the CLOSED trial without the genetic assessment.

Anticipated difficulties

A comparable RCT, the Safety profiLe, Efficacy and Equivalence in Paediatric intensive care Sedation (SLEEPS) study, has been previously undertaken in the UK.[33] One of the major challenges faced by the investigators was the recruitment. The sample size had been calculated on 1000 subjects. Unfortunately, only 129 subjects were randomised. Contributing factors to this impaired recruitment have been identified by the investigators, including:

- Conflict with other studies
- Earlier extubation in elective cardiac surgery patients
- Parental issues and timing of consent
- Clinicians' issues
- Research nurse time
- Delay in study start
- Compliance with the protocol.

It is likely that in the participating centres with excellent research facilities, multiple trials are being performed at the same time. Children are not allowed to participate in multiple intervention studies, so we recommend to have a thorough look at the inclusion and exclusion criteria of studies and set up clear agreements about patient allocation.

Early extubation in cardiac surgery patients is now common practice, and estimations of recruitment rates have excluded these patients. However, it is likely that ventilation strategies will change over the coming years. We have recognised the increasing use of non-invasive ventilation such as Non-Invasive Positive Pressure Ventilation (NIPPV). As these patients may still need continuous sedation, we will include these in the study. In general, patients on continuous positive airway pressure (CPAP) do not need additional sedation, thus these will be excluded.

Parental issues are to be expected in any clinical trial in the PICU. Parents having their child admitted to an ICU are under high stress and may therefore be reluctant to participate. In the calculations of estimated recruitment, a high refusal rate (approximately 40%–50%) should be taken into account, based earlier experience with other trials. Also, a parent organisation is involved in the trial and they will provide information to parents from their perspective. We anticipated to include 300 patients within 18–24 months in total. In The Netherlands, deferred consent is used in emergency care trials. The Ethical Committee of the Erasmus Medical Centre, Rotterdam, has approved the use of deferred consent in this trial so this could be applied in the largest recruitment centre.

When faced with a critically ill child, doctors and nurses may tend towards conservatism. At the beginning of the SLEEPS trial, the involved professionals could have been afraid of the cardiovascular side effects of clonidine especially in unstable patients. Their study has shown that its use is relatively safe in critically ill children, as well as other literature.[34,58] Moreover, in the CLOSED consortium recruitment centres, a lot of clinical experience with clonidine has been built so caregivers may be less hesitant to support this clinical trial.

Research nurse time is always an issue, especially in the 24/7 business of an ICU. In the larger centres, dedicated researchers/nurses have been identified and trained adequately to perform this trial. In the smaller centres, Principle Investigators (PI)s may be able to coordinate the lower amounts of participants.

During the first months of patient recruitment in two centres, no patients could be included. In the majority of cases, exclusion criteria made the screened patients ineligible. No consent was given in the very few eligible patients. Therefore, a revision of the exclusion criteria has been made.

The major exclusion criteria on which patients failed screening are:

- Anticipated need for sedation <24 hours. It has been considered to change this duration. It has been decided however to keep this minimum as the therapeutic aim of the study is long-term sedation.
- No sedation despite ventilation. To our surprise, many newborn patients on the ventilator would not need any sedation, or were comfortable on low-dose opioids. This could not be mitigated.
- Circulatory insufficiency. The Goldstein criteria[59] have been used for the definition of this exclusion criterion. However, many patients received inotropic or vasopressor agents as supportive therapy in both recruiting centres. We have therefore modified these criteria and removed the use of inotropes/vasopressors in the second protocol amendment.
- Neurological pathology. It has been suggested to include patients with minor head trauma, but as the clinical picture may change very rapidly, we have decided not to include these patients into the trial.
- Use of clonidine in the last 7 days. As clonidine has a long half-life, patients would be excluded if they have received clonidine for any indication in the previous 7 days. However, for midazolam, there was no similar exclusion criterion; instead, patients would undergo an extra PK blood sample before start of the study medication. This has now been introduced for clonidine as well in the second protocol amendment.

A delay in study start has been encountered in the CLOSED study. Several obstacles, such as obtaining the appropriate licenses for handling, importing and exporting controlled drugs, have caused a significant delay in recruitment start. A second major issue has also been an amendment of the dose reduction scheme (see the 'Study treatments' section). A third issue has been the generation of robust quality data that is sensitive enough to support a future PUMA application as well as the Investigational Medicinal Product Dossier (IMPD) and clinical trial application.[60]

Compliance with the protocol was a significant issue in the SLEEPS trial, as they provided a strict sedation regimen. Therefore, the CLOSED sedation regimen merely reflects clinical practice, although some important aspects may cause difficulties in clinical practice. The lock-out periods, for example, are not according to clinical practice and special attention needs to be paid by the research nurses and other investigators to keep the protocol compliance as tight as possible. When problems are recognised, the possibility of amendments should be discussed early. Early recognition is facilitated by implemented monthly investigators' teleconferences.

Also, there will be an ongoing evaluation of the COMFORT-B scale training of the nurses in the participating centres. Good interobserver reliability is defined by a Cohen's kappa >0.65 and nurses in all centres have received training by trained nurses.

In summary, many known challenges should be managed by appropriate measures taken. However, there could always be unknown challenges and it is therefore crucial to have regular contact between principal investigators of each recruitment site.

Reflection

After 9 months of recruiting, we included far fewer children than anticipated. Therefore, two amendments have now been added to potentially increase the number of eligible patients. Unfortunately, recruitment did not improve. Even though we had been warned by the early discontinuation of the SLEEPS trial,[33] we faced other challenges. For example, many postoperative neonates do not need any additional sedation to intravenous paracetamol and continuous intravenous morphine. Also, parents are reluctant to participate. Either they think their child is not stable enough, or their child is finally stable and therefore changes in treatment for study purposes are not welcomed.

Also, the anticipated recruitment rate was based on the number of admitted ventilated patients in previous years. However, this turned out to be a significant overestimation, a phenomenon also known as Lasagna's Law.[61] These challenges have a big impact on the feasibility of the trial and force us to consider alternative options. We will open (at least) two

new recruitment sites, Bari (Italy) and Tallinn (Estonia). Furthermore, we need to rethink the primary objective of this study and may change it to a PK/PD study for which 50 patients in each arm are sufficient instead of the original 150 patients per arm.

The lessons from both the SLEEPS trial and this trial are important for further investigations in paediatric critical care and careful preparation is warranted for any trial performed in this population. This preparation should at least include adequate piloting over a longer period. In our experience, we monitored eligible patients over one month in one centre and expected no significant recruitment problems. This monitoring was performed during winter time, when many patients with respiratory viral infections in need of mechanical ventilation were admitted. This caused our expectations of eligible patients to be high; if we had performed this during summer time, we may have been warned earlier.

Other aspects to enhance the number of included patients are adequate staff training and motivation, collaboration with investigators having experience in paediatric critical care trials and keeping the exclusion criteria of a trial to a minimum.

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5

High anticholinergic drug burden in patients with pediatric delirium and/or iatrogenic withdrawal symptoms.

Manuel A. Baarslag, Ela Hutten, Joost van Rosmalen, Kate Madden, Erwin Ista, Robert C. Tasker and Monique van Dijk.

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ABSTRACT

Objective: To determine the anticholinergic drug burden in critically ill children with pediatric delirium (PD) and/or iatrogenic withdrawal syndrome (IWS).

Design: Single-center, retrospective observational cohort study.

Setting: A 28-bed level III pediatric intensive care unit (PICU).

Patients: All patients admitted to the PICU between January 1st 2014 and 31st December 2016; and receiving one or more anticholinergic drugs. The cohort was divided into 4 subgroups: 1) patients with diagnosed PD but without diagnosed IWS; 2) patients with diagnosed IWS but without diagnosed PD; 3) patients with diagnoses of both PD and IWS; and 4) patients without a diagnosis of either PD or IWS.

Interventions: None.

Measurements and main results: The anticholinergic drug burden was calculated using the Anticholinergic Drug Scale (ADS) and the Anticholinergic Cognitive Burden Score (ACBS). The average anticholinergic drug burden in affected patients was higher than that in the unaffected group: median ADS score in PD patients was 2 (IQR 2-3), in IWS patients 2 (2-2.5) and in PD/IWS patients 3 (2-4) vs. 1.5 (1-2) in the unaffected group, p-value <0.001. In none of the affected subgroups the anticholinergic drug burden had increased in the seven days prior to onset of PD and/or IWS.

Conclusions: Patients with PD and/or IWS have a higher anticholinergic drug burden compared to unaffected patients receiving anticholinergic drugs. These findings warrant both scientific and clinical consideration of the contribution of anticholinergic drugs to PD or IWS symptom development.

INTRODUCTION

Iatrogenic withdrawal syndrome (IWS) and pediatric delirium (PD) are frequently encountered in the pediatric intensive care unit (PICU). The reported prevalence of IWS in the PICU ranges from 17% to 57%[1]; that of PD from 5-47%.[2-6] Early detection of both conditions is crucial, as both are associated with increased mortality and longer length of stay.[1,7] Thus, several PD screening tools and IWS screening tools have been developed and validated for children[1,5,8,9] to detect these conditions early on. Yet, symptoms of IWS and PD seem to overlap to a great extent, such as sweating, agitation, tremors and increased muscle tension. This overlap has been used in the development of a delirium assessment tool, the Sophia Observation withdrawal Symptoms-Pediatric Delirium,[10] with the use of ten overlapping items derived from the previously existing Sophia withdrawal Observation Symptoms scale.[8] In a recent literature review of several IWS and PD screening tools. Another possible overlapping phenomenon was identified: the anticholinergic toxidrome (AT).[11] This toxidrome may be caused by the use of direct anticholinergic agents such as glycopyrronium or atropine, medications with anticholinergic properties such as oxybutynine, or other exposures outside the hospital. These agents block the muscarinic acetylcholine receptors in the peripheral and central nervous systems. Classically, the AT leads to a clinical presentation as 'dry as a bone, blind as a bat, red as a beet, hot as a hare and mad as a hatter',[12,13] but more subtle signs, such as isolated agitation, confusion and/or tachycardia may also occur.[14,15]

No data are available on the prevalence of AT in the PICU, but the literature contains multiple case reports of drug-induced AT in children.[14,16-22] Yet, the authors of the above-mentioned review hinted at a possible association between AT and PD/IWS.[11] Moreover, a recent study reported a high anticholinergic drug exposure in children admitted to the PICU for more than two weeks.[23] They also reported a possible association between a high anticholinergic drug burden and the development of withdrawal syndrome. Therefore, we have carried out a retrospective, case-control study of critically ill children, with the goal of determining the anticholinergic drug burden in those who developed IWS and/or PD. To see whether there is an association with the development of PD or symptoms of IWS we compared this drug burden with that of critically ill children who did not develop IWS or PD.

METHODS

Study design

The Erasmus MC medical ethics review board provided a waiver for ethics approval and informed consent according to the Dutch law on research in humans (MEC 2017-358) for this retrospective case-control study of patients admitted to the PICU of the Erasmus MC-Sophia's Children's Hospital between January 1st 2014 and December 31st 2016 and having received at least one anticholinergic drug.

The cohort was divided into 4 subgroups: 1) patients with diagnosed PD but without diagnosed IWS; 2) patients with diagnosed IWS but without diagnosed PD; 3) patients with diagnoses of both PD and IWS (the overlap group); and 4) a control group of patients without a diagnosis of either PD or IWS. Patients in the first three groups are classified as 'affected' whereas patients in group four are classified as 'unaffected' controls. Diagnosis of PD and/or IWS was made according to the following criteria:

For pediatric delirium:

Two or more consecutive SOS-PD scores ≥4 in 24 hours AND/OR PD confirmed by consulting child psychiatrist

For iatrogenic withdrawal syndrome:

Two or more consecutive SOS scores ≥4 in 24 hours

There were no exclusion criteria. In patients with multiple admissions we only examined the first admission.

Instruments

PD and IWS assessment

IWS is screened for by the validated Sophia Observation withdrawal Symptoms (SOS) scale,[24] which consists of 15 items representing symptoms of the opioid and/or benzodiazepine withdrawal syndrome and with a score ranging from 0-15. At least two consecutive scores ≥4 are considered to indicate the presence of IWS. The SOS scale is used in children who have received continuous infusions of opioids and/or benzodiazepines for more than 4 days, or whenever IWS was suspected. PD is screened for with a modification of the SOS scale, – the Sophia Observation withdrawal Symptoms-Pediatric Delirium (SOS-PD) scale[10] – which in total consists of 22 items). Seventeen items refer to symptoms of PD (10 of which overlap with the SOS scale). At least two consecutive SOS-PD scores ≥4 and/or confirmed diagnosis by the child psychiatrist are considered to indicate the presence of PD. A child psychiatrist is in any case consulted when there are two consecutive scores ≥4, or whenever "unrecognizable behavior" is present. All patients who are admitted for >48 hours have PD assessments 3 times a day.

Anticholinergic burden assessment

The anticholinergic burden was assessed with the Anticholinergic Drug Scale (ADS)[25] and the Anticholinergic Cognitive Burden Score (ACBS).[26] These two scales have been selected because they include drugs that are frequently administered in the PICU.[27] Drugs are rated numerically from 0 to 3, whereby 0 indicates no anticholinergic activity and 3 indicates significant anticholinergic activity. The total sum of all drugs indicates the total anticholinergic burden per admission day, calculated separately for both scales.

We calculated the anticholinergic burden per day of admission for the three patient groups and the control group. Since many drugs are used off-label, or administered by continuous infusion in rapidly changing doses, we have not applied a dose-dependent coefficient (e.g., when a patient receives double the standard dose, the score should be doubled). We also specifically looked at the anticholinergic burden from analgesics and sedatives. As such, we classified these agents into three groups: benzodiazepines (including clonazepam, diazepam, lorazepam, midazolam and temazepam); opioids (including fentanyl, meperidine, morphine, oxycodone, tramadol); and antihistamines (including alimemazine, chlorpromazine, promethazine).

Data collection

Data were collected from the electronic patient data management system, which also includes the digital drug prescription system. The following patient characteristics were retrieved: age, sex, length-of-stay (LOS), use of mechanical ventilation, use of anticholinergic drugs, and mortality.

For the affected subgroups, we retrieved also data on reason for admission, severity of illness as assessed by the pediatric risk of mortality (PRISM-III) score,[28] pre-existing developmental delay and the time of onset of PD and/or IWS. To determine whether the anticholinergic drug burden and symptoms of IWS/PD had increased before the onset of PD and/or IWS we also collected ADS, ACBS, SOS and SOS-PD scores from the seven days before the onset of PD and/or IWS. For comparison we collected ADS and ACBS scores from the first ten days of admission in the control group as the mean onset of PD and/or IWS was 8 days. For logistics reasons, PRISM-III scores could not be calculated for the unaffected group.

Statistical analysis

Demographic data are summarized using descriptive statistics. For comparisons between the affected subgroups we used the Kruskal-Wallis test for non-normally distributed data or a one-way analysis of variance (ANOVA) for normally distributed data, using a Dunn-Bonferroni correction for multiple comparisons. For comparisons of the affected group with the unaffected group we used the Mann-Whitney U test for non-normally distributed data and the Student's t-test for normally distributed data. Chi-square tests or Fisher exact tests were used for categorical data.

RESULTS

Over the 3-year period (2014 – 2016), in total 3241 patients had been admitted to the PICU. Of those, 2,340 (72.2%) met the inclusion criteria. We included 174 affected patients and 2166 unaffected patients. Demographic data are shown in Table 1. Affected patients were significantly older and had a longer PICU LOS. Also, more affected patients died during admission compared to the unaffected group, 9.2 % versus 3.9% (p=0.016). The affected group consisted of 64 children with PD, 33 with IWS and 77 with both (Table 2).

Table 1. *Demographic data of the cohort.*

Variable	Affected group (n=174)	Unaffected group (n=2166)	p-value
Age, median (interquartile range [IQR]) in months	29 (6-125)	20 (1-101)	0.01
Sex (n,%)	M 104 (59.8%) F 70 (40.2%)	M 1254 (57.9%) F 912 (42.1%)	0.63
Length of stay, median (IQR) in days	19 (10-42)	2 (2-5)	<0.001
Mechanical ventilation (n, %)	149 (85.6%)	905 (41.8%)	<0.001
PICU mortality (n, %)	16 (9.2%)	85 (3.9%)	0.016
Reason for admission (n, (%))			
Respiratory	51 (29.3)	-	
Neurological	35 (20.1)	-	
Cardiac	34 (19.5)	-	
Surgical (non-cardiac)	25 (14.4)	-	
Infection/sepsis	10 (5.7)	-	
Post resuscitation	7 (4.1)	-	
Metabolic	7 (4.1)	-	
Hematologic/oncologic	3 (1.7)	-	
Polysomnography	2 (1.1)	-	

Table 2. *Affected subgroup characteristics.*

	PD group	IWS group	Overlap group	Overall
Primary diagnosis (n, %)	64 (36.8%)	33 (18.9%)	77 (44.3%)	174 (100%)
Developmental delay (n, %)	8 (12.5%)	4 (12.1%)	5 (6.5%)	17 (9.8%)
Time to onset IWS and/or PD in days (median, IQR)	4 (2-6)	13 (8-27)	10 (7-17)	8 (5-17)
PRISM-III score (median, IQR)	10 (5-19)	12 (5-19)	13 (8-21)	12 (7-20)

Both the median and highest anticholinergic scores during admission were higher in the affected group than in the control group (Table 3). Figure 1 shows the boxplot of distribution of data. Within the affected subgroups, median ACBS was slightly higher in the overlap group than in the PD group (2, IQR 1-2) vs. 1 (IQR 1-2).

In all three affected subgroups the anticholinergic burden from analgesics and sedatives was not higher than in the unaffected group (see Table 4).

Table 3 a. *Medians with IQR of the median and highest ADS and ACBS score per patient. P-values are given for across-group comparisons(a). Adjusted significance levels of pairwise comparisons using Dunn correction are given below (b).*

	PD group (n=64)	IWS group (n=33)	Overlap group (n=77)	Control group (n=2166)	p-value
Median score per patient					
ADS score (median, IQR)	2 (2-3)	2 (2-3.5)	3 (2-4)	1.5 (1.0-2.1)	<0.001
ACBS score (median, IQR)	1 (1-2)	1 (0-2)	2 (1-2)	1.0 (0.5-1.5)	<0.001
Highest score per patient					
ADS score (median, IQR)	4 (2-5)	5 (4-6)	6 (4-7)	2 (1-3)	<0.001
ACBS score (median, IQR)	2 (1-3)	3 (2-5)	3 (2-5)	1 (1-2)	<0.001

Table 3 b. *Medians with IQR of the median and highest ADS and ACBS score per patient. P-values are given for across-group comparisons(a). Adjusted significance levels of pairwise comparisons using Dunn correction are given below (b).*

	Control-PD	Control-IWS	Control-Overlap	PD-IWS	PD-Overlap	IWS-Overlap
Median ACBS	1.0	1.0	<0.001	1.0	0.013	0.105
Median ADS	<0.001	<0.001	<0.001	0.655	0.069	1.0
Highest ACBS	<0.001	<0.001	<0.001	0.303	0.005	1.0
Highest ADS	<0.001	<0.001	<0.001	0.052	0.001	1.0

In the seven days before the onset of the IWS and/or PD, the anticholinergic burden had not increased and the PD and/or IWS scores had not changed (see figures 2a and 2b) There was also no change in anticholinergic drug burden in the first ten days of admission in the control group (figure 2c).

Figure 1. *Boxplot showing the average anticholinergic scores for the patient groups and the control group (left).*

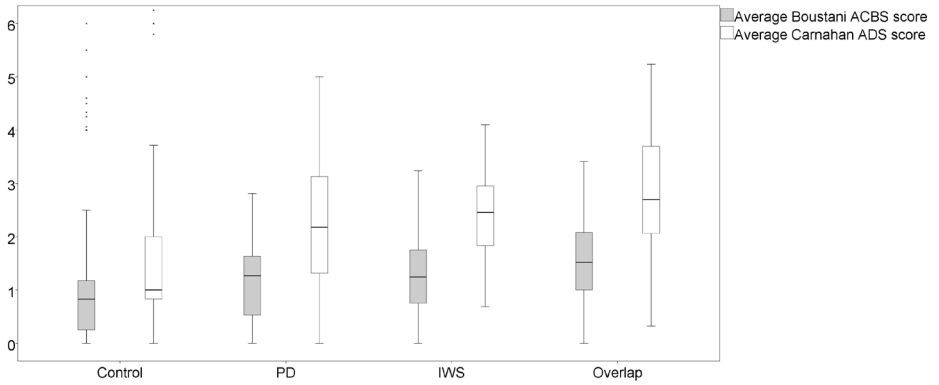


Table 4 a. *Median anticholinergic drug scores of analgesics and sedatives per study subgroups and controls. P-values are given for across-groups comparisons. Adjusted significance levels of pairwise comparisons using Dunn correction are given below (b).*

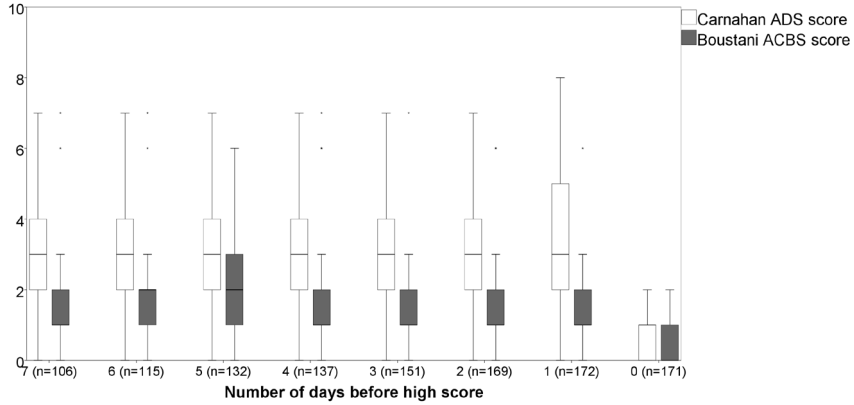
	PD group (n=60)	IWS group (n=32)	Overlap group (n=77)	Control group (n=1636)	p-value
Benzodiazepines					
No. of patients receiving (n, %)	56 (93.3)	32 (100)	76 (98.7)	1107 (67.7)	
Median ACBS (median, IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.719
Median ADS (median, IQR)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	0.011
Opioids					
No. of patients receiving (n, %)	50 (83.3)	28 (87.5)	74 (96.1)	1386 (84.7)	
Median ACBS (median, IQR)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	0.006
Median ADS (median, IQR)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	0.052
Antihistaminics					
No. of patients receiving (n, %)	10 (16.7)	12 (37.5)	19 (24.7)	59 (3.6)	
Median ACBS (median, IQR)	0 (0-0)	0 (0-0)	1 (1-1)	1 (1-1)	0.684
Median ADS (median, IQR)	1 (1-1)	1 (1-1)	0 (0-0)	0 (0-0)	0.684

Table 4 b. *Median anticholinergic drug scores of analgesics and sedatives per study subgroups and controls. P-values are given for across-groups comparisons. Adjusted significance levels of pairwise comparisons using Dunn correction are given below (b).*

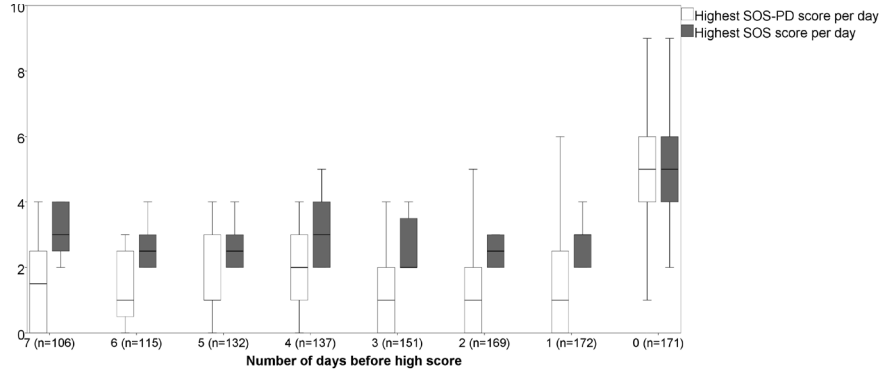
	Control-PD	Control-IWS	Control-Overlap	PD-IWS	PD-Overlap	IWS-Overlap
Benzodiazepines						
Median ADS	0.008	1.0	1.0	1.0	0.008	1.0
Opioids						
Median ACBS	0.004	1.0	1.0	0.491	0.01	1.0

Figure 2a-c. *Boxplots showing anticholinergic drug scores (2a) and SOS/SOS-PD scores (2b) in the seven days before onset of PD and/or IWS. For the control group, anticholinergic drug scores of the first 10 days of admission are displayed (2c).*

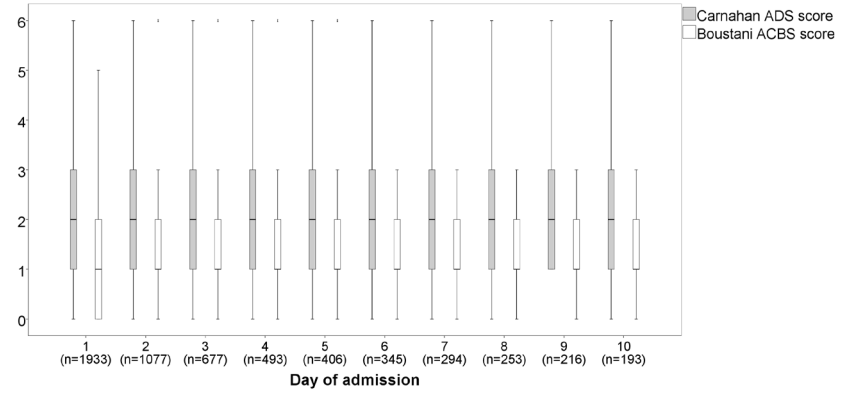
a.



b.



c.



DISCUSSION

From this exploratory, retrospective case-control study it appeared that the PICU patients who had developed PD, IWS, or both, had on average a higher anticholinergic burden from the received medications than other PICU patients receiving anticholinergic drugs. This could implicate an association between anticholinergic drugs and the development of PD and/or IWS.

To date, little is known about the association between anticholinergic drug burden and the development of PD, or PD symptoms, in critically ill children. A prospective observational study from the United States in 1,547 children found that those who had received any anticholinergics during PICU admission had an increased risk of PD development (OR 2.17, 95% CI 1.41-3.42).[7] But in an international point prevalence study of PD in 994 patients across 25 PICUs worldwide, anticholinergic drug consumption was not associated with PD, whereas narcotics, benzodiazepines, antiepileptics and vasopressors were. In a geriatric population an association was found between the use of anticholinergic drugs and the development of delirium (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.04-2.17).[29,30] Yet, studies in adults receiving intensive care have reported conflicting results. A prospective, observational single-center study in the Netherlands in 1,112 patients found no association between anticholinergic drug burden and the development of delirium.[31] But a Canadian prospective, observational single-center study in 520 patients found an increased risk for delirium development with the use of high-potency anticholinergics in the preceding 48 hours (hazard ratio [HR] 2.45, 95% CI 1.08–5.54).[32]

Regarding IWS, Madden et al. found an association between high anticholinergic drug scores and the development of IWS. This may not be surprising as midazolam and morphine accounted for the majority of high ADS scores. Data on the time of IWS onset after such high scores were not provided, unfortunately. In our study, we did not find a higher contribution of sedatives to the anticholinergic burden in the IWS subgroup, however.

We found a median ADS score of 1 (IQR 0.8-2.0) in the control group, whereas the median scores for the affected group did not exceed 3 (2.2 (IQR 1.3-3.1), 2.5 (IQR 1.8-3.2) and 2.7 (IQR 2.1-3.7), respectively). However, in the retrospective study of Madden et al., a median score of 5 (IQR 3-7) was found.[23] Also, their maximal ADS per patient was higher (8 (IQR 6-10) versus 6 (IQR 4-7) in our overlap subgroup, which had the highest maximal ADS in our study). This could possibly be attributed to a difference in clinical practice, as we did not use diphenhydramine for example, which is a strong anticholinergic drug (3 score points in the ADS) and accounted for 40% of high ADS scores in the Madden et al. study.

One of the problems with studying the role of anticholinergic drugs is the use of different definitions of 'anticholinergic' drugs. In previous studies of Traube et al. a clear definition is lacking.[2,7] Burry et al. used a classification of drugs with low or high anticholinergic potency,[32] and Wolters et al. calculated anticholinergic drug burden with use of the ADS.[31] Valid comparisons between studies can only be made if a clear definition is provided.

Moreover, a limitation of using anticholinergic drug burden scales is that they list different drugs list and also rate the burden of the same drug differently.[29] For example, frequently used drugs in the PICU such as midazolam, vancomicin and gentamicin are only assessed by the ADS, but alimemazine, metoprolol, haloperidol and paracetamol are only assessed by the ACBS. This could be attributed to the fact that expert opinion plays an important role in the development of these individual scales. Some scales have used validation against serum anticholinergic activity (SAA) as an objective measurement.[25,33] Yet, SAA may not reflect CNS anticholinergic activity as the blood-brain-barrier has different permeability for different drugs.[34] Cut-off or threshold values in the scales are lacking. Boustani et al. suggest the use of a ACBS cut-off value of ≥ 3[26] for having an increased risk of cognitive problems. However, this value has been established in a geriatric population with cognitive function as primary end point. In future pediatric studies, existing anticholinergic scales should first be validated for the population in question.

Another problem that limits this study is the identification of PD and the discrimination from IWS and preferably also AT. This is illustrated by the fact that almost half of affected patients in this study had been diagnosed with an overlapping condition, which could lead to misdiagnosis. It is therefore important to be able to discriminate between PD as a condition and the expression of PD-like symptoms in for example IWS or AT.

This exploratory study describes a possible association between anticholinergic drugs and the development of PD and/or IWS. Although this study has several limitations, our findings warrant further study on the contribution of drugs with anticholinergic properties to the development of delirium and/or withdrawal symptoms. We would recommend prospective evaluation of risk factors for PD, IWS and AT in patients admitted to the PICU. Candidate risk factors should include 'sweating' and 'seizures'. Sweating could possibly discriminate between PD/IWS on the one hand and AT on the other. As AT is characterized by dry skin, there could be a role for skin conductance here[35] besides the use of a validated screening tool. Seizures may also be typical for AT but seizures may be triggered by many other events.

As we found that critically ill children with PD and/or IWS have a higher anticholinergic drug burden compared to patients who did not develop PD and/or IWS despite receiving anticholinergic drugs, clinicians should be aware that the anticholinergic drug burden may be associated with symptoms of PD or IWS in children. AT is probably rare, which makes it difficult to identify this in a standardized way.

Although more causative research is needed to support this association, the role of anticholinergic drugs in children with PD and/or IWS should be considered in future research and in clinical practice.

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PART III

FROM RESEARCH INTO CLINICAL PRACTICE

6

How often do we perform painful and stressful procedures in the PICU? A prospective observational study

Manuel A. Baarslag, Sharan Jhingoer, Erwin Ista, Karel M. Allegaert, Dick Tibboel and Monique van Dijk.

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ABSTRACT

Background: Adequate analgesia and sedation is crucial in critical care. There is little knowledge on the extent of painful and stressful procedures on children admitted to a paediatric intensive care unit (PICU) and its analgesic and/or sedative management.

Objective: The primary objective was to determine the number of painful and stressful procedures per patient per day in our PICU patients, including the numbers of attempts. A secondary objective was to map PICU nurses' perceptions of the painfulness of the included procedures.

Methods: A prospective, single-centre observational cohort study in a tertiary PICU. All patients admitted to the PICU over a 3-month period were eligible. Readmissions, polysomnography patients, and patients without any data have been excluded. The number of painful and stressful procedures was collected daily, and use of analgesics and sedatives was assessed and recorded daily. Twenty-five randomly assigned nurses rated the painfulness of procedures based on their personal experience using a numeric rating scale from 0 to 10.

Results: In a 3-month period, a total of 229 patients were included, accounting for 855 patient days. The median number of painful and stressful procedures per patient per day was 11 (interquartile range = 5 - 23). Endotracheal suctioning was the most frequent procedure (45%), followed by oral and nasal suctioning. Arterial and lumbar puncture, peripheral IV cannula insertion, and venipuncture were scored as most painful ranging from 3 to 10. Procedural analgesia or sedation was often not used during these most painful procedures.

Conclusions: Mechanically ventilated patients undergo more than twice as many painful procedures than non-ventilated patients, as endotracheal suctioning accounts for almost half of all. Nurses regarded skinbreaking procedures most painful; however, these were rarely treated by procedural analgosedation and only covered in the minority of cases by adequate background analgosedation.

INTRODUCTION

Adequate sedation and analgesia (or analgosedation) are crucial elements of paediatric critical care. Paediatric guidelines recommend continuous administration of both a sedative (mainly benzodiazepines) and an analgesic (mainly opioids)[1,2] to reduce pain and stress. This continuous background analgosedation may not be sufficient to alleviate procedural pain and distress in critically ill children, who are subjected to multiple possibly painful and stressful procedures everyday.[3]

Several studies have determined numbers of daily painful and stressful procedures and analgesic management in the neonatal intensive care unit (NICU),[4-8] summarised in a systematic review of 18 studies which reported a mean of 7.5 - 17.3 daily painful procedures per patient in the NICU setting.[9] Only two studies to date have addressed this issue in paediatric intensive care unit (PICU) patients. One is a retrospective multi-centre chart study published in 2011 which reported a median number of 12 (interquartile range [IQR] = 6 - 18) painful procedures per patient day in 799 PICU patients aged between 0 and 18 years.[3] The second study, dating back to 1993, is a single-centre, prospective observational study in 55 PICU patients aged between 0 and 12 years which reported median numbers of 2 and 3.5 procedures per day, depending on length of stay.[10] These two studies were limited to painful procedures only and did not account for the numbers of procedural attempts. To provide an in-depth analysis of the prevalence of painful and stressful procedures in our PICU, a prospective observational cohort study, also including stressful procedures and numbers of attempts per procedure, was undertaken.

The aim of this study was to determine the numbers of daily painful and stressful procedures, including numbers of attempts and to determine whether there is a relationship with age, mechanical ventilation, and surgery as these factors were found to be risk factors in NICU patients.[5-7] The secondary aim was to map PICU nurses' perception of the painfulness of the procedures and to evaluate procedural pharmacological analgesic and/or sedative treatment for the most frequent painful procedures.

MATERIALS AND METHODS

Design, patients and setting

In this prospective observational cohort study, all patients admitted to the PICU between 9th May 2016 and 9th August 2016 were eligible. This PICU is a 28-bed tertiary care unit for all medical and surgical specialities - including extracorporeal life support – for children aged 0 - 18 years including neonates with major congenital anomalies. The centre has a standard analgosedation protocol in place that has been published previously.[11,12] If a patient was admitted more than once in the study period, only the first admission was included for analysis. Patients admitted for observation only during polysomnography were excluded. The Institutional Review Board waived the need for informed consent (MEC 2016-310).

Data collection

A paper checklist was designed including 40 possibly painful and stressful procedures, with a blank field to add a procedure if applicable. The list was based on literature findings and expert opinion of the study team (MvD, EI, MB, KA). The checklist was tested for completeness during a 1-week pilot study among all attending PICU nurses. The data from this pilot have not been included for analysis. After this pilot study, two items were added: "Activities of Daily Living" and "Nebulising". The final version (see Appendix 1) contained 42 procedures, of which 31 were regarded painful and 11 stressful. Painful procedures were defined as skinbreaking procedures, skin-manipulating procedures or procedures involving the insertion or removal of lines, tubes, or catheters. Stressful procedures were defined as all other procedures without risk for pain, e.g. electrocardiography, magnetic resonance imaging, or computed tomography scans, physiotherapy, etc. Although painful procedures are likely to be stressful as well, we classified them separately as pain and stress and treated them differently.

The bedside nurses were instructed to record the listed procedures that each patient underwent during the shift. New checklists were provided daily to nurses on the morning shift. Furthermore, the nurses were asked to record the numbers of attempts needed to successfully perform the following procedures: heel and finger stick, venipuncture, peripheral intravenous (IV) cannula insertion, lumbar puncture, arterial puncture (arterial catheter insertion), central venous catheter insertion, nasogastric tube insertion, urinary catheter insertion, nasopharyngeal tube insertion, and endotracheal intubation. Each failed attempt and the final successful one was counted as a separate procedure in the overall analysis. Data were collected related to relevant patient characteristics such as age, gender, mechanical ventilation (collected per patient-day), extracorporeal membrane oxygenation treatment (collected per patient-day), severity of illness, and reason for admission. Severity of illness

was calculated using the paediatric index of mortality-2 (PIM-2)[13] score and the paediatric risk of mortality (PRISM-III) score.[14] Further, any use of background analgesics, including paracetamol, non-steroidal anti-inflammatory drugs, fentanyl, morphine, tramadol, and remifentanil, and sedatives, including propofol, midazolam, lorazepam, clonidine, ketamine, chloral hydrate, and pentobarbital was assessed daily and recorded as having been received (yes/no). Procedural analgesics and sedatives were not collected prospectively. Retrospective collection of procedural drug prescription was often incomplete and could only be done for the top five of most painful procedures.

For each patient, data were recorded across the entire PICU stay. The data collected at the bedside were double-checked by one investigator (SJ) for completeness in - and completed by data from - the patient data management system and the electronic patient records.
To determine the painfulness of procedures, 25 randomly chosen nurses (with number of experience years in the PICU ranging from 1 to 30 with a median of 15) were asked to assign a numeric rating scale (NRS) pain score (ranging from 0 to 10; 0 represents no pain and 10 represents the worst pain imaginable) to all procedures based on their general impression of painfulness, so no patient observation was involved. Procedures routinely performed under sedation or analgesia, such as thoracic drain insertion/removal, were not selected. Subsequently, we recorded the administration of procedural sedatives and analgesics during these top five procedures.

In the study PICU, endotracheal suction is performed based on a set of clinical indications, including increasing ventilation pressures, decreasing oxygen saturations, decreasing tidal volume or ventilator minute volume, increasing end-tidal CO2, visible secretions, and saw-tooth pattern in the expiratory curve of the flow-volume loop.

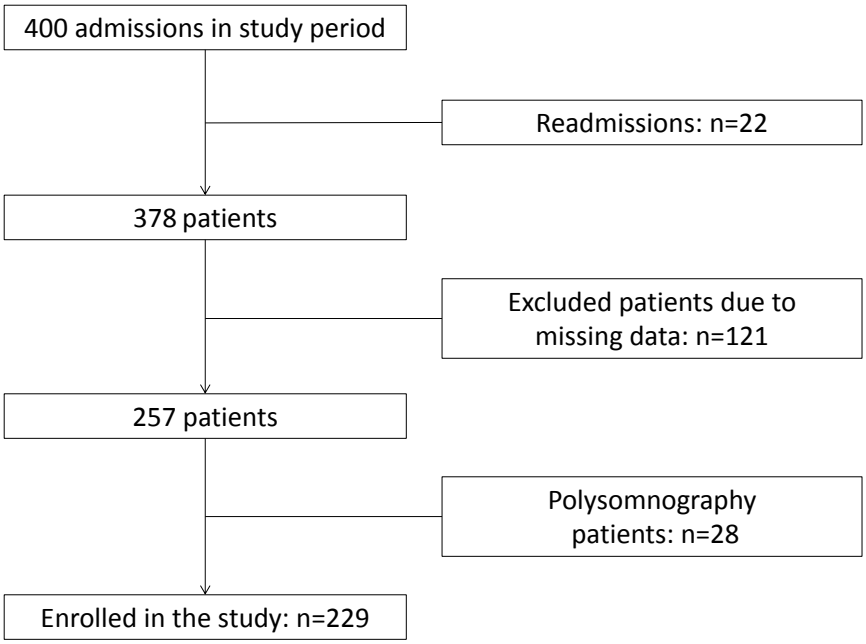
Statistical analysis

Demographics are presented with descriptive statistics as medians with IQRs. Neonatal vs. non-neonatal, postsurgery vs. non-postsurgery, and mechanically ventilated vs. non-mechanically ventilated patient group comparisons were based on the mean number of daily procedures per patient (i.e. the total number of recorded procedures per patient divided by the number of observation days) and performed with the Mann-Whitney U test for non-normal distributions of variables and Student *t* test for normally distributed variables. A Pearson correlation coefficient was performed for the linear correlation of severity-of-illness and the number of painful/stressful procedures. Data were collected per calendar day, and therefore, the patient's first observation day is not equal to the first 24 h of admission. SPSS (version 21; IBM Corp.,Armonk, NY, USA) was used for all analyses. A p-value <0.05 was considered statistically significant.

RESULTS

Four hundred admissions occurred during the study period, one-quarter of the total number of admissions (n = 1597) in 2016. After exclusion of readmissions (n = 22), of patients of whom no record forms were available (n = 121) and of patients admitted for polysomnography (n = 28), 229 patients were enrolled, accounting for 855 patient days (see Figure 1). Of the 121 excluded patients with missing record forms, 91 (75%) had been admitted for less than 24 h and 28 (23%) had been admitted for 24-48 h. Of all included patients, 97 (42%) had been admitted for less than 24 h. Patient characteristics are displayed in Table 1.

Figure 1. *Inclusion flowchart.*



Painful and stressful procedures

In total, 14,723 procedures were recorded during 855 patient days. A median number of 11 (IQR = 5 - 23) procedures had been recorded per patient per day, with a maximum of 113 in a patient who needed frequent endotracheal suctioning (93 times).

Table 1. *Patient characteristics.*

Characteristic	**Value**
Age in months (median, IQR)	15 (3-111)
Neonate (aged ≤28 days) n, (%)	40 (17.5%)
Boy/girl, n (%)	131/98 (57.2/42.8)
Length of stay in days (median, IQR)	2 (2-5)
Study observation days per patient (median, IQR)	2 (1-4)
Mechanical ventilation during data collection period, n (%)	
Not	166 (72 %)
Part of admission	36 (16 %)
Whole admission	27 (12 %)
ECMO, n (%)	5 (2.2%)
PRISM-III score (median, IQR)	3 (0-6)
PIM-2 score (median, IQR)	0.7 (0.3-2.1)
Diagnosis category	**N (%)**
Postoperative	
Yes	116 (51%)
No	113 (49%)
Cardiac	56 (25%)
Respiratory	54 (24%)
Neurological	47 (21%)
Gastro-intestinal	24 (11%)
Musculoskeletal	14 (6%)
Infection	5 (2%)
Urogenital	4 (2%)
Otolaryngological	3 (1%)
Other	22 (10%)

Abbreviations: ECMO: extracorporeal membrane oxygenation; IQR: Interquartile range; PIM: Pediatric Index of Mortality; PRISM: Pediatric RISk of Mortality

Further exploration of painful and stressful procedures identified that the median number of painful procedures was 7 (IQR = 2 - 19) and the median number of stressful procedures was 3 (IQR = 1 - 5). Endotracheal suctioning was the most frequent procedure (n = 6697, 45.5%). Table 2 identifies the top 10 most frequent painful and stressful procedures, including the median (IQR) pain score assigned by the 25 nurses (see also Fig. 2). The daily number of procedures tended to increase with longer duration of admission (Fig. 3).

The number of painful and stressful daily procedures in the group of neonates (median = 9, IQR = 7 - 17) was significantly higher than in the group of children >28 days (median = 7, IQR = 4 - 14) (p = 0.05). Regarding a comparison between mechanically ventilated and non-mechanically ventilated patients, the total number of procedures was significantly

higher in the former group: median = 15 (IQR = 9 - 22) versus median = 6 per day (IQR = 3 - 10), ($p < 0.001$). Non-ventilated patients received significantly less painful procedures than ventilated patients: median = 2 (IQR = 1 - 6) versus median = 10 (IQR = 5 - 19). They also received fewer stressful procedures: 2 (IQR = 1 - 5) versus 3 (IQR = 2 - 5).

Table 2. *Top 10 most frequently performed painful and stressful procedures with their perceived painfulness according to 25 nurses. All failed attempts and the final successful ones are counted as separate procedures.*

	Procedure	Total number of procedures (%)	Median (IQR) NRS pain
	Painful procedures		
1	Endotracheal suctioning	6697 (45.5%)	2 (1-5)
2	Oral suctioning	1166 (7.9%)	2 (2-5)
3	Nasal suctioning	1153 (7.8%)	3 (2-5)
4	Adhesive removal	326 (2.2%)	3 (2-4)
5	Heel stick attempts	282 (1.9%)	4 (3-6)
6	Finger stick attempts	220 (1.5%)	4 (3-6)
7	Nasal flow cannula or nasal prongs placement	176 (1.2%)	1 (0-1)
8	Peripheral IV cannula insertion attempts	170 (1.2%)	6 (4-8)
9	Peripheral IV cannula removal	137 (0.9%)	1 (1-2)
10	Wound dressing	119 (0.8%)	4 (4-6)
	Stressful procedures		
1	Spraying	1074 (7.3%)	0 (0-1)
2	ADL care	930 (6.3%)	not asked
3	EMV score	421 (2.9%)	not asked
4	X-ray	202 (1.4%)	not asked
5	General ultrasonography	127 (0.9%)	not asked
6	Weighing	103 (0.7%)	not asked
7	Electrocardiography	82 (0.6%)	not asked
8	Physiotherapy	69 (0.5%)	not asked
9	Cranial ultrasonography	33 (0.2%)	not asked
10	Electroencephalography	26 (0.2%)	1 (0-3)

Postoperative patients underwent significantly fewer procedures per day (median = 7, IQR = 4 - 12 versus median = 9, IQR = 4 - 17, $p = 0.03$), with no significant difference in the number of painful procedures but a significantly lower number of stressful procedures: median = 2 (IQR = 1 - 4) versus median = 3 (IQR = 1 - 5).

There was a low correlation between severity of illness and the mean number of procedures per patient per day. Correlation for the PRISM-III score was 0.26 (95% confidence interval = 0.13 - 0.38) and for the PIM-2 score 0.20 (95% confidence interval = 0.07 - 0.32).

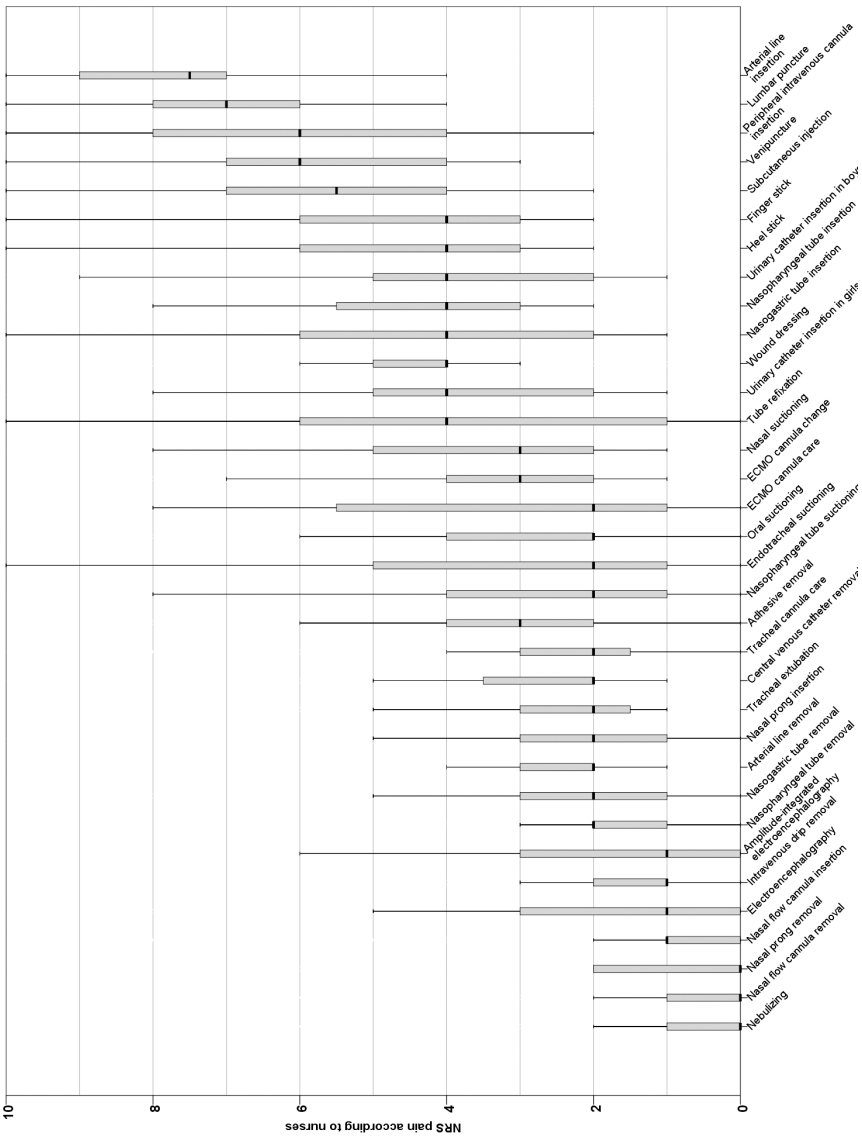
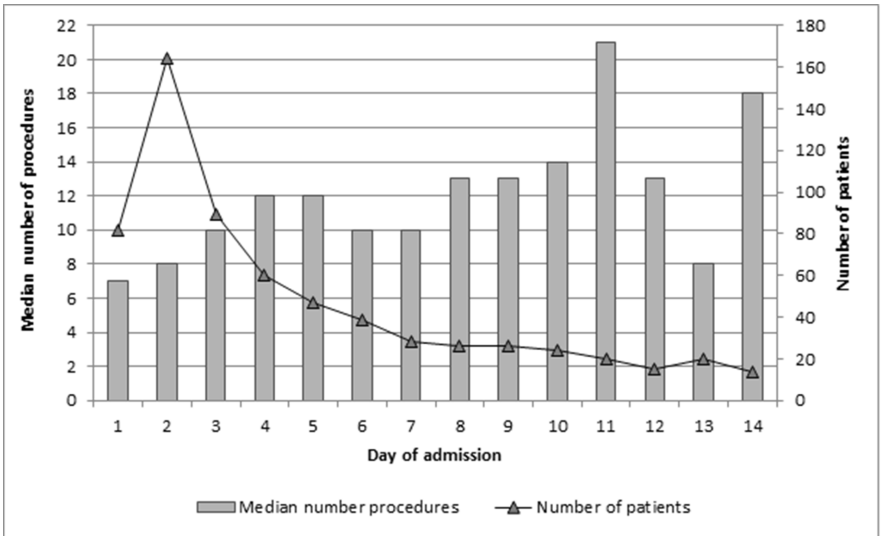


Figure 2. *Box plot of ratings by 25 paediatric intensive care nurses of the painfulness of the listed procedures in ascending order.*

Figure 3. *Number of procedures per admission day and the number of patients per admission day included for analysis.*



Day 1 of admission reflects calendar day 1, not the first 24 h of admission.

Table 3 shows the total numbers of attempt per intended procedure. We observed a lower success rate (i.e. procedures without multiple attempts) for lumbar puncture, arterial line insertion, peripheral IV cannula insertion, and venipuncture (Table 4).

Procedural analgesia and sedation

Background analgosedation during procedures is illustrated by Figure 4a (for the procedures rated most painful) and Figure 4b (for the most frequent procedures).

Continuous opioid administration was used in less than 40% of these procedures. For a full overview of background analgosedation during all procedures see Appendix 3. Table 5 shows the procedural analgesic and sedative treatment of the top five most painful procedures: arterial line insertion, lumbar puncture, peripheral IV cannula insertion, venipuncture, and subcutaneous injection. Although in the top five, venipuncture and subcutaneous injection have not been treated with procedural systemic analgesics or sedatives at all. Arterial line insertion was also covered in 25% of procedures. Two out of three lumbar punctures were covered by procedural analgosedation. Ketamine was the most frequently used agent, often accompanied by midazolam or propofol.

One patient underwent endotracheal suctioning 93 times in a day. This patient was admitted for a viral airway infection and received continuous midazolam and morphine.

Table 3. *Numbers of attempt and success rate per painful procedure.*

Procedures	Number of intended procedures	Total number including failed attempts	Percentage of procedures with success in one attempt
Subcutaneous injection	34	34	100%
Thoracic drain insertion	5	5	100%
Urinary catheter insertion	25	26	95.8%
Nasogastric tube insertion	90	93	95.7%
Finger stick for blood sampling	192	220	90.2%
Heel stick for blood sampling	256	282	89.9%
Central venous catheter insertion	23	36	86.4%
Endotracheal intubation	9	11	77.8%
Peripheral IV cannula insertion	88	170	68.8%
Lumbar puncture	3	7	66.7%
Arterial line insertion	23	45	65.0%
Venipuncture for blood sampling	28	50	57.9%

IV = intravenous

Table 4. *Number of painful and stressful procedures covered by an analgesic or a sedative.*

	Painful procedures	Stressful procedures
Paracetamol	1950 (17.1%)	791 (23.7%)
Paracetamol + NSAID	119 (1.0%)	102 (3.1%)
Any opioid	321 (2.8%)	111 (3.3%)
Sedative alone	988 (8.7%)	189 (5.6%)
Sedative + PCM	1128 (9.9%)	211 (6.3%)
Sedative+opioid	4378 (38.5)	888 (26.6%)
No analgesic or sedative	2502(22%)	1045 (31.3%)

NSAID = non-steroidal anti-inflammatory drugs; PCM = paracetamol.

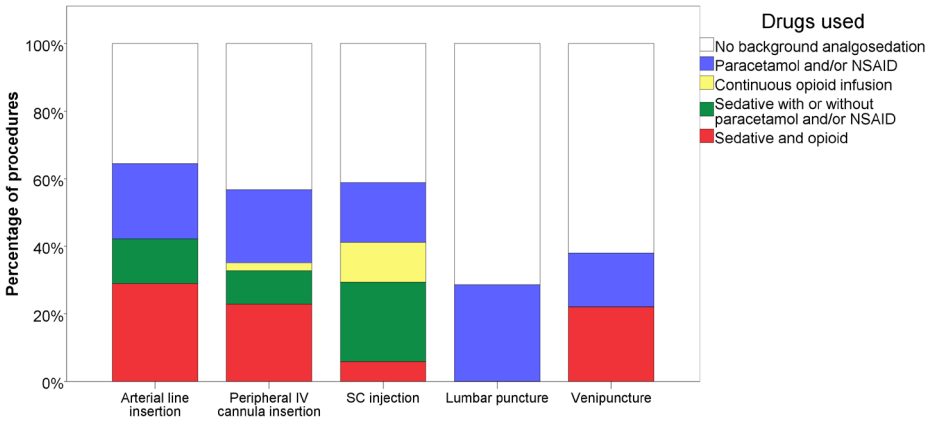
Table 5. *Procedural analgesic and sedative bolus administration for treatment of pain during the 5 most painful procedures.*

Procedure	Covered by procedural analgosedative (n, %)	Drugs used
Top 5 most painful procedures		
1. Arterial line insertion (n=20)	5 (25%)	Ketamine (n=3) Propofol (n=3) Fentanyl (n=2) Midazolam(n=1)
2. Lumbar puncture (n=3)	2 (67%)	Ketamine (n=2) Propofol (n=1) Midazolam (n=1)
3. Peripheral IV cannula insertion (n=77)	5 (6.5%)	Midazolam (n=3) Ketamine (n=1) Propofol (n=1)
4. Venipuncture (n=28)	0 (0%)	
5. SC injection (n=27)	0 (0%)	

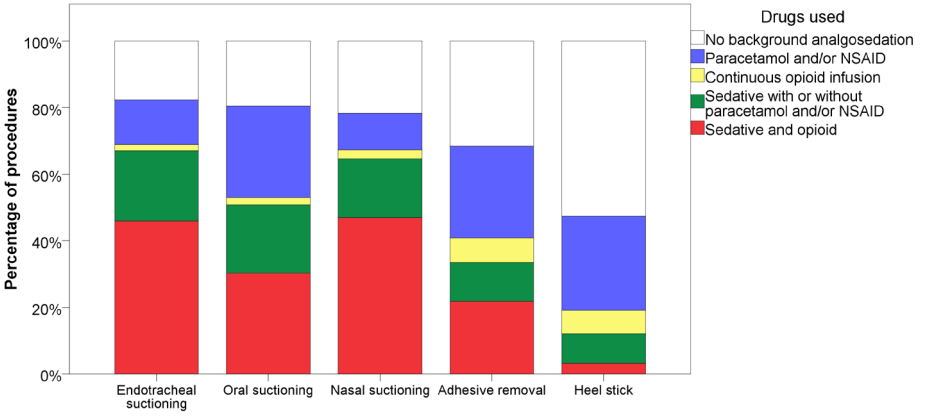
IV= intravenous; SC=subcutaneous

Figure 4. *Background analgosedation in patients during the most painful (a) and most frequent (b) procedures. NSAID = non-steroidal anti-inflammatory drugs; SC = subcutaneous*

a)



b)



DISCUSSION

This first prospective observational cohort study on the frequency of painful and stressful procedures in the PICU setting revealed a median number of 11 per patient per day. Endotracheal suctioning was most frequent, followed by oral and nasal suctioning. Nurses ranked lumbar puncture, arterial puncture, peripheral IV cannula insertion, and venipuncture as the most painful procedures, and for those, often more than one attempt was needed to be successful.

The findings of this study are comparable to findings from previous studies in the NICU setting,[5-7,9] although the total population differs. The current study includes neonates, and this group formed 17.5% of the total population. The median number of procedures (9, IQR = 7 - 17) in this group was lower than that in the NICU studies. Possible explanations are the inclusion of more premature neonates in the NICU studies compared to the study PICU where neonates are admitted after surgery only. Additionally, the neonates in this study had already undergone many procedures before admission at the PICU, for example endotracheal intubation and the insertion of arterial lines, central venous lines, peripheral IV cannulas, bladder catheters, and nasogastric tubes as part of the perioperative procedures in the operating room. The number of procedures also varied between studies. The current study included a total of 40 procedures compared to the study by Carbajal et al.[5] which included 24, and the studies by Simons et al.[7] and Roofthooft et al.[6] included 34 procedures. The current study overlapped with the total of these two studies, but extracorporeal membrane oxygenation and tracheal cannula care, nebulising, computed tomography and magnetic resonance imaging scans, and urinary catheter insertion were not listed. The inclusion of these additional procedures in the NICU studies could have increased their number of painful and stressful procedures.

With regard to the PICU, a multi-centre study in 15 Canadian PICUs from 2007 to 2008 recorded a median of 12 painful procedures per day.[3] In our present study, 9 years later, we found a median of seven painful procedures per day. This lower number could be explained by the fact that this study did not include procedures performed before admission to the PICU, such as endotracheal intubation, line insertion, and needle sticks in the emergency department, operating room, or referring hospitals. Whether Stevens et al. included these procedures is not clear. In addition, healthcare professionals may have become more aware of the amount of consistent procedural pain and tried to minimise the number of painful procedures, for example by changing routine endotracheal suctioning to criteria-led suctioning.

Not surprisingly, the number of daily procedures is highest in the mechanically ventilated patients, as suctioning involves almost half of all procedures. In the NICU studies, nasal and endotracheal suctioning are also the most frequent procedures.[6,7] In the current study, low numbers of both procedural and background analgosedation were observed for the most painful procedures, despite a well-balanced and published analgosedation regimen in place.[11,12] Background analgosedation was used more often during the most frequent procedures; this could be attributed to the fact that suctioning is performed more often in mechanically ventilated patients who are usually sedated.

Limitations

One of the limitations of this study is the risk of bias by underreporting. For lack of time or attention, nurses may not have recorded all procedures on the checklist during a shift or considered some procedures not painful or stressful as they could have not had enough time to review the case report form. Also, selection bias could have occurred due to the missing data from short admissions, although the majority of these patients were admitted for polysomnography and otherwise excluded from the study. The researchers double-checked reporting against the medical records, which nevertheless might also be incomplete. Also, the most painful procedures were selected based on survey results among 25 randomly selected nurses (accounting for 15% of total PICU nursing staff). This is a method prone to a certain degree of subjectivity. Still, in another observational study, skin-breaking procedures were ranked most painful as in the current study.[15] Moreover, painfulness and stressfulness cannot always be easily distinguished. For example, the most frequent procedure, endotracheal suctioning, has been regarded as painful in the literature[16,17] but may be stressful as well.[18-20] Our survey shows a high variability in responses by nurses to endotracheal suctioning. The observed pain behaviour during endotracheal suctioning in studies using several pain scales could also be a response to stress, as this is a very frightening, unpleasant procedure.

Interpretation

The painfulness of a procedure can vary within and between patients, although this needs further study. For example, activities of daily living may normally not be painful but may be very painful in a patient after severe trauma. Perceptions of painfulness may also affect pain management. For example, in our hospital, topical anaesthesia is frequently used before peripheral IV cannula insertion but is rarely ever used before heel or finger sticks. This is remarkable as these procedures may not differ in painfulness. Further study is warranted to explore the perception of painfulness of procedures and standardisation of procedural pain management by performing prospective evaluation of pain during procedures.

FUTURE PERSPECTIVES

Painful and stressful procedures are, unfortunately, unavoidable in paediatric critical care. Measures to reduce the number of these procedures should be considered. To reduce the frequency of endotracheal suctioning, which was found most frequent, we could recommend re-considering the indications for endotracheal suctioning. In the study centre, suctioning is performed only at indications supported by current evidence. Prospective evaluation of these indications in relation to the need of suction could possibly reduce the frequency of suctioning by identifying the strongest indications and by performing suctioning only for the strong indications.[21]

Another way of reducing the frequency of painful procedures is to improve technical skills to reduce the number of attempts for certain procedures that required multiple attempts. These were also ranked as most painful procedures: lumbar puncture, peripheral cannula insertion, arterial puncture, and venipuncture. The number of lumbar puncture attempts may be improved through the use of simulation training[22] or with the use of ultrasound.[23,24] Ways of improving venipuncture and peripheral IV cannula insertion are yet to be established because so far vein visualisation techniques have not been proven to be effective in reducing the number of failed attempts of IV cannula insertion or venipuncture.[25-27]

Standardisation of pain-reducing measures, both pharmacologic and non-pharmacologic, could improve the quality of care for critically ill children. NICU guidelines recommend several measures such as oral sucrose administration, facilitated tucking position, and non-nutritive sucking.[28] However, guidelines for the PICU are not available yet. In the study centre, oral sucrose is administered to neonates; however, this is not a standardised practice. Eutectic mixture of local anaesthetic is also available but is only used in older children and is also not standardised. Uniform guidelines should be established to improve the analgesic management of painful procedures.

CONCLUSIONS

The PICU patients in this study on average underwent seven painful and three stressful procedures per day. Mechanically ventilated patients undergo more than twice as many painful procedures than non-ventilated patients, as endotracheal suctioning accounts for almost half of all. Nurses regarded skin-breaking procedures most painful but these procedures were rarely covered by procedural analgosedation and only in less than half of the cases continuous background analgosedation was used. Measures to reduce the number of painful procedures could include revision of indications for endotracheal suctioning and improving technical skills through training and/or the use of assistant devices such as ultrasound guidance.

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7

Clinically effective implementation of intravenous paracetamol as primary analgesia after major surgery in neonates and young infants

Manuel A. Baarslag, Erwin Ista, Tom G. de Leeuw, Joost van Rosmalen, Monique van Dijk, Dick Tibboel and Saskia N. de Wildt.

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ABSTRACT

Background: A previous RCT showed equipotency of paracetamol IV compared to morphine IV after surgery in infants, and significantly reduced morphine consumption. Many RCT results are neither implemented nor evaluated in real-life clinical care. We implemented and studied the efficacy of and adherence to a protocol dictating paracetamol IV instead of morphine IV as primary analgesic in infants.

Methods: Data were collected from infants after major surgery. The protocol prescribed a morphine bolus dose (100 mcg/kg, IV) followed by paracetamol IV and rescue morphine if needed. Outcome measures were: 1. for therapeutic efficacy: total morphine need, rescue morphine, pain scores and adverse events; and 2. for protocol adherence: type of analgesics and doses given. These data were compared to RCT results.

Results: Of 75 patients, 62 were aged <11 days (82.7%). 1. Therapeutic efficacy: The median cumulative morphine consumption 48 hours postoperatively, was 121 mcg/kg (IQR 93-320). This was similar to the RCT paracetamol arm: 121 mcg/kg (IQR 99-264), p=0.72. Forty (53.3%) patients did not receive rescue morphine; 8 patients only received boluses (median n=2, IQR 1-4), 27 also received continuous morphine (median 7.9 mcg/kg/hr (IQR 5-10)). 2. Adherence: Seventy-four (98.7%) patients received IV paracetamol. Sixty (80.0%) patients received a median morphine (n=50) or other opioid (n=10) loading dose of 100 mcg/kg (IQR 88.2-112.4). Morphine was started sooner and at higher doses than the protocol dictated.

Conclusions: IV paracetamol as primary analgesic in postsurgical infants was successfully implemented. This finding supports wide-spread implementation of IV paracetamol as primary analgesic in infants.

INTRODUCTION

Applying findings of a randomized controlled trial (RCT) in clinical practice is a big challenge. It will take around 17 years and is affected by barriers such as low acceptance by health care professionals, lack of motivation and lack of awareness about and 'forgetting'.[1-3] Moreover, clinical outcomes of an intervention in real-life clinical practice may differ from those in a research setting. An important cause is the difference in study population of trials and clinical practice, as in most trials strict inclusion and exclusion criteria limit the inclusion of 'outlier' patients. Clinical implementation studies are needed to determine the success of new interventions in clinical practice after good RCT results have been obtained. This implementation study describes the successful implementation of a new postoperative pain protocol in infants undergoing major non-cardiac surgery.

Opioids have a key role in the postoperative analgesia of children after major thoracic and abdominal surgery. Regrettably, these can cause adverse effects such as respiratory depression, oversedation, urinary retention and gastrointestinal paralysis.[4] Paracetamol as an alternative analgesic was found to be potentially opioid-sparing in adults and older children.[5-8] Another study with rectal paracetamol in children below the age of 4 did not find a morphine-sparing effect after major surgery.[9] This was explained by the plasma level variability of rectal paracetamol. Both study groups also received a high background morphine infusion, which could not be decreased in the first 24 hours after surgery.[9] In 2013 we published the results of a double-blind RCT in our institution: infants between 0 and 1 years old received either intravenous (IV) paracetamol (n=33) or IV morphine (n=38) as a first-choice analgesic after major abdominal or non-cardiac thoracic surgery.[10,11] Morphine rescue medication was given on demand in both groups. The main finding was a 66% lower overall morphine consumption in the paracetamol group with similar pain scores.[12] This motivated our team to implement these study findings into our hospital's clinical practice.

The aim of this study was to evaluate 1. The 'real-life' efficacy of paracetamol IV as primary analgesic after major surgery in neonates and young infants and compare this efficacy to the trial results, and 2. Staff adherence to the new clinical protocol.

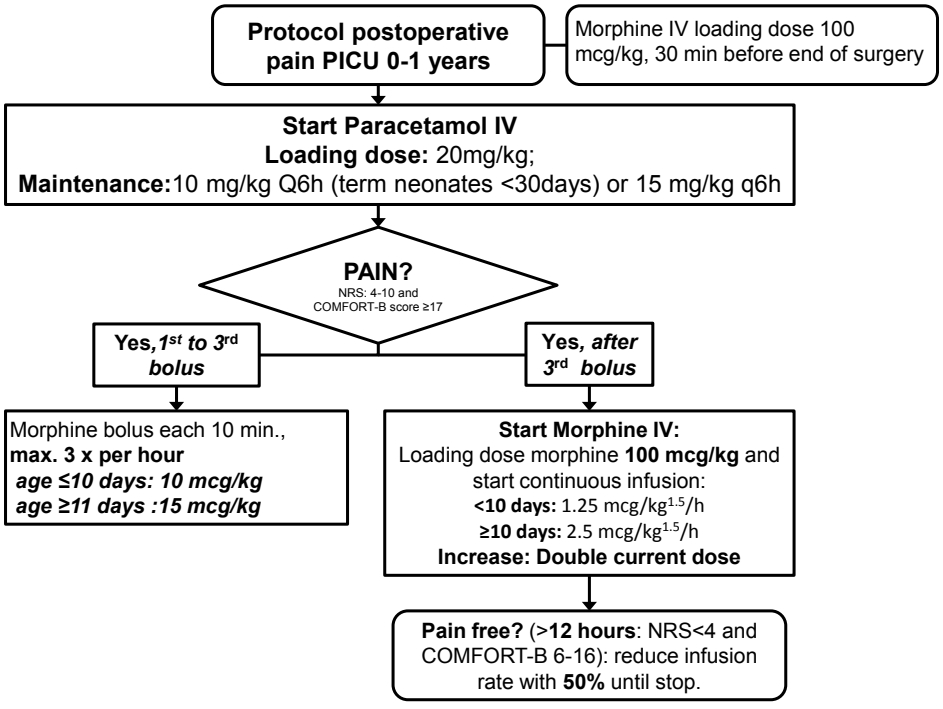
METHODS

Study design

This retrospective implementation study was performed in the level-three intensive care unit (ICU) of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands. Patients were included from 1st February 2014 till 1st December 2015.

Patients younger than 1 year admitted to the ICU after major (non-cardiac) thoracic or abdominal surgery were eligible for inclusion. For patients operated more than once in the study period, only the first surgery was included. Patients having received morphine in the 24 hours before surgery were excluded, as well as patients having received loco-regional blockade or epidural anesthesia perioperatively. The Erasmus MC research ethics board provided a waiver for ethics approval and informed consent according to the Dutch law on research in humans (MEC 2016-087).

Figure 1. *Bedside Pain Protocol flowchart.*



Postoperative Pain Protocol

By the new protocol (Figure 1), an IV morphine bolus of 100 mcg/kg was administered +/-30 minutes before the end of surgery. The previous protocol then prescribed continuous morphine infusion (10-20 mcg/kg/h) but this was now changed to paracetamol IV as follows: postoperatively, patients were given a loading dose of IV paracetamol (20 mg/kg) within 1 hour of arrival on the ICU. Intravenous paracetamol was given in accordance with the Dutch Pediatric Drug Handbook (Figure 1).[13] Pain and distress were assessed with the COMFORT Behavior scale (COMFORT-B scale) and the Numeric Rating Scale-11 (NRS-11) by the attending nurse every two hours or when clinically indicated. Both scales have been validated for this age group and indication.[14-17] Up to three morphine rescue boluses (Figure 1) were given within one hour if scores indicated pain (COMFORT-B ≥17 and/or NRS-11 ≥4). Another change to the protocol concerned the dose of the morphine rescue infusion. If pain persisted, continuous morphine was started (1.25 mcg/kg$^{1.5}$/h if ≤10 days vs. 2.5 mcg/kg$^{1.5}$/h if ≥11 days) after a bolus of 100 mcg/kg. These morphine infusion rates were validated in a previous population PK model, resulting in similar morphine plasma concentrations across the age range of 0 to 1 year, and was also used in the RCT.[18] The morphine infusion rate could be increased until adequate analgesia was reached, each increase preceded by a 100 mcg/kg IV loading dose.

Implementation

During a three-month implementation period, nurses and physicians were educated in a 30-minute session, in which the background of the protocol changes and the revised procedure was explained. New staff recruited during the study period was also instructed. To remind the nurses and physicians using the new pain protocol we used a bedside flowchart (Figure 1), pocket cards, and screen-savers on all the desktops in the PICU. Further, we appointed local opinion-leaders encouraging colleagues to work according to the protocol (e.g. during daily rounds).

Study end points

The primary end points were:

1. Efficacy of paracetamol IV as defined by the total opioid consumption (mcg/kg in morphine equivalent doses) in the first 48 hours postoperatively, including the intraoperative loading dose, the rescue morphine doses and the continuous infusion dose. Secondary end points were: the number of rescue morphine doses per patient, number of patients receiving rescue doses and/or continuous morphine, time to first rescue dose, mean NRS-11 and COMFORT-B scores, and morphine-related respiratory adverse effects. Morphine-related respiratory adverse effects were defined as: (1) apnea, defined as oxygen saturation less than 92%, or longer than 15 seconds, or reported by the nurse with a subsequent intervention like extra oxygen supply; (2) reintubation; (3) naloxone administration.

2. Adherence to the protocol, defined by correct morphine loading dose, correct IV paracetamol loading and maintenance doses, rescue doses given on the basis of pain scores, cases in which at least three morphine rescue boluses had been given before the start of continuous morphine, morphine rescue infusion dose.

Data collection

Data were retrieved from the electronic patient data management system. Collected patient data included age at surgery, sex, type of surgery, severity-of-illness scores (PIM-2),[19] surgical stress score[20] (calculated retrospectively), postoperative mechanical ventilation duration, and relevant co-medication.

The collected drug dosing data included administration route, dosage, the use of a morphine or equivalent opioid loading dose, the use of a paracetamol loading dose, number of morphine rescue boluses and dosages, and the use of continuous morphine and its dosages during the first 48 hours. Complete protocol adherence was defined as having received an intra-operative opioid loading dose of 100 mcg/kg (+/- 10%), and having received an IV paracetamol loading dose of 20 mcg/kg (+/- 10%) and having received appropriate IV paracetamol maintenance doses. For patients who received rescue morphine, the next criteria apply as well: Up to three boluses of IV morphine in the appropriate dose and in case of continuous morphine, started with the correct dose and having been preceded by three boluses.

During data analysis, we noticed that not all patients had received a morphine loading dose during surgery; either because they were given piritramide instead of morphine or received additional fentanyl boluses towards the end of surgery. In the latter case, the anesthesiologist refrained from giving the morphine bolus as these fentanyl doses were expected to provide similar analgesia directly postoperatively. We included the piritramide and fentanyl doses by calculating morphine equivalents as follows: 1 mg morphine equaled 0.015 mg fentanyl, and 1 mg piritramide.[21]

Statistical analysis

Summary statistics are presented as medians (interquartile range [IQR]) or means (standard deviation [SD]) for continuous variables and as percentages for categorical variables. Primary and secondary outcomes of this study were compared with individual patient data of the intervention group of the RCT by Ceelie et al.[10] using a Mann-Whitney U test as the data were not normally distributed. Categorical data were tested with Fisher exact test. Mean COMFORT-B and NRS scores were calculated for the individual patient during the first 48 hours. A two-side p-value of < 0.05 indicated statistical significance. All statistical analyses were performed using SPSS version 21.0 (IBM SPSS Statistics).

RESULTS

Patients

Data of 75 of 135 eligible patients were included in the analysis (Figure 2). Excluded patients were significantly older (49% ≥ 11 days of age; p <0.0001), but sex, type of surgery, and mechanical ventilation did not differ from the included patients. The median age of included patients was 3 days (IQR 1-6) and 62 (83%) were ≤ 10 days of age (Table 1). Sixty-one patients were ventilated after surgery with a median duration of 24 hours (IQR 16-78.5). The included patients were significantly younger; more often mechanically ventilated; and had higher surgical stress scores than the patients in the paracetamol group of the RCT (see Table 1).

Figure 2. *Inclusion flowchart*

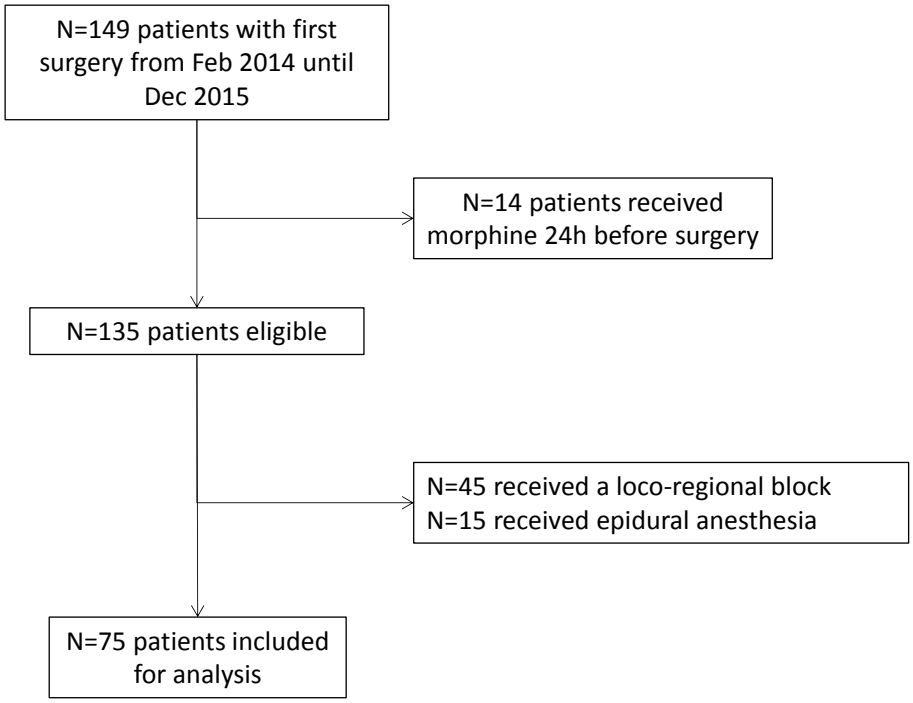


Table 1. Patient characteristics

	Implementation cohort (n=75)	RCT – paracetamol group (n=33)	p-value
Age in days [median (IQR)]	3 (1-6)	5 (2-65)	0.07
Age groups [n=(%)]			0.001
-≤10 days	62 (82.7)	17 (51.5)	
-≥11 days	13 (17.3)	16 (48.5)	
Weight in kg [median (IQR)]	3.0 (2.7-3.6)	3.4 (2.7-4.7)	0.04
Sex [n= (%)]			
-Male	48 (64.0)	18 (54.5)	0.39
-Female	27 (36.0)	15 (45.5)	
Major surgery in history [n=(%)]	3 (4.0)	ND	-
Type of surgery [n= (%)]			0.17
-Thoracic	24 (32.0)	5 (15.2)	
-Abdominal	51 (68.0)	28 (84.8)	
Ventilation after surgery [n=(%)]	61 (81.3)	15 (45.5)	<0.0001
Duration of ventilation after surgery in h [median (IQR)]	24 (16-78.5)	34 (15-45)	0.03
PIM2 percentage [median (IQR)]	1.5 (0.5-4.1)	1.3 (0.6-1.9)	0.39
Surgical stress score [median (IQR)]	9 (8-10)	10 (9-11)	0.001

RCT – Randomized Controlled Trial; ECMO - Extracorporeal Membrane Oxygenation; PIM – Pediatric Risk of Mortality; IQR – Interquartile range

Efficacy: Morphine loading and rescue dosing

The median cumulative morphine dose per patient was 121.1 (IQR 92.6-319.9) mcg/kg per 48 hours (Table 2) and an overall median of 0 (IQR 0-3.0) bolus doses. More in detail: sixty (80.0%) patients received a median 100.0 mcg/kg (IQR 88.2-112.4) morphine (n=50) or morphine equivalent (n=10) loading dose before transfer to the PICU. Thirty-five (46.7%) patients received morphine rescue bolus doses with a median number of 2 per patient (IQR 1-4). Twenty-seven of those (36.0%) also received continuous morphine, at a median rate of 7.9 mcg/kg/hr (IQR 5.0-10.0).

The cumulative morphine dose in patients ≤ 10 days of age was significantly lower than that in older patients (p=0.034). The median cumulative morphine dose was similar to that in the RCT (p=0.42); the proportion of patients receiving rescue morphine was almost significantly lower than in the RCT (46.7% vs 66.8%, p=0.06) (Table 2). The overall median number of morphine rescue doses per patient was significantly lower than that in the RCT: 0 (IQR 0-3) vs 2 (0-5) (p=0.012). The median loading dose of morphine or equivalent other opioid was not significantly different from the dose in the RCT (p=0.185).

Table 2. *Outcome measures of implementation cohort versus original RCT*

	Implementation cohort (n=75)	**RCT – paracetamol group (n=33)**	***p-value***
Morphine consumption‡ in mcg/kg/48h			
[median (IQR)]	121.1 (92.6-319.9)	121 (99-264)	0.724
[mean (SD)]	234.3 (256.5)	209.6 (196.4)	0.624
According age groups			
- ≤10 days	111.7 (89.7-267.2)[a]	111.1 (96.4-169)[c]	0.361
- ≥11 days	262.3 (134.5-542.9)[b]	151.6 (112-346)[d]	0.121
Morphine equivalent loading dose*‡			
[median (IQR)]	100.0 (88.2-112.4)	98.7 (95.0-100.2)	0.185
[mean (SD)]	94.0 (6.7)	99.4 (2.1)	
Rescue morphine dose in mcg/kg			
[median (IQR)]	0 (0-194.9)	25 (0-164.0)	0.365
[mean (SD)]	140.3 (27.9)	110.2 (34.2)	
Number of rescue morphine doses [median (IQR)] all patients	0 (0-3.0)	2 (0-5.0)	0.012
Number of patients receiving rescue morphine [n= (%)]	35 (45.5)	22 (66.8)	0.06
Number of patients receiving continuous morphine [n= (%)]	27 (35.1)	8 (24.2)	0.372
Number of rescue morphine doses [median (IQR)] in patients receiving rescue (n=35)	2 (1-4)	ND	
Time to first morphine rescue dose in minutes [median (IQR)]	120 (66-366)	ND	
COMFORT-B score [mean (SD)]	12.1 (2.1)	13.1 (2.1)	0.03
COMFORT-B ≥17 [n= (%)]	30 (40)	22 (66.7)	0.008
NRS Score [median (IQR)]	0 (0-0.4) **	1 (0-1) ***	0.003
NRS ≥4 [n= (%)]	21 (28.0) **	22 (68.8) ***	<0.0001

*RCT – Randomized Controlled Trial; NRS – Numeric Rating Scale; IQR – Interquartile Range; SD – Standard deviation; a: n=64; b: n=13; c: n=17; d: n=16; * n=69 patients received an intraoperative loading dose of morphine or other opioid; NRS scores available in **n=67 patients; ***n=32 patients; ‡ morphine consumption and loading dose depict morphine and morphine-normalized doses of other opioids.*

The median COMFORT-B and NRS-11 scores were significantly higher for patients who had received rescue morphine compared with patients who received only intravenous paracetamol (COMFORT-B score: 13.7 [IQR 11.2-14.8] vs 11.0 [IQR 10.1-11.7], p<0.0001; and NRS-11: 1.3 [IQR 0.5-2.3] vs 0 [IQR 0-0.3], p<0.0001). Also, the proportion of high COMFORT-B scores (≥17) was significantly higher in patients who had received rescue morphine 77% vs 23% (p<0.0001).

Morphine-related respiratory adverse events were observed in 13 of 75 (17 %) patients. These were counteracted by the following interventions: oxygen supply (n=6), change in ventilator setting (n=4), administration of naloxone (n=1), and re-intubation (n=2). Re-intubation was needed in one case for tube dislocation and in one case for bradypnoea after abdominal surgery.

Protocol adherence

Sixty of 75 patients received an opioid loading dose before transfer to the PICU, of whom 10 received piritramide or fentanyl instead of morphine. Seventy-four (98.7%) patients received an intravenous paracetamol loading dose and maintenance doses. One other patient received rectal paracetamol. For 63/75 (84.0%) patients the paracetamol loading and maintenance doses were in accordance with the Dutch Pediatric Drug Handbook guidelines. Twenty-seven patients started on continuous rescue morphine, of whom only 7 (25.9%) correctly received 3 bolus rescue doses before start; all other patients received fewer boluses prior to the start of continuous infusion. Five of those 27 (18.5%) patients received the correct infusion dose; all others received higher doses than the protocol prescribed. Of all 62 morphine rescue boluses given, 57 (91.9%) were given after a NRS≥4 and/or a COMFORT-B score ≥17. In total, 10/75 (13.3%) patients of patients were treated with complete protocol adherence.

DISCUSSION

Intravenous paracetamol as primary analgesic in neonates and young infants after major surgery was effectively implemented in clinical practice as the morphine consumption was as low as in the paracetamol arm of the RCT. Moreover, only half of patients needed small morphine rescues doses and one third an additional continuous morphine infusion. In the RCT, the additional rescue morphine dose did not differ between patients receiving paracetamol IV and those receiving morphine continuous infusion, and pain scores were similar in these groups.[10] These findings suggest that we have overcome some of the traditional barriers to successful implementation, such as lack of awareness and agreement.[22,23]

Adherence to the first part of the protocol, i.e. the instruction to give an opioid loading dose followed by IV paracetamol as first-choice analgesic, was high. Also, rescue boluses were given in more than 90% of cases when pain scores indicated pain. Interestingly, morphine infusions were often started before the patient had received all 3 boluses doses and at a higher rate than the protocol dictated, contributing to the relatively low overall protocol adherence. The relative complexity and newness of the morphine dosing might explain that the infusion doses prescribed were higher than the protocol recommendation. Nevertheless, the earlier start of rescue morphine infusions with higher doses did not result in overall higher morphine requirements. Hence, we still consider the clinical implementation of paracetamol IV as primary analgesic successful in daily practice.

We also found that patients under the age of 11 days needed less rescue morphine than older children, in line with earlier findings.[10,18] This might suggest either that the opioid-sparing effect of IV paracetamol with morphine rescue is more pronounced in this age group or that older infants (10 days to one year) experience more postoperative pain. The latter explanation is supported by a similar observation in our RCT: in the trial arm receiving continuous morphine, the neonates needed less rescue morphine than the older children, while morphine plasma concentrations were similar.[18] A PK-PD study showed an increasing hazard ratio for additional morphine doses post cardiac surgery with increasing age, with the largest increase in the first year of age, which may support our findings.[24]

This study has several limitations. Several patients received other opioids than morphine as loading dose at the end of surgery. We included this dose after correction for opioid strength, but this still may have biased the comparison of total morphine dose between the RCT and the present study. Also, the number of children older than 10 days in our study was relatively small, which may limit the extrapolation of the results to the children older than 10 days. Reassuringly, though, like in the RCT, the older children needed more morphine than the younger children.[10] Moreover, demographics of our cohort differed from those

of the paracetamol group in the RCT. The median age was lower, albeit not significantly, and more patients were ventilated and for a longer period of time. Yet this did not affect the cumulative morphine doses. Further, the statistically significant 1-point difference in the surgical stress score cannot be considered as clinically relevant. Lastly, the present study was performed in the unit that was the setting of the original trial. The continued attention to adequate pain assessment by trained nurses and nurse-led protocolized analgesia in this unit may have positively influenced the results of the present study. Implementation of our protocol to other PICUs may be more challenging as many studies indicate that pain assessment is not systematically performed in neonates and infants; in developing and developed countries alike.[25-29]

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8

General discussion

GENERAL DISCUSSION

This thesis addresses several important issues of pain and sedation management in the PICU. **Chapters 2 and 3** make clear that solid evidence for the current clinical practices is lacking. We identified the problems of trial design and absence of objective and reliable clinical end points. **Chapter 4** describes a planned RCT which for several reasons was significant delayed and had a dismal inclusion rate. **Chapter 5** is an exploratory study on anticholinergic drug burden in patients with and without pediatric delirium and/or iatrogenic withdrawal syndrome. We found a higher drug burden in affected patients and this calls for further research. In **chapter 6** we counted a median of 11 painful and stressful procedures in patients admitted to the PICU and this leaves room for improvement. **Chapter 7** addresses the facilitators and barriers to implementing a new pain management protocol for postoperative infants, with paracetamol as first line analgesic drug. These studies raised a lot of questions and in this general discussion several of these questions will be addressed.

Drug therapy in the pediatric intensive care unit

Pediatric intensive care patients receive a median of 14 (IQR 9-19) different drugs during their admission,[1] often including analgesics and sedatives.[2] It has been realized for years that children are not 'small adults' and that their drug metabolizing capacity is still developing during the first years,[3] or even the first days,[4] of life. However, children admitted to a PICU are not representative of healthy children and their drug metabolizing capacity is influenced by other factors. Many extrinsic factors such as mechanical ventilation altering the hepatic and renal blood flow,[5-7] extracorporeal membrane oxygenation (ECMO), surgery[8] or therapeutic hypothermia,[9] can alter both pharmacokinetics (PK) and pharmacodynamics (PD).

Critical illness itself impacts PK. For example, inflammation, by affecting CYP3A metabolism, reduces midazolam clearance by 65%.[10] Patients with severe inflammation should therefore receive lower than usual midazolam. Multi-organ failure also reduces clearance due to liver and kidney dysfunction. On the other hand, treatment may also have an impact. ECMO affects both drug elimination and the volume of distribution.[6,7] Therapeutic hypothermia strongly reduces morphine clearance by diminishing enzymatic activity.[6,7,9] Positive pressure ventilation as well as cardiac surgery alters hepatic blood flow,[5] thereby affecting the PK of morphine.[11] It is therefore not surprising that critically ill children and neonates show greater inter-individual variation in clearance than their non-critically ill comparators.[12,13]

Inter-individual variation in PK and PD means that a one-size-fits-all drug dosing approach is not appropriate. 'Personalized' or 'precision' medicine is the way to go in the PICU.[14] But how can we achieve this? Most recent advances in pediatric critical care drug research have been made *in silico,* which means that trials are now being simulated *in silico*. The results

can be used in adaptive trial designs.[15] This approach allows for changing the sample size during the trial using pre-specified rules, based on the results from interim analyses. Also, population-PK models, and even PK-PD models, have led to a more precise dosing of morphine in children.[16,17] Yet, there are way more steps to be taken in this direction. An integrative, system-based approach, in which many variables are taken into account such as hepatic blood flow, critical illness, pharmacogenomics, could determine what drug dose is needed for an individual patient.[18] Hepatic blood flow can be measured non-invasively using Doppler ultrasound,[19] but there are no time- or age-dependent normalized values and the technique needs real expertise. Despite modeling efforts that take hepatic blood flow into account,[20] the contribution of hepatic blood flow to the clearance of high hepatic extraction ratio drugs in children has seldom been studied. Hence, we need pediatric physiologically based PK (PBPK) studies that take hepatic blood flow into account as a covariate with subsequent measurements of the hepatic blood flow in each patient with the exact date and time recorded.

There is a growing body of literature on the influence of pharmacogenomics on PK and PD in children.[21] Matic et al. found two genes that play a role in morphine pharmacokinetics in neonates, *UGT2B7*[22] *and SLC22A1* (OCT1),[23,24] and two genes that could be involved in opioid pharmacodynamics in neonates, *COMT* and *OPRM1*.[25,26] However, this genetic influence needs to be quantified in prospective studies and I would therefore recommend to sample blood or oral swabs for DNA analysis in future analgesic trials in the PICU. Residual material should be stored, as new candidate genes can be discovered. The storage costs should be budgeted and separate informed consent for sampling and DNA analysis should be asked. Still, most of these developments would only contribute to appropriate drug dosing. The evidence for using a drug in a specific population is predominantly based on the drug's safety and efficacy. First I will highlight a specific safety issue which applies to drug therapy in the PICU population: the long-term effect of drug exposure on the brain.

A developing brain might be impacted much more than a 'fully matured' brain by the administration of a drug acting on the central nervous system. Animal studies have shown alterations in brain development and neuroapoptosis after administration of opioids,[27] benzodiazepines[28] and narcotics in infant animals.[29] This could be explained by the 'growing into deficit' phenomenon, where early damage may have larger consequences later in life.[30] Fortunately, human data so far do not suggest a dramatic impact of opioid administration in young infants.[31-35]

This is nevertheless challenging to study further, as several factors may influence study end points. For example, untreated pain has also its effects on the developing human nervous system.[36-39] So if we observe altered brain structure in later life of neonates who received

opioids, does this mean the dosing was not sufficient to prevent pain-induced damage[38,40] or were they overdosed? Also, critical illness and its treatment influence neurodevelopment.[41] So how can we unravel the effects of the different components?

A good example of a trial addressing the long-term safety of anesthetics is the GAS-trial,[42] which compared the effects of local anesthesia on cognitive performance with those of general anesthesia. The study population consisted of children undergoing elective inguinal hernia repair. This study used stratification according to gestational age to control for prematurity. The investigators found no significant influence of short-term general anesthesia (sevoflurane) on cognitive performance two years later, like in other similar studies.[31,32] It should be noted, however, that the GAS-trial concerned relatively healthy children, and that the general anesthesia exposure was shorter than 60 minutes.

But how can we translate such research to the PICU, where children systematically receive opioids and benzodiazepines and sometimes need multiple surgeries? One possibility is a clinical trial with stratification according to diagnosis. Sedatives might have different effects in fairly healthy children with respiratory insufficiency than in children with brain injury. Moreover, local anesthesia techniques such as epidural or locoregional anesthesia may reduce the consumption of opioids in children and could serve as a basis for comparison between patients with low or high opioid consumption after surgery.[43]

Another important point of interest is our hypothesis that the earlier the damage has occurred, the larger the consequences later in life (growing into deficit).[44] However, the brain is known for its plasticity, especially the young and maturing brain.[45] Therefore, deficits may on the one hand cause bigger deficits in later life, but it could also be that the brain is able to compensate by restructuring mechanisms in order to "repair" damage. This could explain why a significant long-term effect of neonatal exposure to anesthetics, benzodiazepines or opioids has not been found yet.

De Graaf et al. investigated the long-term effect of routine morphine infusion in mechanically ventilated neonates.[31,32] At the age of 5 years, these children had a lower IQ on 'visual analysis' than those who had not received morphine; other significant differences were not found. At the age of 9 years, none of the outcomes was significantly different between the groups. These findings were supported by Van den Bosch et al. who found an average neurocognitive performance, assessed by the NEPSY-II-NL test, in 10-year-old who had been exposed to morphine at neonatal age.[35] Therefore, no major concerns about neonatal morphine exposure have been raised.

Table 1. An overview of studies investigating the possible harmful long-term effect of anesthesia exposure in young children.

Author, year of publication	Study design	N=
Ing et al., 2014[48]	Retrospective observational cohort study. in children exposed to anesthetics exposure ≤3 years of age	112 patients
Sun et al., 2014, PANDA trial[49]	Sibling matched ambidirectional cohort study	105 sibling pairs
Backeljauw et al., 2015[50]	Observational cohort study, patients exposed to anesthetics exposure ≤4 years of age	53 patients, 53 controls
Hansen et al., 2015[51]	Retrospective observational case-control study. Cases: Anesthetics exposure for neurosurgery in infancy	228 patients 14,698 controls
Graham et al., 2016[52]	Population-based case-control cohort study in children undergoing minor surgery <4 years of age	4,470 patients with one exposure, 3,640 patients with multiple exposures, 13586 controls
O'Leary et al., 2016[53]	Population-based case-control cohort study in children undergoing minor surgery <4 years of age	28,366 patients, 55,910 controls
Conrad et al., 2017[54]	Longitudinal follow-up study in children with cleft palate	87
Davidson et al., 2017, GAS-trial[42]	RCT between local anesthesia vs. general anesthesia for a short-term procedure	722 randomised
Glatz et al., 2017[55]	Population-based case-control cohort study in children undergoing minor surgery <4 years of age	33,514 patients, 159,619 controls
Hu et al., 2017[56]	Retrospective observational case-control study. Cases: single or multiple anesthetics exposure <3 years of age	1,057
Ing et al., 2017[57]	Retrospective observational case-control study. Cases: Anesthetics exposure ≤5 years of age	38,493 patients 192,465 controls

Primary outcome	Follow-up duration	Overall outcome on neurodevelopment	Age subgroup analysis?
Neuropsychological assessment, comorbidity and school grades	Up to 10 years of age	Increased risk of deficit assessed by neuropsychological testing, no difference in school grades	Not available
IQ	Up to 15 years of age	No difference exposed vs. unexposed	No difference across age groups
Neurocognitive assessment and MRI	Up to 18 years of age	Diminution of language abilities and cognition	Not available
Mortality and school grades	Up to 16 years of age	Significant but very small difference in school grades (lower grades in exposed group)	Not available
Early Development Index	Age 5-6 years	Decreased performance on the EDI in the exposed group	Age at exposure: ≤2 years: no significant difference >2 years of age: significant difference
Early Development Index	Age 5-6 years	Decreased performance on the EDI in the exposed group	Age at exposure: ≤2 years: no significant difference >2 years of age: significant difference
Cognitive, growths and brain measures	Up to 17 years of age	Increased frontal lobe size, no other significant effects	Not available
Neurocognitive function (BSID-III)	2 years of age	No difference exposed vs. unexposed	Not available
School grades at 16 years of age	Age up to 16 years	Lower school grades in exposure group	Significant difference for age 3-4 years at exposure, younger age groups no significant difference
Learning disabilities, ADHD, individual education programs or performance on standardized tests	Up to 18 years of age	Single exposure: Increased risk of lower reading and language achievement	Not available
Mental disorder in later life	Up to 18 years of age	Increased risk of mental disorder after anesthetic exposure (HR 1.26)	11 subgroups: no differences across age categories

Table 2. An overview of studies investigating the possible harmful long-term effect of opioid or benzodiazepine exposure in young children.

Author, year of publication	Study design	N=
Brain imaging studies		
Van den Bosch et al., 2015[35]	Follow-up of prematurely born neonates participating in an RCT of routine morphine infusion for ventilated neonates	19
Zwicker et al., 2016[38]	Prospective cohort study of very preterm neonates	136
Duerden et al., 2016[58]	Follow-up study of very preterm born neonates exposed to midazolam	138
Neurodevelopmental studies		
MacGregor et al., 1998[59]	Follow-up study of premature infant participants in two RCTs of morphine vs. other interventions during mechanical ventilation	95 (62 exposed)
Roze et al., 2008[60]	Population-based follow-up study of extremely premature born neonates (GA≤33 weeks)	1572
De Graaf et al., 2011[31]	Follow-up of prematurely born neonates participating in an RCT of routine morphine infusion for ventilated neonates	90 (49 of the morphine group)
Guerra et al., 2011[61]	Prospective follow-up of infants with cardiac surgery ≤6 weeks of age	135
Ferguson et al., 2012[62]	Pilot follow-up study of extreme premature infants (GA 23-32 weeks) that participated in an RCT of routine morphine infusion for ventilated neonates (NEOPAIN trial)	19 (14 exposed)
De Graaf et al., 2013[32]	Follow-up of prematurely born neonates participating in an RCT of routine morphine infusion for ventilated neonates	80
Van Zellem et al., 2014[46]	Follow-up study of children admitted to the PICU with meningococcol septic shock	77
Kocek et al., 2015	Retrospective chart review study of 100 extreme low birth weight infants	100 (60 high-dose patients)
Steinhorn et al., 2015[63]	Follow-up study of very preterm neonates admitted to the NICU	230 (57% exposed to morphine)
Van den Bosch et al., 2015[34]	Follow-up of prematurely born neonates participating in an RCT of routine morphine infusion for ventilated neonates	19

Primary outcome	Follow-up duration	Overall outcome on neurodevelopment	Age subgroup analysis?
Brain morphology with MRI and neuropsychological functioning	10 years after admission	No overall deviations from the Dutch average	Not available
MRI brain volume and BSID-III	18 months of age	Greater morphine exposure was associated with smaller cerebellar growth and poorer neurodevelopmental outcome (uncorrected)	Not available
MRI brain volume and BSID-III	18 months of age	Higher midazolam cumulative dose was associated with decreased hippocampal volumes and microstructural alterations, poorer cognitive function	Not available
WPPSI-R, Movement ABC, and the Child Behaviour Checklist	5-6 years of age	No significant difference between groups, trend toward better performance in exposed group	Not available
Presence of moderate or severe disability at 5 years of age (Kaufman Assessment Battery for Children)	5 years of age	No association between prolonged sedation and/or analgesia and poor neurodevelopmental outcome	Not available
RAKIT, Beery test, CBCL	5 years of age	Lower performance on visual analysis in morphine group, no other differences observed	Not available
BSID-II and BSID-III, and parent-derived Adaptive Behavior Assessment System	18-24 months of age	No association between cumulative analgesia or sedative dose and neurodevelopment	Not available
Head circumference, several parent-guided behavior assessment, Stanford-Binet test and WRAT4	5-7 years of age	Lower head circumference in exposed group, lower performance of memory tasks in exposed group, increased parent-reported behavioral issues in exposed group	Not available
WSIC-III, Beery test, CBCL, CANTAB	8-9 years of age	No effect of morphine on neurodevelopmental outcome	
WSIC-III, Stroop, TMT, Score!, Beery test and 15 Word test	Up to 6-17 years of age	Opioid use was associated with poorer neurodevelopmental outcome, barbiturates and benzodiazepines showed no effect	Not available
BSID-III	20 months of age	No effect of cumulative morphine dose	Not available
MRI and WASI, WRAT4, SDQ, CELF4 and BRIEF	7 years of age	No difference in cortical volumes. At 2 years, behavioral dysregulation was observed but at 7 years there were no significant difference between exposed and non-exposed patients	Not available
NEPSY-II-NL	8-9 years of age	Neurodevelopment was in line with Dutch reference	Not available

Our group did find a statistically significant effect of opioids on the long-term neurodevelopmental outcome in survivors of meningococcal septic shock; that is, poor test outcomes on several neuropsychological domains.[46] These children (n=77), tested at an age of 5-6 years, had a median age of 2 years when admitted to the PICU. It could be hypothesized that severe damage such as from a meningococcal meningitis,[47] considerably alters the plasticity of the brain, and that the possible second damage hit of opioid-induced neuroapoptosis has a larger detrimental effect on the brain. On the other hand, prolonged exposure to opioids and anesthetics may be more damaging in older children like in this 2-years old patients, as plasticity of the brain decreases over time. To illustrate this, I will focus on anesthetics, which have been much studied regarding their long-term effects. Table 1 provides an overview of pediatric studies investigating the long-term effect of anesthetics in children.

These studies had relatively large sample sizes, but had a retrospective design with a great risk of confounding. Therefore, the question on long-term effects of anesthetics cannot yet be properly answered. However, the O'Leary study,[53] the Graham study[52] and the Glatz study[55] all found significant differences only in the oldest age category, which could possibly contradict the current hypothesis of 'the earlier the exposure, the greater the damage' due to the greater plasticity of the younger brain covering up the evoked damage.

Prospective trials such as the GAS-trial are needed to provide a more robust insight in the long-term effects of anesthetics. Although an RCT comparing surgery with or without anesthesia is not at all feasible, as surgery will never be performed without anesthesia, efforts can be made to reduce the dose of general anesthesia. A good example of such a trial is the upcoming T-REX study (NCT03089905, clinicaltrials.gov), which investigated the long-term outcome of surgery performed with high-dose general anesthesia (2.5-3% of end-tidal sevoflurane concentration) or with dexmedetomidine + remifentanil + low-dose sevoflurane (0.8% of end-tidal sevoflurane concentration or less).

With regards to future studies of opioids and benzodiazepines, the focus should shift away from the neonatal age towards the entire developmental life span. Table 2 provides details of studies investigating the long-term neurocognitive outcome of opioids and benzodiazepine exposure. There is a trend for a possible negative long-term outcome in older children when compared to prematures.

Besides the recommendation to stratify according to diagnosis, age stratification can be recommended. This approach requires large sample sizes, for which both national and international collaboration is warranted. Nevertheless, such clinical trials will be only successful if several barriers have been overcome. These are addressed in the next section.

Challenges in pediatric clinical trials

A randomized controlled trial in young children will take much effort and resources, and is subject to many regulatory and ethical considerations. These efforts and resources are spent in vain, however, if a trial is not as successful as hoped for. Yet, in pediatrics, 19% of all trials were discontinued before the end of the trial, and another 30% of trial results remained unpublished.[64] The main reasons for discontinuation were poor recruitment, logistic conduct problems and trial futility. A scoping review of published RCTs found a comparable percentage of early discontinued trials in the PICU setting: 15%.[65] The actual percentage may be even higher as such trials have a higher chance not to be published.[66] For the sake of comparison, percentage of 25% of prematurely discontinued trials in adults has been reported.[67]

The CloSed trial (Clonidine for Sedation of mechanically ventilated children; NCT02509273) was designed as a European multi-center, non-inferiority, active-controlled phase III trial investigating clonidine as sedative for mechanically ventilated children.[68] This study adhered to EMA regulations in that a Paediatric Investigational Plan was prepared. It was to lead to licensing clonidine for sedation purposes and developing pediatric-specific formulations of clonidine. This could be achieved by obtaining a Paediatric-Use Marketing Authorisation (PUMA), which means that off-patent drugs can be patented again for the exclusive use in children, whilst retaining the existing brand name. Also, we had planned to study PK, PD, pharmacogenomics of morphine, clonidine and midazolam, and the effects of clonidine compared to midazolam in neonates on neurodevelopmental outcome at age 1. Yet, we were confronted with poor recruitment and logistic issues. A timeline of predicted vs. observed milestones is shown in figure 1.

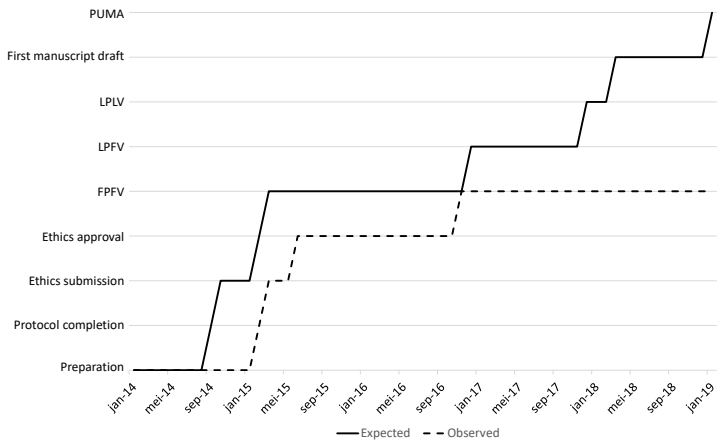
In general, we can identify three major reasons for failure of recruitment of patients in this trial:

1. Logistic issues
2. Inadequate trial design
3. Dismal inclusion rate

Logistic issues

Several regulatory, ethical and logistic issues need to be solved before one can start with actual patient recruitment. In the CloSed trial, handling controlled drugs appeared to raise several unforeseen barriers such as obtaining an import license and a license for handling controlled drugs in a research setting, as the study drugs had to come from Germany. Moreover, after obtaining the import license, the exporting country needed to apply for an export license as well. This surprised us because both clonidine and midazolam are being used in standard clinical practice but still a separate handling license was needed for the pharmacy as it now concerned an Investigational Medicinal Product (IMP).

Figure 1. *Expected vs. observed timeline of the CloSed trial.*



The solid line represents the expected timeline. The dotted line represents the actual timeline. DSMB: Data Safety Monitoring Board; EC: Ethics Committee; FPFV: First Patient First Visit; LPFV: Last Patient First Visit; LPLV: Last Patient Last Visit; PUMA: Paediatric Use Marketing Authorization

These issues have delayed the start of trial in our center for months. However, in other centers, even after several years, the ethics and regulatory approval still has not been obtained. This is something to be aware of when performing an international multi-center trial.[69] For example, in the Netherlands, the Competent Authority (CCMO: Central Committee on Research Involving Human Subjects, or the Ministry of Health, Welfare and Sport) only performs an extra review of a clinical trial and delegates all other approval to the Ethical Committee. This extra review is nothing more than checking international pharmacovigilance databases for any suspected adverse reactions that may increase the risk to potential subjects. However, in the Czech Republic and Sweden, for example, the comments received from the Competent Authorities were very detailed.

Inadequate trial design

Even after the logistic issues had been solved, we were faced with another unexpected problem. The sedative dose decrease schedule was designed to prevent oversedation, but did not fully take into account the half-life of drugs. Therefore, if a patient would be oversedated, the study drugs would be tapered off very quickly and the patient would be without any study drug at all within 90 minutes. This oversight necessitated an amendment to the schedule, which took months to establish and to get ethical committee approval again. To prevent this in future trials, we recommend to involve independent treating physicians and ICU nurses in the design of the trial, as well as parents. In the CloSed trial, a parents' support group from the Dutch national patient umbrella organization for rare and genetic disorders (the VSOP) was consulted, but adequate patient representation is hard to realize considering the heterogeneity in diagnoses found in the PICU.

Overall, the CloSed trial can be regarded as fairly complex, and not easy to explain to health professionals whose cooperation is needed. Complex trial design is an important reason for RCT failure.[67] Alternative trial designs such as comparative effectiveness trials could be a solution (see: 'RCT validity').

Dismal inclusion rate

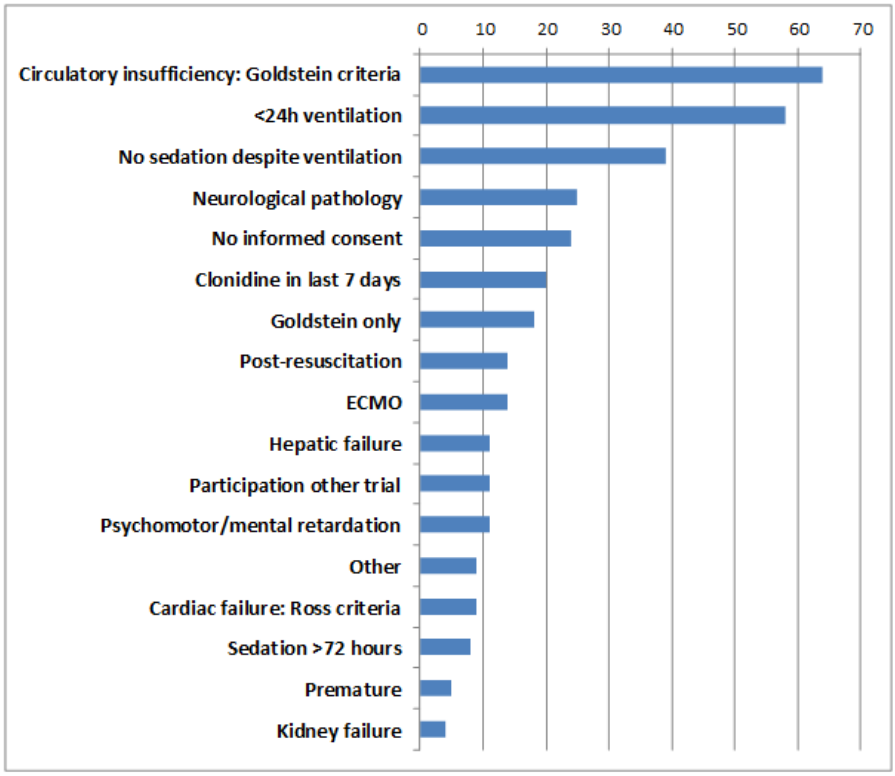
"As soon as a study begins, the number of patients available instantly drops from a theoretical pool of 100 percent down to 20 percent; as soon as a study stops, the pool jumps back to 100 percent", Bachenheimer 2007.[70] Researchers have always been too optimistic about inclusion rates for their studies. Insufficient trial preparation, lack of pilot studies[71] and over-estimation of consent rate[72] could belie their optimism. This holds also true for the CloSed trial. For our center, inclusion of subjects was based upon the number of mechanically ventilated patients receiving midazolam >24 hours: around 300 eligible patients yearly. Based on previous experience we assumed that informed consent would be withheld in 50% of cases. Thus, 150 patients were expected to be included within one year. The actual number included in the first year was 2.

And why was that? Not taking into account the exclusion criteria may have been a major reason. Figure 2 illustrates the main reasons for exclusion of patients in the first year in Rotterdam.

To our surprise, thirty-eight patients were excluded because they did not need sedation although they were mechanically ventilated for at least 24 hours. These were mainly post-operative neonates <14 days of age receiving adequate analgesia with IV paracetamol and low-dose opioids.

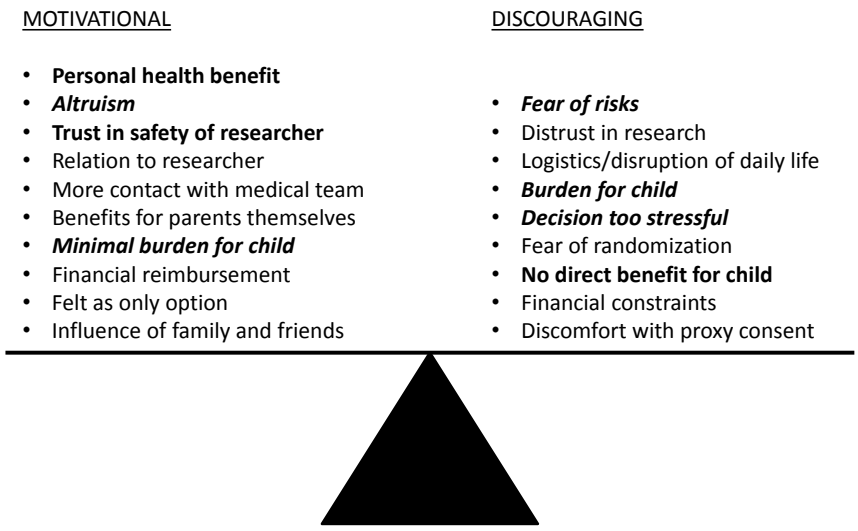
This is an example of the changing 'unmet medical need', for which investigators should be warned. Also the SLEEPS-study (ISRCTN 02639863), the 'predecessor' of the CloSed trial,[73] should have put us on alert. This study, too, was terminated due to poor recruitment. The aim was 1000 participants, but no more than 129 could be included in two years, even though the inclusion and exclusion criteria were adapted several times. The new early extubation strategy for cardiac surgery patients, with often extubation within 12 hours after surgery was identified as one of the main reasons for the dismal inclusion rate in that study. The investigators nevertheless could demonstrate theoretical non-inferiority of clonidine vs. midazolam for sedation, although the 95% CI was too large to demonstrate 'true' non-inferiority. Unfortunately, this study did not gather data on PK and a PK-PD relationship. Analysis of these data could have been interesting as clearance may be decreased in cardiac surgery patients[8] and the CloSed-trial could not include these patients due to their short ventilation period.

Figure 2. *Reasons for exclusion in 214 screened patients; a total of 344 reasons (a number of patients were excluded for more than one reason).*



The consent rate for the CloSed trial in Rotterdam was much lower than the assumed 50%, that is: 23% (5/22 parents). Three of the consenting parents had been approached before surgery, but their child was unfortunately not eligible after the surgery. In-depth analysis of reasons for refusal showed a Catch-22 situation: Parents either felt that the child was too ill for participation and possible changes in the sedation regimen, or that the child was finally stable enough and therefore should not be exposed to a change in the sedation regimen. A disadvantage of the CloSed-trial is the timing of consent. Early participation is desired but this means consenting in the acute setting. Parents may be very distressed in the acute setting and therefore refuse participation. However, not all parents declined and there were even parents who desperately wanted their child to participate (but unfortunately the child became ineligible after surgery). This asks for a deeper look into parental motivating and discouraging factors for participation in a clinical trial. Tromp et al. systematically reviewed reasons for participation and refusal of parents.[74] They identified several motivating and discouraging factors, which are balanced against each other in figure 3.

Figure 3. *Balance between motivational and discouringing factors for parents to letting their child participate in a clinical trial.*



Bold factors could theoretically be applied to the Closed trial; bold and italic factors have explicitly been mentioned in the informed consent approaches. Derived from Tromp K et a.l, Motivations of children and their parents to participate in drug research: a systematic review. Eur J Pediatr 2016;175(5):599-612.

When applied to the CloSed trial, this figure shows that discouraging factors dominate. Especially 'decision too stressful' was a discouraging factor, and this is not only applicable to the CloSed trial. In another study in our PICU, a randomized controlled trial investigating the calming influence of ear plugs during 'rush hours' at the ICU, thirty-four of 166 screened patients were regarded eligible and asked for informed consent. Only 2 patients or the parents consented in participation, as they felt the decision was too stressful as well. Other PICU trials have shown to be more successful. A comparable trial with the CloSed trial is the Daily Sedation Interruption trial performed by Vet et al.,[75] which had a consent rate of 60% (after exclusion of clinically ineligible patients). The inclusion period was five years, however. A pediatric microdosing study of paracetamol had a consent rate of 40%[76] – still much higher than the CloSed trial with a consent rate of 23%.

A strategy to make the decision-making less stressful is the use of deferred consent,[77] when patients are recruited in the acute setting, and consent is being asked afterwards. This should not be applied if there is a possibility that the intervention is postponed, but can be applied to critical care interventions. The use of deferred consent is accepted by families,[78] healthcare professionals and institutional research boards and has increased inclusion rates in other trials.[79] Our study group applied deferred consent in the PePANIC trial (early vs.

late parenteral nutrition in critically ill children),[80] with 593 children included in three years – all with the use of deferred consent. This study had less impact on the children, however, as it was not a drug study that could affect the child's comfort.

Participation in a trial may also be influenced by culture. A large RCT in Brazil on vasopressors/inotropes in children with sepsis had a surprisingly high recruitment rate of 96%.[81] In their reply to an editorial, the authors mentioned the specific cultural aspect of informed consent, which is the hierarchal relationship between patients and doctors.[82]

Implementation of RCT results

Even if a RCT has been successful, it may take several years for the results to be implemented in daily clinical practice. Several barriers may impede implementation, such as low acceptance by health care professionals, lack of motivation and lack of awareness and 'forgetting'.[83] We investigated the implementation of IV paracetamol as primary analgesic in infants after major surgery, and found that this was adhered to in 98.7% of patients. Furthermore, 80% of patients received an adequate loading dose of morphine at the end of the surgery. This success could be attributed to staff being aware of the trial and enthusiastic to cooperate, as well as good implementation strategies such as the mini-course offered to new personnel.

On the other hand, implementation of certain elements of this new pain management protocol was less successful. For example, morphine continuous infusion dosing was often too high, probably because we have a national formulary in place[84] which dictates other doses than our new protocol. It is telling that in 21 of 22 cases (95%) these 'wrong' doses were in accordance with the national formulary. Even though the new morphine dosing had been used in the RCT, staff seemed not aware of this. Therefore, results of a trial should not only be implemented in specialty-related guidelines, but also in other national or international guidelines.

RCT validity

Another major general issue in implementation is the validity of RCT results.[85] The study population often does not reflect the majority of patients in daily clinical practice due to strict in- and exclusion criteria. Moreover, the setting of a RCT is often different from daily clinical practice, as experienced and well-trained research personnel is available to secure protocol adherence. Therefore, we need to reconsider the status of RCTs providing the highest level of evidence. There is a tendency in research to move away from the 'classical' RCTs, aimed at establishing the *efficacy* of an intervention (explanatory trials), towards trials and other studies aimed at establishing the *effectiveness* of an intervention, also taking the routine clinical practice into account (pragmatic trials).[86] This 'comparative effectiveness' research also focuses mainly on patient-centered outcomes, which are receiving increasing attention.[87]

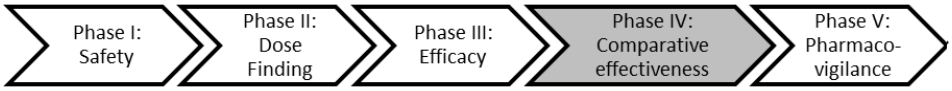
To take the CloSed trial as an example, an exhaustive list of exclusion criteria ensured the validity of the primary end point (neurological injury impedes scoring of the COMFORT-B scale) or patient safety (patients at risk for hypotension are excluded). Still, clonidine is being used in clinical practice: despite no more than two participants in the CloSed trial, continuous clonidine was given to 75 patients in the one-year screening period in Rotterdam. It has been proven safe in patients after cardiac surgery, so maybe the cardiovascular exclusion criteria might have been less strict.[88-90] For future studies comparing the effect of clonidine with midazolam in ventilated children, I would suggest to include all patients for who the treating physician would consider clonidine or midazolam administration in clinical practice, while still using a population-PK derived dosing scheme.

Lastly, drug approval is mainly based on the results of phase-III trials, which are mainly explanatory trials. Classically, drug studies are in three phases (dose finding - phase I, safety assessment -phase II and clinical efficacy - phase III). Sometimes, pharmacovigilance studies after marketing authorization are added as a phase IV (see figure 4).[91]

Figure 4. *Classical route of clinical trials in drug research.*

I would, however, suggest that the current phase IV be changed to comparative effectiveness research, just after approval on the market, in combination with pharmacovigilance, which then should be the new phase V (figure 5).

Figure 5. *New proposed route of clinical trials in drug research, with a fixed place for comparative effectiveness research.*



Fortunately, all roads lead to Rome, and other studies have been published on the use of clonidine in the PICU. Kleiber et al. studied the pharmacokinetics of clonidine in ECMO-treated patients (n=22) with or without continuous veno-venous hemofiltration using a

population-PK approach.[92] They found a significant increase of the volume of distribution (55%) and clearance (100%), indicating that higher loading doses and maintenance doses are needed in ECMO-treated patients.

In another study, Kleiber et al. investigated targeted vs. pre-emptive sedation regimens in children after cardiac surgery (n=66).[93] The targeted sedation group received boluses of clonidine until adequate sedation was reached; the pre-emptive group received routine midazolam infusion. The primary end point was cardiovascular stability and this did not differ between both groups. This study underscores the feasibility of clonidine use in hemodynamically compromised patients.

These studies illustrate that information on clonidine can be obtained in separate studies with smaller sample sizes. If the CloSed trial will not lead to success, we need to consider alternatives like these studies.

The problem of outcome measures

The issue of good outcome measures in clinical trials has been recognized for years.[94-96] Many trials make use of surrogate markers for clinical end points. Clinical trials can also be used to validate outcome measures.[97] We identified several problems in analgesic outcome measures. In this section I will address some of these problems and present future perspectives.

Outcome measures in pain studies

Pain is a subjective experience. Therefore the golden standard in pain research in subjects from the age of 6 years is the self-reported pain intensity on a numeric rating scale from 0-10. This is not feasible, however, for infants and young children. To assess these children's pain, several physiological and behavioral scales for observation have been developed. The downside of these scales is that pain may interfere with other conditions and the question could be raised, for example: does a COMFORT-B score of 25 indicate pain or distress? The validated cut-off point is 17 for pain[98] and 22 for undersedation,[99] so what should we treat first?

This problem also holds for other, more physiology-based assessment methods, such as heart rate variability,[100] pupillometry[101] and skin conductance,[102] which are all based on phenomena caused by the sympathetic nervous system. Therefore, we need to take a deeper look inside the brain where pain perception takes place.

Near-infrared spectroscopy (NIRS)[103,104] reflects the oxygen consumption in a certain, as yet unknown, region of the brain. Once 'the' brain region for pain has been identified, we can measure changes in oxygen consumption after noxious stimuli in this region. To date, NIRS has not yet been validated for measuring pain. Interestingly, in a multimodal study using both a

behavioral observational tool (the Face, Legs, Activity, Cry, Consolability (FLACC) scale[105]) and NIRS, a NIRS response was noted in both conditions (the same noxious stimuli with and without sucrose administration), whereas a FLACC response was noted only in the 'without sucrose' condition.[106] This means that the noxious stimulus was recorded in the brain, but we do not know whether it was painful to the neonate and whether oral sucrose is an effective analgesic.[107]

A more promising method of neuronal pain assessment is the EEG-based nociceptive brain activity measurement,[108] which recently has been validated in both preterm and term born clinically stable neonates under controlled circumstances. The EEG response to noxious stimuli has been extensively investigated in 18 infants; activity of all electrodes has been analyzed over a 1000 msec poststimulation period. The activity in the Cz region, which is the vertex position on the midline of the scalp, was identified as the strongest, in a time range from 400-700 msec poststimulation.

This method has also shown a discrepancy between pain responses assessed by physiologic parameters (cortisol and HRV) and behavioral parameters (PIPP score), as a linear relationship between the EEG measurement and cortisol or HRV was found but no relationship was found between the EEG measurement and the PIPP score. Yet, in children with low background stress, i.e. low baseline cortisol levels, a linear relationship between the PIPP and EEG measurement was found, indicating that children in stress are less capable to express their pain[109] or express if differently, in a way that cannot be picked up by the PIPP. It has been described earlier that exposure to multiple stressors attenuates behavioral stress responses, although the mechanism of action is unclear.[110]

The EEG-derived method allows for non-invasive assessment of procedural pain. However, patients admitted to a PICU or a NICU also may experience postoperative or continuous pain, for example the pain caused by an endotracheal tube[111] or by pressure ulcers due to immobilization.[112] Table 3 provides an overview of current pain assessment methods, including the type of pain for which it has been designed, whether it has been validated, which part of Loeser's pain model[113] it is reflecting, and whether there could be overlap with undersedation or distress. The pain model as developed by Loeser reflects the multimodality of pain and illustrates the path from the actual noxious stimulus (nociception) towards the 'ouch' or grimacing of a patient (pain behavior). It shows that pain is not only biological, but biopsychosocial and should be approached as such.

From this table we appreciate that nociception itself is not being measured, as this would require measurement of the nerve potentials in A and C fibers of the dorsal horn. Using reduction of distress and other factors as outcome measures could improve the research of HRV and pupillometry, as these measures are objective and have the potential to be

continuous. Yet, bedside behavioral tools are the current practice in NICUs[122] and PICUs.[123] We should look further to identify the most sensitive items to pain of these behavioral scales. Multimodal studies comparing for example the COMFORT-B scale to the EEG-derived nociceptive brain activity measurement could be a way to go.

Table 3. Currently available pain assessment methods.

Assessment method	Types of pain assessment	Validated in children	Part of Loeser's pain model	Overlap with distress or undersedation?
Behavioral scales[98, 105, 114-117]	Procedural, chronic	+	Pain behavior	+
Nociceptive brain activity[108]	Procedural	+	Pain perception	-
NIRS[103]	Procedural	-	Pain perception	
aEEG[118]	Procedural	-	Pain perception	+/-
Skin conductance[102]	Procedural	-	Suffering	+
SSEP[119]	Procedural	-	Pain perception	+/-
Pupillometry[101]	Procedural, chronic	-	Suffering	+
HRV[100]	Procedural, chronic	-	Suffering	+
fMRI[120]	Procedural	-	Pain perception/ suffering	-
Salivary and plasma cortisol levels[121]	Chronic	-	Suffering	+
Adrenaline assessment[121]	Procedural, chronic	-	Suffering	+
Noradrenaline assessment[121]	Procedural, chronic	-	Suffering	+

Outcome measures in sedation

Adequate sedation entails a combination of distress reduction, anxiety reduction, metabolism reduction and allowing for cooperation with procedures and/or mechanical ventilation.[124,125] Sedation is usually assessed either by level of consciousness (e.g. the Ramsay score[126]) or by level of comfort (COMFORT(-B) scale,[99,127] State Behavioral Scale[128]). However, these measures are subject to a certain degree of subjectivity and may also be influenced by other factors such as pain and critical illness. For example, a patient may be too ill to express discomfort and therefore may appear oversedated.

Adequate sedation is crucial in anesthesia for surgery. Depth of anesthesia used to be measured using the Bispectral Index (BIS).[118] The BIS is validated for children >1 year and is non-invasive. However, the BIS has only been validated for deep sedation and only measures frontal lobe EEG. Validation for conscious sedation, which is the preferable state of sedation in the ICU, has proven more difficult as clear cut-off values have not been

established.[129-131] The use of BIS for sedation assessment will probably not be an option, as it is no longer the standard of practice for anesthesia and physiologic parameters such as blood pressure and heart rate provide enough information.

Other methods to assess sedation depth do not yet exist. Physiologic measures such as heart rate, respiratory rate and blood pressure are not primarily used in the PICU as they can be influenced by factors such as raising the inspiratory O2 fraction, fluid resuscitation and the use of inotropic/vasopressor drugs. Yet, behavioral observational tools may also miss the presence of distress – indicative of inadequate sedation – if a patient is not able to express distress, for example when a patient is on paralyzing medication.

In the light of patient-centered outcome measures, it would be interesting to know more about the relationship between the level of sedation and the memories a patient keeps after ICU admission. It is known that patients may recall certain events during ICU admission even if they were deeply sedated.[132,133] Studies investigating sedative drugs should therefore include a follow-up visit with a recall assessment, linked to the overall level of sedation.

Other challenges of outcome measures

A major issue of analgosedative outcome measures is the overlap in symptoms between pain, distress, undersedation[134] and other clinical states such as delirium and withdrawal syndrome.[135] Several studies have addressed this overlap using different techniques, such as applying the Item Response Theory to behavioral scales[136] or constructing a scale than can detect two clinical states with overlapping symptoms, such as the SOS-PD scale to detect pediatric delirium and iatrogenic withdrawal syndrome.[137]

Other clinical conditions may occur which go unrecognized. We addressed such a previously unrecognized condition in the study presented in chapter 5, the anticholinergic toxidrome. This toxidrome is caused by the use of anticholinergic drugs or other substances such as the Angel's Trumpet (*Brugmansia sp.*), Jimson weed (*Datura stramonium*), Deadly nightshade (*Atropa Belladonna*) or muscarinic mushrooms. These agents block the muscarinic acetylcholine receptors, both in the peripheral nervous system and in the central nervous system. Typically, this leads to a clinical presentation as 'dry as a bone, blind as a bat, red as a beet, hot as a hare and mad as a hatter'.[138,139] Table 4 shows the symptoms of this toxidrome, broken down into central and peripheral symptoms.

We found a higher anticholinergic burden in patients with symptoms of delirium and/or withdrawal syndrome in this study but were not able to correct for disease severity and other risk factors for delirium and/or withdrawal syndrome. Moreover, we do not know whether such a burden would be enough to cause an anticholinergic toxidrome. I would recommend a prospec-

tive observational study in all children admitted to the PICU, and determining their anticholinergic burden on a daily basis and actively screening for anticholinergic symptoms. This could inform us on whether the anticholinergic toxidrome is a real problem in our PICU population.

Table 4. *Central and peripheral symptoms of the anticholinergic toxidrome.*[139]
Central anticholinergic symptoms
Delirium
Mydriasis
Amnesia
Hallucinations
Seizures
Coma
Peripheral anticholinergic symptoms
Tachycardia
Hyperthermia
Dry skin
Functional ileus
Urinary retention
Hypertension

Another major issue is the influence of environmental factors on a patient's level of sedation. It has been shown that environmental factors may affect the level of pain.[134] Much research is focused on the pharmacological management of sedation, but trials on non-pharmacologic interventions are few. The earplug study, mentioned above, is a good example of a relatively easy intervention which, by reducing noise exposure, could markedly improve a child's sedation state. In addition, early mobilization strategies may also enhance the child's comfort.[140-142]

In the Netherlands, two newly built pediatric ICUs make use of single bed-rooms. It would be enlightening to perform a prospective trial comparing units with and without single-bed rooms, with end points such as cumulative sedative consumption, COMFORT-B scores, pain scores, length of stay and duration of mechanical ventilation. Moreover, older children should be interviewed on discharge on how comfortable they were during their stay. Results of such trials can convince architects and executive boards to provide single-bed PICUs in all new children's hospitals.

Also, parents may want to be more involved in the child's bedside care. The concept of Patient and Family Centered Care is the new approach to hospital care, in which parental participation in care is indispensable. Parents, if they are up to it in view of the stressful situation, can be instructed to apply a pain scale, as in the 'Together less Pain' initiative in our hospital. Open discussion between parents and healthcare professionals may improve mutual understanding – and thereby the care for the critically ill child.

FUTURE PERSPECTIVES

A recent publication on the global research agenda in pediatric critical care identified 'Comfort' of children as one of the areas deserving scientific attention, particularly the long-term effects of analgesics and sedatives.[143] It is recommended by the authors to study on which age drug-induced neuro-apoptosis exerts the most damage. Also, the sedation paradigm is changing from unconscious sedation towards conscious sedation. To illustrate this: ten years ago, a patient on ECMO was heavily sedated and received high doses of opioids or even sometimes neuromuscular blocking agents to prevent the accidental removal of cannulas. Nowadays, children on ECMO, if clinically stable, may watch TV.

A second focus area is the rethinking of the RCT as golden standard for evidence-based medicine. Intensive care no longer focuses on life-saving procedures and medically stabilizing the patient, but also on adverse events reduction and good long-term outcome. The PICU patient population is changing as the life-expectancy of children with complex co-morbidity increases on the one hand, but their vulnerability necessitates frequent re-admissions.[144] Moreover, children who have been withheld life support therapy, such as those with trisomy 13/18; Rett syndrome or SMA type 1, will nowadays be treated in the PICU in some countries. Carrying out a 'classical' RCT runs the risk that these complex patients will meet an exclusion criterion.

Yet, there is still a long way to go and it seems that current ethical, regulatory and patient factors impede clinical trials in the PICU. Nevertheless, alternative trial designs may enhance both patient accrual and external validity and can guide the design of future trials.

So far, pain and sedation management mainly relies on surrogate end points. Future research should focus on the development of more objective and specific measurements as current end points are frequently influenced by external factors, in particular stress. The development of the EEG-derived nociceptive brain activity method may pave the way for future analgesic trials and may serve as a basis for other pain and sedation assessment methods that could also be EEG-based.

Third, pharmacometric advances such as PBPK modeling and *in silico* trial simulation generate a wealth of new information that helps us understand what is going on in the developing, critically ill child regarding pharmacokinetics and pharmacodynamics.

And fourth, I have found that the paradox 'expect the unexpected' is certainly applicable to science. As the authors of the SLEEPS-study encountered unexpected early extubation strategies in cardiac surgery, the investigators of the CloSed trial were 'surprised' by neonates who did well without sedatives.

Besides improving pain and sedation management, new clinical strategies can also lead to improved sedation and analgesia in the PICU. In the first paragraph of this discussion, I addressed the complex pharmacology that should be dealt with. It is therefore essential that a dedicated hospital pharmacist is appointed to the PICU. A few reports support the presence of a dedicated pediatric pharmacist present during rounds and medication prescription.[145-147] In Erasmus MC, a pharmacist is present on the adult ICU, but in the PICU only PICU orders are reviewed and possible drug-drug interactions are screened for by a pharmacist. Focused review strategies can be the first step for hospitals with budget shortage,[148] although the presence of a pharmacist in one study resulted in an annual cost saving of $ 120,000 by lowering adverse event rates.[147] An alternative option is to have a clinician/clinical pharmacologists in place, which is the current situation in our center. Yet, regular clinical work may stand in the way of dedication to clinical pharmacology and therefore it is essential to appoint a dedicated pharmacist.

In conclusion, the 'war against suboptimal pain and sedation management' will continue and thus I conclude that it is certainly *not quiet at the bedside front*.

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9

Summary

SUMMARY

Pain and sedation management are crucial elements in pediatric critical care. Despite the major advances that have been made over the last decades, we still have a long way to go to reach optimal analgesia and sedation in children. One of the major obstacles in optimization of pain and sedation management is the lack of evidence-based pharmacotherapy. This thesis analyses the challenges in the development of evidence-based pain and sedation pharmacotherapy on multiple levels.

Part I contains an overview of the literature of pediatric pain and sedation research with the aim of looking for lessons learned from the past.

In **chapter 2** we provide an overview of currently used drugs for the sedation of critically ill children with their pharmacological properties. This chapter provides the current available evidence for the use in the PICU, as well as an overview of ongoing studies providing more information on the pharmacokinetics and pharmacodynamics of these sedatives. We show that little evidence is available for the PICU population, but that for most agents new pharmacokinetic and pharmacodynamic data are on the way. These studies often use advanced population modeling techniques and laboratory assessment methods.

Chapter 3 is a general overview of pain research in infants and neonates. We identified multiple important challenges that pain researches face when performing an analgesic trial in this population. These challenges include the definition of pain, the multimodality and different types of pain, lack of objective and validated end points, lack of knowledge on PK and PD, unknown long-term side effects of analgesics and the heterogeneity of the population. Based on this literature review, we recommend to focus on the development of objective outcome measures, the use of 'new' analgesics in this population and ways of studying long-term effects in future research.

In **part II**, we focus deeper into specific challenges that pain and sedation researchers may encounter in the PICU.

Chapter 4 is a clinical study protocol paper describing the design of the CloSed trial. The CloSed trial is a multi-center randomized controlled non-inferiority trial comparing clonidine with midazolam for the sedation of mechanically ventilated patients. This project faced several challenges which are being discussed, such as patient recruitment problems due to extensive exclusion criteria and changes in clinical practice which have not been foreseen. We therefore recommend to perform a thorough pilot study before the initiation of any pediatric critical care trial.

In **chapter 5**, we explore a possible new challenge that could interfere with pediatric critical care research: the anticholinergic toxidrome. The anticholinergic toxidrome has similar symptoms as pediatric delirium (PD) and iatrogenic withdrawal syndrome (IWS), impairing the screening for and diagnosis of these phenomena. This toxidrome may be the result of multiple drugs with anticholinergic properties which are often used in the PICU. This study describes the anticholinergic burden of patients with a positive screening for PD and/or IWS. We found a higher anticholinergic drug burden in patients with pediatric delirium and/or iatrogenic withdrawal syndrome, which raises awareness for the anticholinergic drug burden in patients with symptoms of PD and/or IWS.

Part III bridges the clinical trial setting to the daily clinical practice.

In **chapter 6**, we report on the number of painful and stressful procedures which patients in the PICU need to undergo on a daily basis. This study aims to explore the need for analgesic and sedative management of procedures in the PICU by determining the amount of procedures, but also which procedures are ranked most painful by healthcare professionals. Endotracheal suctioning was by far the most frequent procedure, followed by oral and nasal suctioning. Skin-breaking procedures such as arterial and lumbar puncture, IV cannula insertion and venipuncture have been ranked most painful according to a nurse survey.

Chapter 7 show the results of an implementation study of IV paracetamol for postoperative analgesia in infants. In a previous randomized controlled trial, a morphine consumption reduction of 66% was found when IV paracetamol was used as primary analgesic. After implementation of a new postoperative pain management protocol for infants in our PICU, with IV paracetamol as primary analgesic, we compared the morphine consumption in postoperative infants in daily practice to that of the RCT. We found equal morphine consumption to the RCT, and thus a successful implementation of IV paracetamol as primary analgesic.

Chapter 8 is a reflection on the results of the studies performed and provides and integrative discussion of these results. We conclude that there is a lack of sound evidence for current pain and sedation management in the PICU and we have identified some major challenges that pediatric pain and sedation research will encounter. We propose a research agenda for the coming years, specifically aiming at the development of clinical end points and the safety of drugs administered to very young children.

10

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Adequate pijnbestrijding en sedatie zijn cruciale onderdelen van de zorg voor kritisch zieke kinderen. Ondanks de grote vooruitgang die is geboekt over de afgelopen decennia, hebben we nog een lange weg te gaan naar optimale pijnbestrijding en sedatie voor kinderen. Eén van de grootste obstakels in het optimaliseren van pijnbestrijding en sedatie is het gebrek aan wetenschappelijk onderbouwde farmacotherapie. Dit proefschrift onderzoekt de uitdagingen die liggen in het ontwikkelen van wetenschappelijk onderbouwde farmacotherapie voor pijn en sedatie op verschillende niveaus.

Deel I bevat een overzicht van beschikbare wetenschappelijke literatuur over pijnbestrijding en sedatie bij kinderen met als doel om te zoeken naar lessen die we uit het verleden kunnen trekken.

In **hoofdstuk 2** wordt een overzicht gegeven van medicijnen die op dit moment worden gebruikt voor sedatie van kritisch zieke kinderen, inclusief de farmacologische eigenschappen van deze medicijnen. Dit hoofdstuk presenteert het huidige beschikbare wetenschappelijke bewijs voor gebruik in de kinder-IC, evenals een overzicht van onderzoeken die op dit moment lopen en die meer informatie zullen opleveren over de farmacokinetiek en farmacodynamiek van deze sedativa. We laten zien dat er weinig bewijs is voor de populatie op de kinder-IC, maar dat er voor de meeste sedativa nieuwe farmacokinetische en/of farmacodynamische gegevens onderweg zijn. Deze onderzoeken gebruiken vaak geavanceerde populatie-modeltechnieken en laboratoriummethodes.

Hoofdstuk 3 is een algemeen overzicht van pijnonderzoek bij zuigelingen en pasgeborenen. We identificeerden meerdere belangrijke uitdagingen die pijnonderzoekers tegen kunnen komen als zij een pijnstiller onderzoeken in deze groep patiënten. Deze uitdagingen omvatten onder andere de definitie van pijn, de multimodaliteit en verschillende typen van pijn, het gebrek aan objectieve en gevalideerde uitkomstmaten, gebrek aan kennis over PK en PD, onbekende langetermijneffecten van analgetica en de grote onderlinge verschillen binnen deze populatie. Op basis van dit literatuuronderzoek bevelen we aan om te focussen op de ontwikkeling van objectieve uitkomstmaten, het gebruik van 'nieuwe' analgetica in deze patiëntengroep en manieren om langetermijneffecten te bestuderen in toekomstig onderzoek.

In **deel II** gaan we dieper in op speficieke uitdagingen die pijn- en sedatieonderzoekers tegen kunnen komen op de kinder-IC.

Hoofdstuk 4 is een beschrijving van een protocol van een klinische trial, de CloSed trial. De CloSed trial is een multicenter, gerandomiseerde, dubbelblinde gecontroleerde non-inferiority-trial die clonidine met midazolam vergelijkt voor de sedatie van kunstmatig beademende kinderen. Dit project is meerdere problemen tegengekomen die worden beschreven, zoals patiëntenwervingsproblemen door uitgebreide exclusiecriteria en veranderingen in de klinische praktijk die aanvankelijk niet zijn voorzien. Daarom bevelen we aan om een degelijk proefonderzoek uit te voren vóór het starten van een wetenschappelijk onderzoek bij kritisch zieke kinderen.

In **hoofdstuk 5** verkennen we een mogelijke nieuwe uitdaging die kan interfereren met onderzoek op de kinder-IC: het anticholinerg toxidroom. Het anticholinerg toxidroom heeft vergelijkbare symptomen met delirium op de kinderleeftijd (PD) en iatrogeen ontrekkingssyndroom (IWS), welke het screenen op en diagnosticeren van deze fenomenen bemoeilijkt. Dit toxidroom kan het resultaat zijn van verschillende medicijnen met anticholinerge eigenschappen welke vaak worden gebruikt op de kinder-IC. Dit onderzoek beschrijft de anticholinerge-medicatie'last' van patiënten met PD en/of IWS. We vonden een hogere anticholinerge-medicatielast bij patiënten met PD en/of IWS, wat aandacht vraagt voor deze last bij patiënten met symptomen van PD en/of IWS.

Deel III slaat een brug van de onderzoekssetting naar de dagelijkse klinische praktijk.

In **hoofdstuk 6** rapporteren we het aantal pijnlijke en stressvolle handelingen die kinderen op de IC dagelijks moeten ondergaan. Dit onderzoek richt zich op het verkennen van de noodzaak tot pijnstiller- en sedativagebruik tijdens procedures door het aantal handelingen vast te stellen, maar ook door welke handelingen als meest pijnlijk worden ervaren door de zorgverlener. Endotracheaal uitzuigen was verreweg de meest frequent uitgevoerde handeling, gevolgd door oraal en nasaal uitzuigen. Procedures waarbij de huid doorbroken moet worden zoals lumbaal-, arterie- en venapunctie en infuus prikken werden als meest pijnlijk gescoord in een verpleegkundigenenquête.

Hoofstuk 7 geeft de resultaten van een implementatieonderzoek van paracetamol IV voor postoperatieve pijnbestrijding bij zuigelingen. In een vorige gerandomiseerde gecontroleerde studie (RCT) werd een reductie van 66% in het gebruik van morfine gevonden als paracetamol IV als eerstekeus pijnstiller wordt gebruikt. Na implementatie van een nieuw postoperatief pijnbestrijdingsprotocol voor zuigelingen op onze kinder-IC, met paracetamol IV als eerstekeus pijnstiller, vergeleken we het morfinegebruik van postoperatieve zuigelingen in de dagelijkse praktijk met die van de RCT. We vonden een even grote morfineconsumptie als in de RCT en zodoende een succesvolle implementatie van paracetamol IV als eerstekeus pijnstiller.

Hoofdstuk 8 is een reflectie op de resultaten van de uitgevoerde onderzoeken en bespreekt een integratieve discussie van de resultaten. We concluderen dat er een gebrek is aan solide wetenschappelijk bewijs voor het huidige pijnbestrijdings- en sedatiebeleid op de kinder-IC en we hebben enkele grote uitdagingen geïdentificeerd waarmee pijn- en sedatieonderzoek kan worden geconfronteerd. We stellen een onderzoeksagenda op voor de komende jaren, met name gericht op het ontwikkelen van klinische uitkomstmaten en de veiligheid van medicijnen die aan zeer jonge kinderen worden gegeven.

11

Appendices

LIST OF ABBREVIATIONS

ABC	Airway, Breathing, Circulation
ACBS	Anticholinergic Cognitive Burden Score
ADS	Anticholinergic Drug Scale
AE	Adverse Event
aEEG	Amplitude-integrated electroencephalography
AICU	Adult Intensive Care Unit
ANOVA	Analysis of Variance
BBB	Blood-Brain Barrier
BDE	Bodyweight-Dependent Exponent
BIS	Bispectral Index
BPCA	Best Pharmaceutical's for Children's Act
BSID-III	Bayley Scales of Infant and Toddler Development-III
CH	Chloral Hydrate
CNS	Central Nervous System
CRF	Case Record Form
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CVC	Central Venous Catheter
DSI	Daily Sedation Interruption
ECMO	Extracorporeal Membrane Oxygenation
EEG	Electroencephalography
EMA	European Medicines Agency
EMLA	Eutectic Mixture of Local Anesthetics
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLACC	Face, Legs, Activity, Cry and Consolability scale
GABA	Gamma-Amino Butyric Acid
GCP	Good Clinical Practice
HIE	Hypoxic-Ischemic Encephalopathy
HRV	Heart Rate Variability
IASP	International Association for the Study of Pain
IM	Intramuscular
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IQR	Interquartile Range
ITT	Intention To Treat

IV	Intravenous
IWS	Iatrogenic Withdrawal Syndrome
LCMS/MS	Liquid Chromatography Mass Spectometry/Mass Spectrometry
LOS	Length of Stay
MDZ	Midazolam
MRI	Magnetic Resonance Imaging
MV	Mechanical Ventilation
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
NIRS	Near-Infrared Spectroscopy
NISS	Nurses Interpretation of Sedation Score
NMDA	N-methyl-D-aspartate
NONMEM	Non-linear Mixed Effects Modeling
NRS	Numerical Rating Scale
OIH	Opioid-Induced Hyperalgesia
OR	Odds Ratio
PBPK	Physiology-Based Pharmacokinetics
PCM	Paracetamol
PD	Pharmacodynamics; OR Pediatric Delirium
PICU	Pediatric Intensive Care Unit
PIM-2	Pediatric Index of Mortality
PIPP	Premature Infant Pain Profile
PK	Pharmacokinetics
PO	Per Os
PRD	Pupillary Reflex Dilation
PRIS	Propofol Infusion Syndrome
PRISM-III	Pediatric Risk of Mortality-III
PUMA	Paediatric Use Marketing Authorisation
RASS	Richmond Agitation-Sedation Scale
RCT	Randomized Controlled Trial
SAA	Serum Anticholinergic Activity
SAE	Serious Adverse Event
SBS	State Behavioral Scale
SC	Subcutaneous
SES	Safety Evaluation Set
SNP	Single Nucleotide Polymorphism
SOS	Sophia Observation withdrawal Symptoms
SOS-PD	Sophia Observation withdrawal Symptoms-Pediatric Delirium
SPC	Summary of Product Characteristics

SSEP	Somatosensory Evoked Potentials
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCA	Trichloroacetic acid
TCE	Trichloroethanol
UMSS	University of Michigan Sedation Scale
WAT-1	Withdrawal Assessment Tool 1
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence Third Edition

LIST OF PUBLICATIONS

1. Biere-Rafi S, **Baarslag MA**, Peters M, Kruip MJ, Kraaijenhagen RA, Den Heijer M, et al. Cardiovascular risk assessment in haemophilia patients. Thromb Haemost. 2011;105(2):274-8.

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8. **Baarslag MA**, Jhingoer S, Ista E, Allegaert K, Tibboel D, van Dijk M. How often do we perform painful and stressful procedures in the paediatric intensive care unit? A prospective observational study. Aust Crit Care. 2018. May 17. pii: S1036-7314(17)30500-3. doi:

PHD PORTFOLIO

Name PhD student: Manuel Baarslag	PhD period: 01-09-2014-01-09-2018
Erasmus MC Department: Intensive Care Kinderen	Promotor(s): Prof. dr. D. Tibboel
Research School: Molecular Medicine	Supervisor: Prof. dr. M. van Dijk

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
- Research Integrity	2015	8 hours/0.3 ECTS
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek'	2015	28 hours/1 ECTS
- CPO Course 2015	2015	8 hours/0.3 ECTS
- Systematic Literature Retrieval	2014	28 hours/1 ECTS
- PhD-Day Erasmus MC	2015	6 hours/0.2 ECTS
- NIHES course Biostatistical Methods I: Basic Principles	2015	160 hours/5.7 ECTS
Specific courses (e.g. Research school, Medical Training)		
- NIH Course 'Principles of Clinical Pharmacology'	2014-2015	30 hours/1 ECTS
- Course 'How to work with Open Clinica'	2015	8 hours/0.3 ECTS
- Circulation workshop, Vilnius, Lithuania	2015	8 hours/0.3 ECTS
Seminars and workshops		
- Evidence Based Pharmacotherapy in newborns and children	2014	30 hours/1 ECTS
- Pharmacokinetics, Kinesis Pharma, Breda	2016	28 hours/ 1 ECTS
Presentations		
- The use of naloxone in critically ill and postsurgery patients	2015	28 hours/1 ECTS
- IV paracetamol for analgesia after major surgery in neonates and infants	2017	28 hours/1 ECTS
(Inter)national conferences		
- Amsterdams Kindersymposium	2015	8 hours/0.3 ECTS
- ESPNIC Congress, Vilnius, Lithuania	2015	30 hours/1 ECTS
- Sophia Research Day	2015	16 hours/0.6 ECTS
- Leiden/Rotterdam Pharma Day	2015-2018	32 hours/1.2 ECTS
- ESPNIC Congress, Lisbon, Portugal	2017	28 hours/1.0 ECTS
Other		
- Voorjaarsbijeenkomst Dutch Society of Clinical Pharmacology and Biopharmacy including poster presentation	2016	15 hours/ 0.5 ECTS
- Dutch Medicines Days	2017	16 hours/0.6 ECTS

2. Teaching

	Year	Workload (Hours/ECTS)
Supervising practicals and excursions, Tutoring		
- Coaching Bachelor students	2016-2018	28 hours /1 ECTS
Supervising Master's theses		
- Master's thesis Sharan Jhingoer	2016	15 hours /0.5 ECTS
- Master's thesis Ela Hutten	2017	8 hours/ 0.3 ECTS
Other		
- Fellowship Clinical Pharmacology	2015-2017	280 hours/10.0 ECTS

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Manuel

ABOUT THE AUTHOR

Manuel Baarslag was born in Bogotá, Colombia, on the 11th of September 1987. He graduated from high school in 2005 at the Veenlanden College in Mijdrecht (Atheneum degree). In that same year he started his medical training at the VU Medical Center in Amsterdam. In medical school, he took place in two student representation organs with special attention to Educational Affairs.

In 2009 he completed his Master thesis on the cardiovascular risk of hemophilia patients at the Academic Medical Center in Amsterdam (supervisors dr. T.P.W. Kamphuisen and dr. M. Peters), resulting in a poster presentation at the ISTH, Boston 2009 and a publication in 'Thrombosis and Haemostasis'. During his clinical rotations, he did his pediatric rotation at the Tygerberg Hospital, Bellville, South Africa. He finished medical school with a clinical elective in Pediatric Surgery at the VU Medical Center Amsterdam.

After finishing medical school in 2011, he started working as an intern in Pediatrics at the Albert Schweizer Hospital in Dordrecht and the Flevo Hospital in Almere. In 2014 he had the opportunity to obtain a PhD position in the Erasmus MC-Sophia Children's Hospital (promotors: prof.dr. D. Tibboel and prof.dr. M. van Dijk) on the subject of pain and sedation management in critically ill children, of which this thesis is the result. As his special interest for clinical pharmacology was confirmed during his PhD programme, he was trained a clinical pharmacologist as well. In January 2018 he started as an intern in the pediatric intensive care of the Leiden University Medical Center under supervision of dr. P.P. Roeleveld.

Manuel is married to Hannelise and they live in Rotterdam together with their son Jeshua.