Analgesics and sedatives in critically ill newborns and infants: the impact on long-term neurodevelopment

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SUMMARY

Inadequate pain and/or stress management in preterm and term born infants has been associated with increased morbidity and even mortality. However, exposure to analgosedatives during early infancy may also be one of the risk factors for subsequent neurodevelopmental impairment, at least in animal studies. Since infants admitted to neonatal or pediatric intensive care units may receive very high amounts of these drugs for prolonged periods of time and the majority of these infants nowadays survive to discharge, this is of major concern. A balanced approach that incorporates the assessment and quantification of both wanted effects as well as unwanted side effects is therefore needed. In this paper, the optimum dose determination of commonly used analgosedative drugs as well as their potential long-term effects on the developing human brain and neuropsychological functioning are reviewed.

INTRODUCTION

Over the last decades, phenomena such as pain, stress, and anxiety/agitation have intrigued a variety of clinicians and scientists. The paradigm that immaturity protects neonates from pain and its negative effects has been questioned years ago by Anand et al. who demonstrated that untreated perioperative pain was associated with increased morbidity and even mortality.[1] These negative effects have been described in greater detail in recent reviews, showing that insufficient pain management in (pre)term infants during painful interventions alters physiological responses, pain thresholds and pain or stress-related behavior.[1-3] However, evidence showing a link between exposure to analgosedatives (analgesics and sedatives) in early infancy and subsequent neurodevelopmental impairment is accumulating as well.[4-6] As the majority of infants admitted to neonatal or pediatric intensive care units now survive to discharge[7,8], this is of major concern. Although there may be long-term effects of anesthetic agents on the brain as well, this has been extensively described and reviewed in the past few years[2,9-13] due to a recent FDA warning about its use in children younger than three years[14], and is therefore beyond the scope of the current review.[2,9-13]

The balance between adequate pain management and the risk of long-term neurodevelopmental impairments reads like a catch-22, but at least indicates that a balanced approach that incorporates assessing and quantifying both wanted effects as well as unwanted side effects is needed. To avoid both pain and stress with all negative consequences as well as over-exposure (too much or too long) to analgosedatives, health care providers should select the most appropriate intervention (either pharmacological or non-pharmacological) based on the best available evidence for a given indication, with adjustments to reach the most effective and shortest exposure.[15] Over the last five years, a number of guidelines have been published and trials have been performed to find the optimum dosage for analgosedative drugs.[16-20] However, we need to be aware that the level of evidence is unfortunately still limited. Data on maturational pharmacokinetics (PK) are a crucial, yet first, step of a drug development program, especially in neonates and young infants. Therapeutic dose-finding studies, even for commonly used drugs, are needed to come up with a valid study design in neonates and infants before comparative phase 3 efficacy and safety trials can be conducted.[21]

In pain management of infants admitted to the neonatal or pediatric intensive care unit, the ultimate goal is to achieve adequate pain management with minimal short and long-term side effects. In reaching this goal, it is imperative to also increase our understanding of how exposure to sedatives and analgesia may affect the developing brain. Based on the existing literature combined with our own research, we will summarize the present knowledge and level of evidence of a number of commonly used

analgosedative drugs which serve as model drugs and their potential long-term effects on the developing brain and neuropsychological functioning in humans.

DOSE DETERMINATION OF COMMON ANALGOSEDATIVE DRUGS

Analgesics

Morphine

Morphine is the most commonly used intravenous opioid to provide potent analgesia in neonates, infants and children. However, age-related differences in both pharmacokinetic (PK) and pharmacodynamic (PD) responses during development pose challenges for selection of an appropriate dose. As sensitivity of the central nervous system to morphine is increased in neonates, a lower initial dose of morphine is recommended which is then adjusted based on individual responses. In addition, the elimination half-life of morphine is more than twice as long as that observed in adults (6-12 hours in neonates versus 3-4 hours in adults[22]), due to immaturity of the neonatal hepatic drug metabolizing enzyme system. Morphine clearance increases in accordance with the maturation of the glomerular filtration rate and by 1 year of age, the ratio of plasma to cerebral spinal fluid concentration is comparable to that of adults. A number of studies have described optimal dosage of morphine. Four studies only included neonates[23-26] and four studies consisted of data solely based on children[27-30] (ranging from 10-40 µg/kg). The use of morphine is, especially in the preterm, still a matter of debate. In the cohort of Simons et al., preterm neonates in need of mechanical ventilation and with a median gestational age of 29 weeks, received either morphine 10 µg/kg per hour or placebo, and additional morphine in case of pain or distress.[31] In the NEOPAIN study of Anand et al., ventilated preterm born children received placebo or morphine as well, but in different dosages. The doses of morphine used in this study were based on gestational age; children born at 23-26 weeks of gestation received 10 µg/kg per hour; 27-29 weeks received 20 µg/kg per hour; and 30-32 weeks received 30 µg/kg per hour.[32] From these two randomized controlled trials it was concluded that the routine use of intravenous morphine is not beneficial in the short term in ventilated preterm newborns.[31,32]

Fentanyl

Fentanyl is commonly used due to its high lipid solubility and potency. Its half-life time is short compared to morphine (ranging between 188-570 minutes in infants and neonates versus 219 minutes in adults[33]), but longer than its derivatives sufentanil, alfentanil or remifentanil.[33] In the search for optimal dosing, using population pharmacokinetic (pop-PK) approaches, large variations were observed in the dose of fentanyl used across studies (ranging between 1-5 µg/kg). In four studies, neonates were included (range

1-71 days) with weight ranging between 1.4 kg and 4.0 kg.[34-37] Two studies included only infants and children (range 1 month-4.5 years) with weight ranging between 3.7 kg and 17.3 kg.[38,39] Only one study included neonates, infants, children and adolescents, although the total number of included subjects (n=17) was limited.[36] Intravenous bolus administration was used in most studies (n=5) followed by continuous infusion (n=2), whereas one study only applied continuous infusion.[34] Only limited PK data are available in preterm neonates[33], which warrants future research.

Acetaminophen

Acetaminophen (paracetamol) is the most commonly prescribed analgesic to treat mild to moderate pain to be administered by rectal, oral or intravenous route. In an attempt to avoid or reduce opioid exposure, intravenous acetaminophen is increasingly used in preterm and term-born neonates.[15] Pooled data with subsequent external validation of intravenous acetaminophen PK in neonates are available.[40,41] The same holds true for the maturation of the different routes (glucuronidation, sulfation and oxidation) involved in acetaminophen metabolism.[42] Flint et al.[43] recently reported a gestational-age-dependent increase in glucuronidation without evidence for saturation of a specific pathway as there was a proportional increase in exposure of acetaminophen and its metabolites in extreme preterm neonates between 24 and 32 gestational age. Despite the availability of these PK data, intravenous acetaminophen is still used off label for specific subpopulations (limited from term neonates onwards in Europe, and still off label in children under the age of 2 years in the United States).

As reported by Laughon et al.[44], this is because efficacy could not be documented in the registration studies perhaps because we miss 'common' models similar to the third molar surgery model, to assess the analgesic effect of non-steroidal anti-inflammatory drugs, including acetaminophen, in adults. The relevance of the study model is also reflected in the fact that the available observations on acetaminophen analgesia during procedures (heel prick, retinopathy of prematurity screening) suggest that acetaminophen is a very poor *procedural* analgesic anyhow.[45] In contrast, there is a proven and clinically relevant (-66%) morphine sparing effect of intravenous acetaminophen after major neonatal non-cardiac surgery.[46] The morphine sparing effect has also been observed in a retrospective analysis on morphine consumption in very low gestational age infants (<32 weeks) before and after introduction of intravenous acetaminophen.[47] Intravenous acetaminophen is also effective for moderate pain relief following traumatic delivery or medical conditions, with an effect compartment concentration similar to children and adults.[48]

Sedatives

Propofol

Propofol is used in many clinical settings in both adult and pediatric populations. However, given the increased risk of metabolic derangements and organ system failures, known as propofol infusion syndrome, propofol should preferably only be used for short-duration sedation.[49] Gestational and postnatal age both contribute to propofol clearance, with very fast maturation of clearance in early infancy. This implicates that neonates in the first week of postnatal life are at an increased risk for accumulation during either intermittent bolus or continuous administration of propofol, irrespective of the age or weight at birth.[50] This PK knowledge was subsequently integrated in a propofol dose-finding study (effective dose for 50% of patients, ED_{50}) through 8 patient strata (postmenstrual and postnatal age) to attain optimal effects for endotracheal intubation in neonates for the INSURE (*intubation, surfactant administration, extubation*) indication.[51,52] It turned out that the ED_{50} dose for preterm neonates varied between 0.7 and 1.4 mg/kg. This is significantly lower than initially suggested in literature.[53,54] Even with these lower doses, clinical recovery was accompanied by permissive hypotension (no clinical shock and no treatment).[51]

Midazolam and clonidine

A recent Cochrane analysis found no arguments for the use of midazolam as drug of choice for sedation in newborns compared with other medications because it did not seem to make the participants more sedated, nor did it reduce anxiety or pain, or made it the procedure easier to perform.[55] However, the evidence was rated to be of low-quality as many trials did not explain how participants were randomized to either midazolam or a different treatment.[55] In a systematic review, Vet et al.[56] identified 25 studies evaluating the level of sedation in pediatric intensive care unit (PICU) patients receiving continuous sedation, the most frequently used drug being midazolam. Of these studies, 23 used sedation level as the secondary outcome, and concluded that the level of sedation in critically ill children is often suboptimal. In particular, over sedation was found to be more common than under sedation, which has been associated with adverse long-term outcomes.[56]

As an alternative for midazolam, many institutions nowadays prefer clonidine. Three randomized controlled trials assessing the use of clonidine in the PICU have recently been published. The first compared the opioid and sedative sparing effect of placebo versus clonidine (fixed at 1 mcg/kg/h; median duration: 168 hours) in ventilated medical and surgical patients.[57] The trial indicated decreased sedative and analgesic requirements in neonates, although this was not found in older children of up to two years of age. In the clonidine group, a mild and well-tolerated decrease in systolic and mean blood pressure was observed compared to the placebo group, while heart rate was

similar between groups.[57] In a pilot multicenter trial, the opioid and benzodiazepine sparing effects of oral clonidine (5mcg/kg every 6 hours) compared to placebo were analyzed. The incidence of significant hypotension and bradycardia was similar between groups.[58] The SLEEPS study, compared the efficacy of clonidine (0.75-3 µg/kg/hour) and midazolam (50-200 µg/kg/hour) for sedation in ventilated children (1 month-15 years), concluding non-inferiority of clonidine to midazolam.[59] Alternative ways of providing sedation such as the concept of daily sedation interruption have not been shown to be effective in critically ill children.[60] In neonates, a recent Cochrane systematic review found only one trial that met the inclusion criteria to assess the efficacy and safety of clonidine used in term and preterm newborn infants for sedation during ventilation, and this evidence was therefore deemed insufficient.[61]

Dexmedetomidine

An increasing number of publications deals with the use of dexmedetomidine mainly in the pediatric ICU population – in particular for sedation in hemodynamic unstable patients, such as post-cardiac surgery. A recent review of the use of dexmedetomidine in the pediatric population showed that evidence favoring dexmedetomidine in children is mainly extrapolated based on adult studies, small randomized controlled trials, and observational studies.[62,63] Pediatric trials are therefore needed with a specific focus on newborns and infants, taking into account the major side-effects documented in the literature for dexmedetomidine being hypotension and bradycardia for which continuous cardiac monitoring is needed. Apart from its sedative effect, dexmedetomidine is also used as an adjuvant analgesic drug as recently published in a systematic review by Schnabel et al.[64]. As many studies deal with optimal dosing and comparative effectiveness of dexmedetomidine, evaluating long-term effects of dexmedetomidine on the developing brain are essential as well.

NEURODEVELOPMENT FOLLOWING COMMON ANALGOSEDATIVE DRUGS

Despite a generally average intelligence, the incidence of academic difficulties is extremely high following neonatal critical illness.[65-70] This finding is highly suggestive of an alternative explanation related to specific neuropsychological deficits rather than general intellectual functioning. Although a complex interplay of deleterious factors associated with neonatal critical illness is likely to be the underlying cause of these long-term neuropsychological deficits, an important first step is to evaluate different potential contributors independently. Recently, more studies have evaluated the negative effects of analgosedatives on the developing brain.[71-73] This is of interest because the adjustment of pain management in order to minimize short and long-term side effects may

improve neuropsychological outcome following neonatal critical illness. Therefore, the clinical endpoints of our review were defined as specific neuropsychological functions, such as memory, attention and executive functioning.

The ontogeny of the nervous system is based on a complex pattern of cell proliferation, migration, differentiation and selective cell survival and includes apoptosis and synaptogenesis. Its development relates to a balance of ongoing excitatory and inhibitory signals.[74] Furthermore, the brain matures in a nonlinear fashion from childhood into adulthood, indicating that the timing of microstructural changes differs per brain region.[75,76] Consequently, the timing of injuries is likely to also have specific effects on the development of the brain.[77] Exposure of nociceptive and non-nociceptive nervous circuits to analgosedatives during this period may modulate receptor-signaling-related brain development, as demonstrated by various animal experimental studies.[74] Alterations are in part drug and dose dependent, and there is an age-related window of vulnerability for apoptosis on the one hand or dendritic changes on the other hand.[74] Moreover, the balance between pain and exposure to analgosedatives may also play an important role.[2] Specifically, the limbic system undergoes rapid development in the third trimester and neonatal period.[78] Embedded within the brain's limbic system, the hippocampus and its connections are essential for memory encoding, consolidation and retrieval.[79] Given the high incidence of memory deficits following neonatal critical illness[80], this gray matter structure may be particularly vulnerable in these children. In utero, hippocampal morphology and positional changes occur and the hippocampus is thought to resemble adult shape at 25 weeks of gestation. A critical period of hippocampal development is from the third trimester throughout the first two years of life when it undergoes a growth spurt.[81] The hippocampus and other limbic system regions may therefore be particularly vulnerable in critically ill preterm and term newborns.[78,82]

In the next section, studies describing the effects of commonly used sedatives and analgesics on the developing brain and neuropsychological functioning later in life following neonatal critical illness are summarized.

Analgesics

Worldwide, opioids such as morphine and fentanyl are regularly used in preterm and term born neonates during admission to the NICU.[73] Neonatal opioid therapy to mitigate the effects of painful and stressful procedures may affect the developing brain as well.[71,83,84] Interestingly, animal models have demonstrated some neuroprotective effects of morphine as a pre-treatment for pain and in case of certain levels of pain or stress.[71,84] However, concerns have been raised as a result of studies showing that opioids such as morphine may induce apoptosis in human microglial cells and neurons, and long-term changes in brain function and memory.[71,85]

Morphine

The long-term effects of morphine administration in preterm born children are comprehensively evaluated in follow-up studies among children from two well-defined cohorts.[31,32] Follow up studies of the cohort of Simons et al. found that morphine exposure was significantly, negatively correlated with only one IQ subtest at the age of 5 years.[86] At 8/9 years of age, however, this negative effect disappeared and morphine was even positively correlated with executive functioning.[5] In line with these findings, a third study did not find major negative effects in children from this cohort who did receive morphine compared to healthy term born children without neonatal morphine exposure at10 years of age with respect to neuropsychological functioning or pain sensitivity.[87] However, whether morphine itself or the underlying condition causes long-term adverse events remains a topic of debate.[88,89]

With regards to brain morphology, van den Bosch et al. found strong, negative correlations between neonatal opioid exposure and volumes of pain-related brain regions, total gray volume and cerebral white matter at school-age in children born preterm (26-36 weeks). However, neuropsychological outcome of those born preterm did not differ from the norm population and was not associated with morphine exposure.[87] In contrast, Ferguson et al. demonstrated differences at term-equivalent age and during childhood in head circumference between 14 morphine treated and 5 placebo treated children born at 23-32 weeks of gestation.[90] At 5-7 years, overall IQ and academic achievement did not differ between these groups, however, short-term memory was significantly worse in children treated with morphine compared to the placebo-treated children.[90] A recent neuroimaging study assessing the effects of morphine on brain development in preterm infants (24-32 weeks), demonstrated that increased neonatal morphine exposure was associated with smaller cerebellar volume at term equivalent age, but not with cerebral volume.[89] Furthermore, greater morphine exposure was associated with poorer cognitive and motor outcomes at 18 months.[89]

A few follow-up studies have been conducted in term-born survivors of neonatal critical illness as well. In a neuroimaging study by van den Bosch et al. school-age ECMO survivors were less sensitive to the detection of cold but showed similar pain sensitivity and chronic pain compared to healthy controls. Importantly, no differences in brain activation during pain or in pain-related brain regions were observed.[91] However, associations with morphine and midazolam exposure were not assessed in this study.[91] Children treated with neonatal ECMO are often exposed to prolonged continuous opioids and sedatives in the absence of major pain.[91] This may contribute to the long-term neuropsychological deficits and brain alterations observed in these patients at school-age and even in adolescence.[66,67,92] In 8-year-old ECMO survivors, specific attention problems were found irrespective of generally average intelligence.[65] However, outcome at eight years was not associated with the time children had been exposed to opioids or other sedatives.[65]

Fentanyl

Fentanyl is another commonly used analgesic in the NICU and may have effects on the developing brain as well. In preterm infants (23-30 weeks), higher cumulative fentanyl dose was associated with a higher incidence of cerebellar hemorrhage as well as lower cerebellar diameter.[93] However, two studies that have analyzed the association between cumulative fentanyl dose and developmental outcome at 2 years of age found no relation between the two.[93,94] This may be due to the fact that at 2 years of age, only general mental functioning can be assessed. The cerebellum has been shown to be involved in various higher-order cognitive functions, such as visuospatial processing, attention, and executive functioning.[95] As these higher-order cognitive functioning cannot be reliably assessed before school-age[68], long-term neuropsychological follow-up of these children is imperative to better understand the impact of morphine and fentanyl exposure on neurodevelopmental outcome in these children.

Acetaminophen

The safety and potential long-term effects of acetaminophen warrant additional exploration. The shift from opioids to acetaminophen is largely driven by the perceived better safety profile.[15] This is likely the case when we compare short term aspects like hemodynamics or respiratory depression following either opioid or acetaminophen administration.[74] However, intriguingly, a recent Cochrane review concluded that acetaminophen given after assisted vaginal birth may lead to an increased response to later painful exposures.[96] Data on long term safety following acetaminophen exposure are based on epidemiological association type studies. These associations suggest a link between fetal exposure and subsequent risks for atopy, fertility or neurobehavioral problems and these links are further supported by animal experimental observations.[45] In particular when it comes to neurodevelopment, concerns have been raised about an increased risk of attention-deficit-hyperactivity disorder, autism spectrum symptoms and neurocognitive deficits following early exposure to acetaminophen, although most studies are based on prenatal exposure or animal studies (reviewed by De Fays et al.[4] and Avella-Garcia et al.[97]). A recent study on the long-term effects of acetaminophen in mice, showed that adverse effects on adult behavior and cognitive function occurred in both male and female mice exposed to paracetamol on postnatal days (PND) 3 and 10, but not when exposed on PND 19. These neurodevelopmental time points in mice correspond to the beginning of the third trimester of pregnancy and the time around birth in humans. These findings suggest particular sensitivity of the brain in the preterm and neonatal brain.[98] Future clinical studies are needed before conclusions can be drawn on the effect of neonatal exposure to acetaminophen on long-term neuropsychological outcome.

Sedatives

Propofol and midazolam

Exposure to propofol and midazolam in the neonatal period has been suggested to negatively affect the developing brain in animals and humans.[6,99] Although studies in humans are scarce, findings from experimental studies suggest that, in particular, hippocampal development and long-term memory are affected after exposure to these agents.[100,101] Interestingly, studies have shown long-term hippocampal alterations and associated memory deficits across survivors of neonatal critical illness, irrespective of gestational age or underlying disease.[92,102,103] The hippocampus is the brain's central hub for memory encoding, consolidation and retrieval.[79] Benzodiazepines, such as midazolam, potentiate the neuronal inhibitory pathways or inhibit the excitatory pathways by binding to gamma-Aminobutyric acid (GABA) or glutamatergic N-methyl-D-aspartate (NMDA) receptors in the brain.[6,99] In the hippocampus, NMDA receptors are highly involved in Long-Term Potentiation (LTP), a system of persistent strengthening of synapses following high levels of stimulation, that results in the ability to form memories.[100,104] If these NMDA receptors become occupied due to the presence of for instance midazolam, memory formation will be disrupted.[14]

In preterm infants, the acute effects of midazolam on the brain have been studied directly. Injection with midazolam led to a decrease in middle cerebral artery blood flow velocity and transient cerebral hypoperfusion.[72] As the hippocampus is selectively vulnerable to cerebral hypoperfusion[105], this may contribute to the specific effects of midazolam on the hippocampus, and thus on memory. A recent clinical study in preterm-born neonates (24-32 weeks of gestation) evaluated how midazolam exposure affected the hippocampus using MRI. They demonstrated a selective, negative effect of midazolam on hippocampal growth from birth to term-equivalent age, even after adjusting for the number of invasive procedures and other common clinical care practices.[6] Long-term outcome studies are needed to evaluate whether the hippocampal growth reductions in response to midazolam exposure are associated with memory deficits, and whether this exists in both preterm and term born survivors.

Dexmedetomidine

Interestingly, rodent studies have shown that dexmedetomidine and clonidine may reduce anesthetic-induced apoptosis, specifically in the hippocampus[106], and diminish subsequent cognitive decline.[107] However, future clinical studies are needed to assess whether these agents are neuroprotective in neonates as well.

DISCUSSION

Although animal studies have fairly consistently demonstrated brain development to be negatively affected by various classes of drugs, such as anesthetics, benzodiazepines and to some extent opioids[71,85], associations in survivors of neonatal critical illness seem less obvious.[6,14] This may be due to differences between animal and human studies, resulting in more contradicting conclusions in humans (for a review on this matter, please refer to van den Bosch et al.[2]). Nonetheless, our findings seem to suggest a link between the use of analgesics such as morphine and fentanyl, and cerebellar volume in critically ill infants.[89,93] Concerning sedatives, direct links between midazolam exposure and hippocampal alterations have been described in preterm infants.[6] Commonly used sedatives such as midazolam and propofol bind either to GABA or NMDA receptors. The GABA and NDMA receptor systems are crucial for neuronal connection and communication in the developing brain, and if unavailable lead to neuroapoptosis.[14] These agents have been suggested to disrupt memory formation through its effects on the hippocampus.[104] Memory formation and recall are dependent on LTP, a system of persistent strengthening of synapses following high levels of stimulation. LTP, which mainly happens in the hippocampus, relies heavily on NMDA. Although based on animal studies, midazolam was found to affect pyramidal neurons in the CA1 region and memory by suppression of LTP.[100] This mechanism may be underlying the negative effects of midazolam found on the hippocampus in preterm infants[6], and may subsequently lead to memory deficits later in life in these children. (Please also refer to a recent review on other proposed mechanisms underlying the effects of analgosedatives and anesthetics on the brain by van den Bosch et al.[2].) As both the cerebellum and hippocampus are important for higher-order cognitive functioning and seem to be targeted by analgosedatives, damage to these brain regions may be (partly) underlying the long-term deficits following neonatal critical illness.[79,95]

The indications that exposure to analgosedatives in neonates and infants may affect specific brain regions responsible for higher-order cognitive functioning warrant future research. Specifically, as these functions, such as memory, do not fully develop until later in childhood, it is imperative that long-term neuropsychological outcomes are measured when studying the effect of analgosedatives following neonatal critical illness. Therefore, studies described in this review that only include the assessment of general intellectual ability at 24 months (corrected age), e.g. with the commonly used Bayley Scales of Infant and Toddler Development–Third Edition[108], as well as general intellectual outcome at a later age are less informative in this respect. Future studies on the effect of commonly used analgosedatives that include neuropsychological assessment and neuroimaging later in childhood are needed to more reliably assess the potential clinical

effect of cerebellar and hippocampal alterations on cognitive outcome before definitive conclusions can be drawn.

Problematically, analgosedatives will remain a necessary treatment as the experience of pain itself has shown to negatively impact neurodevelopment as well. Ranger et al. showed that pain related stress predicted cortical thickness at 7 years in preterm born children, independent of morphine exposure. Also, a higher number of painful (skin-breaking) procedures in preterm born children was found to be associated with reduced white and subcortical gray matter.[2,109] In addition to pain, studying the association between analgosedatives and neurodevelopmental outcome is likely to be affected by differences in dosages. Moreover, critically ill infants are exposed to other factors such as stress, hypoxia-ischemia and neuroinflammation during a vulnerable and critical period of brain development. A complex interplay amongst these factors may lead to (subtle) brain injuries early in life, which become evident only later in life when those brain regions are required for higher cognitive functioning. In particular, the hippocampus, the main hub for memory formation in the brain, has been found to show pronounced vulnerability to factors associated with critical illness, including exposure to sedatives.[6,80] This 'growing into deficit' phenomenon[110], where early hippocampal alterations lead to memory deficits later in life, has recently been identified by our group across survivors of neonatal critical illness.[80] To what extent exposure to analgosedatives contribute to early brain injury in these patients needs further research that combines information on analgosedative exposure and exposure to confounding factors, such as pain, with neuroimaging and elaborate neuropsychological assessment.

Elaborate neuropsychological assessment is essential as an increasing number of studies has found that survivors of neonatal critical illness are at risk of specific memory and attention deficits, rather than intellectual disability.[66-68,111] The majority of clinical studies described in the current review only used general neurodevelopmental outcome measures such as intelligence at pre- or school-age. Therefore, it is difficult to draw any definitive conclusions on how and to what extent analgosedatives affect the brain in critically ill neonates. Better understanding of the association between the brain, cognition and analgosedatives exposure in early life is needed to optimize adequate pain management in neonates. Future studies combining elaborate neuropsychological assessment with multimodal neuroimaging techniques, such as (functional) MRI and Diffusion Tensor Imaging, are therefore needed.

In this vulnerable population, there is a significant need for early predictors of long-term neuropsychological deficits and school problems. As of now, identification of patients at risk relies solely on neuropsychological assessment which cannot be reliably conducted until school-age.[68] By this time, the cognitive deficits may have already hampered school performance in a number of children.[67] Predictors that can be measured as early as during first admission ('biomarkers') are therefore of utmost importance. A

better understanding of how and to what extent analgosedatives affect the brain may contribute to identifying which patients are most at risk. Within this context, interaction with age and developmental stage are essential. Furthermore, given the high incidence of memory deficits following neonatal critical illness[80,112], early identification of patients at risk of memory deficits may become possible using hippocampal volume as a neurobiological marker. The hippocampus can be accurately and non-invasively delineated using structural MRI and is the brain's critical hub for long-term memory formation.[79,81] Because of these features, the hippocampus is an important target for future studies aimed at improving long-term outcomes following neonatal critical illness. In preterm infants, studies have shown that MRI can be reliably performed without sedation and that infant hippocampal volumes, measured at term-equivalent age, correlated with memory outcomes later in childhood.[113,114] However, it is important to note that even the more advanced MR techniques are not sensitive enough to provide us with information on the exact anatomical or molecular mechanisms underlying neuropsychological deficits. The exact contribution of exposure to analgosedatives on neuropsychological outcome therefore remains speculative.

In neonatal pain management, the ultimate goal is to achieve adequate pain management with minimal short and long-term side effects. The search for the lowest, most effective exposure to analgosedatives becomes even more relevant when taking into account their potential effect on long-term neurocognitive outcome.[6,14,71,85] For both new compounds as well as for the already used drugs, dose-finding studies (phase 2) can be very instructive before conducting phase 3 efficacy and safety trials.[74] The earlier mentioned study on morphine sparing acetaminophen in neonates and infants[46] used a much lower dose of morphine in neonates and infants and still resulted in further reduction of the morphine maintenance dose (-66%) in cases co-exposed to acetaminophen. Similarly, the ED_{50} of propofol (0.5-1.5 mg/kg) to enable endotracheal intubation turned out to be significantly lower compared to the routine practices.[51,53,54] Furthermore, the increased use of (new) drugs such as dexmedetomidine will only result in evidence-based pharmacotherapy when assessed using appropriate and comparative effectiveness trials. Together with advanced analysis techniques such as pop-PK and physiology based/PK on sparse datasets, we will reach a higher level of evidence-based dosing of analgosedative drugs in neonates. The same holds true for future application of principles of pharmacovigilance studies. This is especially of interest since experimental studies have suggested that dexmedetomidine may have neuroprotective effects as well.[106,107]

CONCLUSION

Indications from both animal and clinical studies that early exposure to analgosedatives may have long-term effects on the brain and cognition warrant future research. As the number of critically ill neonates admitted to intensive care units grows worldwide and more and more of these patients survive to discharge due to medical improvements[7,8], the long-term outcome after surviving neonatal critical illness can no longer be ignored. It is therefore of utmost importance that we continue to gain insight into how pharmacotherapy affects the developing brain. In future studies, potential long-term sequelae should be primary outcome parameters and this information should be used when optimizing pain management in neonates.

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