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Neonatal pain control and neurologic effects of anesthetics and sedatives in preterm infants

Christopher McPherson, PharmD and Ruth E. Grunau, PhD

Keywords

Pain; Newborn; Premature; Analgesia; Anesthesia; Sedation

Introduction

Historically, pain in the preterm infant has been poorly understood and often unrecognized.¹ There have been major advances in understanding the developmental physiology of nociception and responses of infants to noxious stimuli.² These data clearly demonstrate that nociception occurs in infants, even at the lower limit of viability. Importantly, early maturation of the ascending neural pathways responsible for nociception precedes maturation of descending inhibitory pathways which localize and mitigate pain.³ Additionally, the increased excitability of nociceptive neurons in the dorsal horn of the spinal cord contributes to the development of hyperalgesia and allodynia in the infant.⁴ These physiologic factors create a unique susceptibility of the developing brain to both the acute and long-term adverse effects of prolonged pain exposure.⁵ Greater exposure to stress and pain from procedures during neonatal intensive care is associated with decreased brain growth in the frontal and parietal lobes and alterations in organization and neuronal connections in the temporal lobes.^{6,7} Additionally, greater early repetitive procedural pain-related stress in preterm infants, after adjusting for multiple clinical confounders, is associated with decreased body and brain growth from early in life to term-equivalent age, poorer cognitive and motor function at 8 and 18 months corrected chronological age, and altered spontaneous cortical oscillations in the resting brain at school-age.^{8–10}

Despite increased understanding of the developmental physiology of nociception and long-term consequences of pain and agitation in preterm infants, there is no consensus regarding safe and effective strategies for controlling pain and agitation in many clinical situations. Concern regarding the long-term neurologic impact of available interventions represents a major limitation precluding widespread utilization in clinical practice. Preterm infants experience varied forms of pain and agitation including pain from minor procedures and major surgery and chronic agitation from life-sustaining interventions such as mechanical ventilation. This review summarizes available data regarding the neurodevelopmental

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Address correspondence to: Christopher McPherson, St. Louis Children's Hospital, 1 Children's Place, St. Louis, MO 63110
Telephone: 1-314-454-7556; Fax: 1-314-454-8538; ccm0145@bjc.org.
Contact information for Dr. Grunau: Ruth E. Grunau, University of British Columbia, Vancouver, B.C. Canada, and Queens
University Belfast, Belfast, Northern Ireland UK Telephone: 1-604-875-2447; Fax: 1-604-875-2384; rgrunau@cw.bc.ca

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impact of agents commonly utilized to treat acute and chronic pain and agitation in preterm infants.

Standards of care

The preemptive provision of analgesia or sedation during mechanical ventilation is significantly controversial. In contrast, treatment of acute procedural pain is promoted. Local anesthetics such as lidocaine may be useful for procedures such as chest tube insertion.¹³ Topical anesthetics such as EMLA effectively reduce pain from procedures such as lumbar puncture.¹⁴ Systemic adverse effects appear to be rare, making these modalities appealing to minimize exposure to systemic agents.¹⁵ In conjunction with local or topical anesthetics, systemic analgesia should be provided to avoid pain from major procedures. There is a paucity of clinical trials comparing different opioids for the treatment of acute pain in preterm infants. In general, agents with a rapid onset and short duration of action are preferable. On this basis, remifentanyl may be the most appropriate opioid for procedural pain in the preterm infant.¹⁶ Remifentanyl is metabolized by nonspecific blood and tissue esterases to an inactive form, avoiding the prolonged duration of action observed with renally-eliminated opioids in preterm infants.¹⁷ The cumulative impact of opioids on long-term outcome will be examined in a subsequent section of this review. However, in the setting of established major procedural pain, the deleterious consequences of pain and ethical consideration appear to outweigh potential risks from exposure to pharmacotherapy.

Sucrose for minor procedural pain

During neonatal intensive care, infants experience a median of 10 painful procedures per day.¹⁸ Non-pharmacologic therapies form the foundation of pain and agitation relief for mildly painful routine procedures.¹⁹ Therapies with evidence supporting reduction in pain scores include sucrose, nonnutritive sucking, swaddling, kangaroo care with or without breastfeeding, music therapy, and multi-sensorial stimulation (including massage, voice, smell, and eye contact).²⁰

Clinical data

Sucrose has widely been accepted as a nonpharmacologic intervention effective for the treatment of minor procedural pain in preterm infants.²¹ Studies have extensively documented reduced crying, facial grimacing, and motor activity following oral administration of sucrose prior to minor painful procedures.²² Importantly, recent evidence from both clinical and electroencephalography studies suggests sucrose may exert influences on the neonatal response to pain as a sedative rather than analgesic.^{4,23} Further supporting this view, sucrose has variable effects on physiological indices such as heart rate, heart rate variability, oxygen saturation, and no effect on cortisol.²² There is a dearth of knowledge of the neurodevelopmental outcomes of preterm infants treated repeatedly with sucrose during a period of the most rapid brain development. To our knowledge, only one study has examined repeated sucrose exposure in preterm infants, limited to the first week of life, and only examined outcomes to term equivalent age.²⁴ When compared to placebo, sucrose given for invasive procedures in the first week of life in infants born at < 31 weeks gestation had no impact on measures of motor development or attention/orientation at 36 and 40 weeks postmenstrual age. However, a higher number of doses of sucrose was associated with poorer motor development and attention/orientation scores at 36 and 40 weeks postmenstrual age. This finding was likely not attributable to increased painful procedures, as a similar dose/outcome relationship was not observed in the placebo group. No studies (to our knowledge) have assessed long-term developmental outcomes following repetitive administration of sucrose in preterm infants.

Potential mechanisms of neurologic impact

Understanding the potential negative impacts of repeated sucrose administration on the developing brain requires consideration of the mechanism by which sucrose decreases the response to painful stimuli. Several potential mechanisms have been explored and include mediation of pain and/or agitation through opioid receptors, dopaminergic pathways, and cholinergic pathways. Preclinical data suggest that sucrose mediates response to pain through opioid receptors. β -endorphin levels, a marker of endogenous opioid activity, increase in response to ingestion of sweet foods in animal models.²⁵ Additionally, the impact of sucrose on pain threshold is reversible with co-administration of opioid receptor antagonists.²⁶ Considering data regarding the impact of chronic opioid administration on the developing brain examined in a subsequent section of this article, this mechanism of action would justify concerns regarding long-term developmental impact. However, sucrose administration to preterm human infants does not produce a plasma β -endorphin response.²⁷ Also, a trial in term human newborns found no decrease in the impact of sucrose on pain-related behavior with concurrent opioid antagonist administration.²⁸ These results suggest additional mechanisms may be responsible for the behavioral effect of sucrose observed in infants.

The concurrent findings of pain modulation and impact on motor function and attention prompt consideration of dopaminergic and cholinergic pathways. In rodents, sucrose promotes dopamine release in the nucleus accumbens in a concentration dependent manner.²⁹ Dopamine plays a central role in modulating pain perception through direct action in the descending inhibitory pathways in supraspinal regions.³⁰ Additionally, dopamine has antinociceptive action in the spinal cord through potassium channel activation.³¹ Sucrose administration also promotes the release of acetylcholine.³² Acetylcholine stimulates muscarinic receptors in the spinal cord reducing the release of glutamate (an excitatory neurotransmitter) and increasing the release of γ -aminobutyric acid (GABA; an inhibitory neurotransmitter acting on spinal GABA_B receptors).³³ Early modulation of dopamine and acetylcholine may impact attention and motor function later in life, since these neurotransmitters both play a central role in these functions.^{34–36} Of note, tolerance to the sucrose-mediated release of dopamine develops with repetitive stimulation.³⁷ Downregulation of either the dopaminergic or cholinergic system secondary to early repetitive receptor stimulation may potentially have adverse consequences on neurologic function later in life.

Considering the potential adverse effects of chronic sucrose administration on the developing brain, clinicians should consider utilizing other nonpharmacologic comfort measures for minor procedures, until evidence of long-term safety is available. For example, in general, sucrose produces a similar clinical effect to other nonpharmacologic interventions including facilitated tucking and kangaroo care.²⁰ However, a recent study suggests superior immediate pain reduction with sucrose compared to facilitated tucking.³⁸ These findings highlight the necessity of future studies of sucrose examining long-term neurodevelopmental and behavioral effects.

Anesthetics for major surgery

In 1987, Anand and colleagues published a landmark randomized controlled trial demonstrating decreased hormonal responses to patent ductus arteriosus (PDA) ligation in preterm infants treated with high-dose fentanyl in addition to nitrous oxide and muscle relaxation.³⁹ Additionally, preterm infants randomized to fentanyl experienced fewer post-operative complications. Concerns regarding the toxicity of high-dose opioids have led to the widespread utilization of “balanced analgesia”, an approach emphasizing concurrent administration of several agents to decrease the dosage requirement of each individual agent.

Commonly employed agents include volatile anesthetics, ketamine, and propofol.⁴⁰ Questions remain regarding the neurologic impact of these anesthetics in preterm infants undergoing major surgery.

Clinical data

Complications of prematurity including inguinal hernia, necrotizing enterocolitis (NEC), and PDA often require surgical intervention. Approximately 20% of preterm infants undergo a surgical procedure before discharge from the neonatal intensive care unit. Several large retrospective studies have described an association between early surgical/anesthetic exposure (at < 4 years of age) and learning or behavioral problems in children and adolescents.⁴¹ Despite inconsistent findings and significant limitations, these studies have produced a strong demand for further trials exploring this association.^{42,43} Smaller retrospective analyses focusing specifically on preterm infants have observed similar concerning associations. Preterm infants exposed to surgery and anesthesia have a greater incidence of moderate to severe white matter injury and smaller total brain volumes, with the greatest difference observed in the deep nuclear gray matter. These infants also exhibit poorer performance on cognitive and psychomotor assessments at two years of age, although importantly this finding was not significant after correction for additional risk factors.⁴⁴ However, previous studies have noted an association between both surgical NEC and PDA ligation and cognitive delay at 18–22 months of age after adjustment for confounders.^{45,46} Additionally, the association between surgery requiring general anesthesia and disability persists to 5 years of age.⁴⁷

Clinical data supporting an association between surgery/anesthesia and neurologic impact in preterm infants must be interpreted with caution. An inflammation/infection mediated impact on brain injury, growth, and development has been demonstrated.⁴⁸ Immature oligodendroglia in the cerebral white matter of preterm infants appear to be particularly vulnerable to this insult.⁴⁹ This mechanism has particular relevance to retrospective studies including bowel surgery after necrotizing enterocolitis, but does not explain associations between developmental and behavioral disorders and more minor procedures such as inguinal hernia repair.⁵⁰

Potential mechanism of neurologic impact

Preclinical evidence in newborn rodents and non-human primates *in vivo* suggests that early anesthetic exposure leads to neuroapoptosis and impacts long-term neurodevelopment. Cell death begins early after exposure and dramatically increases with greater doses or longer exposures.⁴⁷ Apoptosis occurs at the level of individual cells and results in rapid phagocytosis of the affected cell.⁵¹ Vulnerability to this effect peaks during synaptogenesis.⁵² Of note, widespread apoptotic cell death occurs during normal development and represents an integral aspect of central nervous system evolution.⁵³ However, exposure to anesthetics in preclinical models dramatically increases apoptosis far in excess of normal physiologic levels. The findings of decreased neuronal density and impaired cognition at maturity argue against the hypothesis that this apoptosis represents accelerated physiologic cell death rather than a pathologic reaction to anesthetic exposure.⁵⁴ Extensive debate continues regarding the applicability of this preclinical evidence to the human infant. Concerns include timing of exposure relative to developmental vulnerability, the duration and degree of exposure relative to exposure in clinical practice, and the absence of surgical pain or stress in many of the preclinical models. However, at a minimum, the mechanisms of impact derived from preclinical models must be considered in the setting of retrospective clinical data in humans indicating the potential for long-term neurologic harm.

Volatile anesthetic have limited selectivity for molecular targets, acting on GABA, glutamate, nicotinic, and glycine receptors.⁵⁵ The impacts of concurrent GABA-receptor agonism and *N*-methyl-D-aspartate (NMDA)-receptor antagonism on the developing brain have been extensively explored. Concurrent GABA-agonism and NMDA-antagonism initially activate the intrinsic apoptotic pathway by increasing cytosolic free calcium and lowering mitochondrial transmembrane potential (Figure 1).⁵⁶ This pathway commences with upregulation of the pro-apoptotic bax protein and downregulation of the counterbalancing anti-apoptotic bcl-2 protein.^{52,57} The bax protein translocates to mitochondrial membranes, where it disrupts membrane permeability allowing the release of cytochrome c into the cytoplasm, triggering the caspase cascade responsible for proteolytic cleavage leading to cell death. After prolonged exposure, volatile anesthetic agents also trigger the extrinsic apoptotic pathway through upregulation of Fas (Figure 1).⁵² This “death receptor” on the plasma membrane initiates the caspase cascade through autocatalysis of procaspases. Finally, volatile anesthetic agents decrease levels of brain-derived neurotrophic factor (BDNF) in the thalamus. This decrease in BDNF precipitates decreased activation of tropomyosin receptor kinase (Trk) receptors resulting in decreased release of Akt serine/threonine kinase, increasing caspase activation (Figure 2). Conversely in the cerebral cortex, volatile anesthetic agents increase levels of BDNF. However, p75 neurotrophic receptors predominate in the cortex and stimulation produces ceramide, which overrides Trk receptor dependent production of Akt.⁵⁸

Ketamine, a potent NMDA receptor antagonist, has anesthetic and analgesic properties. Prolonged, high-dose exposure to ketamine in developing rodents and non-human primate promotes widespread neuroapoptosis.⁵⁹ NMDA receptor stimulation plays a crucial role in synaptogenesis and neuronal survival and blockade of this stimulation may result in apoptosis of the postsynaptic neuron through the intrinsic apoptotic pathway.^{60,61} However, preclinical models producing these molecular effects through relatively prolonged, high-dose ketamine exposure in the absence of surgical stress have questionable clinical relevance.⁶² Preclinical models of clinically relevant doses of ketamine administered prior to inflammatory pain demonstrate amelioration of pain-induced neuroapoptosis.⁶³ This effect is physiologically plausible, likely resulting from a reduction in stress-induced excitotoxic cell death mediated by neuronal entry of calcium via NMDA receptors.⁶⁴ A clinical study of ketamine in infants undergoing ventricular septal defect repair with cardiopulmonary bypass demonstrated attenuation of systemic inflammation and glutamate release in the frontal white matter.⁶⁵ Considering this evidence, further investigation of the neurologic impact of ketamine in the surgical setting appears warranted.

Propofol, a potent GABA agonist, provides sedation and anesthesia with a rapid onset of action. In preclinical models, propofol induces significant apoptotic degeneration of oligodendrocytes in the developing brain.⁶⁶ These findings may be a function of the paradoxical effect of GABA_A receptor stimulation in the developing brain. During synaptogenesis, GABA_A receptor activation results in chloride efflux and neuronal depolarization.⁶⁷ The ensuing increase in intracellular calcium may result in neuronal injury via the intrinsic apoptotic pathway. Additionally, the paradoxically pro-inflammatory nature of GABA_A receptors during development may activate the extrinsic apoptotic pathway.⁶⁸ The relevance of these molecular effects in preterm human infants is unknown, but taken in concert with potential adverse effects discourages use of propofol in clinical practice.⁶⁹

In summary, anesthetic agents have the potential to induce widespread neuroapoptosis through modulation of apoptotic pathways and neurotrophins. The molecular pathways by which GABA-agonism and/or NMDA antagonism promote bax proteins and the Fas receptor, inhibit bcl-2 proteins, and modulate BDNF have not been elucidated. Description of these pathways will be integral to development of anesthetic agents that do not adversely

impact the developing neuron or protective interventions that stabilize these apoptotic pathways. Dexmedetomidine, erythropoietin, melatonin, and many other agents have been explored in preclinical studies as adjuvant therapies that may ameliorate anesthetic-induced neurotoxicity.⁷⁰ The role of these agents in neonatal anesthesia has not been studied. Intravenous acetaminophen is a promising agent that may minimize analgesic requirement in the intraoperative and postoperative period. A recent randomized controlled trial has demonstrated a decreased opioid requirement in infants who receive intravenous acetaminophen for 48 hours following non-cardiac surgery.⁷¹ Outstanding questions include the impact on clinical outcomes and appropriate dosing in very preterm infants.⁷² Future studies must establish the safety and efficacy of adjuvant therapies while ensuring continued provision of appropriate anesthesia to preterm infants undergoing major surgical procedures.

Agents utilized for chronic pain and agitation

Mechanical ventilation is a common stressful experience in the management of very preterm infants during neonatal intensive care.⁷³ On average, preterm infants born at less than 28 weeks gestation require 2–4 weeks of invasive respiratory support.⁷⁴ Routine administration of pharmacologic sedation or analgesia in these preterm infants is not recommended due to concerns regarding the safety and efficacy of pharmacotherapy examined in clinical trials, specifically benzodiazepines and opioids.¹³ However, the use of opioids in clinical practice remains common due to the caregivers desire to treat pain, stress, and agitation from mechanical ventilation and the lack of available alternative therapies.^{75,76}

Benzodiazepines

Clinical data—Two randomized controlled trials have examined the impact of midazolam on acute brain injury in mechanically ventilated preterm infants.^{77,78} The initial randomized trial of continuous infusion midazolam included a small number of preterm infants (N = 25) and avoided administration of a loading dose. This trial detected no difference in the incidence of intracranial hemorrhage or death.⁷⁷ Subsequent pharmacokinetic studies informed the design of the pilot NOPAIN trial and included a 200 mcg/kg loading dose followed by a continuous infusion.^{79,80} The NOPAIN trial randomized mechanically ventilated preterm infants (N = 67) to midazolam, morphine, or placebo.⁷⁸ Infants in the midazolam group had a trend towards a higher rate of the composite outcome of severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), or death compared to infants receiving placebo (32% vs. 24%), although the difference was not statistically significant. However, the difference in composite outcome was statistically significant when compared to morphine (32% vs. 4%, $p = 0.03$). Clinical use of midazolam in mechanically ventilated preterm infants has declined due to the findings of the NOPAIN trial. No data exist, to our knowledge, regarding the long-term neurodevelopmental impact of prolonged benzodiazepine therapy on the preterm infant.

Potential mechanism of neurologic impact—The increase in brain injury observed in the NOPAIN trial likely arises from the hemodynamic adverse effects of midazolam. Midazolam boluses of 200 mcg/kg produce clinically significant hypotension in a large proportion of preterm infants (27–45%), resulting in decreases in oxygen saturation, cerebral oxygenation index, and cerebral blood flow velocity.^{81,82} Fluctuations in cerebral blood flow appear important in the pathogenesis of IVH and PVL.⁸³

Benzodiazepines potentially impact the developing brain beyond the initial risk of acute brain injury. Preclinical models have described widespread neuroapoptosis and suppressed neurogenesis elicited by early benzodiazepine exposure.^{84,85} Additionally, prenatal benzodiazepine exposure in preclinical models produces lasting changes in hypothalamic neuron expression and delayed motor development.^{86–88} Benzodiazepines provide sedation

and anxiolysis by promoting the action of GABA. As described with propofol, potent stimulation of GABA receptors represents the most likely mechanism of benzodiazepine-induced neuroapoptosis.

Opioids

Clinical data—Two large randomized controlled trials have examined the impact of opioids on acute brain injury in mechanically ventilated preterm infants informed largely by the promising results of the NOPAIN trial with regard to morphine. Both trials detected no difference in the composite outcome of severe IVH, PVL, or death.^{89,90} In the larger NEurologic Outcomes and Preemptive Analgesia in Neonates (NEOPAIN) trial (N = 898), subgroup analyses revealed an increase in the incidence of IVH, PVL, or death associated with randomized and open-label morphine.⁹⁰

Conflicting results exist with regard to the long-term neurodevelopmental impact of early morphine exposure in preterm infants. Developmental follow-up of NEOPAIN infants (N = 572) at 36 weeks postmenstrual age found higher popliteal angle cluster scores, indicative of increased tone, in infants randomized to morphine.⁹¹ This finding is corroborated by a prospective longitudinal cohort study indicating an association between greater intravenous morphine exposure and poorer motor development at 8 months of age corrected for prematurity.⁹ A 5–7 year pilot follow-up of a small subset of NEOPAIN infants (N = 19) found no difference in overall intelligence quotient. However, morphine-treated children had smaller head circumference, impaired short-term memory, and social problems compared to placebo-treated children.⁹² Five-year follow-up (N = 90) of participants in the randomized trial of Simons and colleagues found an adverse effect of neonatal morphine on the visual analysis domain of intelligence quotient at age 5 years, indicating the importance of evaluating morphine effects on higher-order neurocognitive functions at later ages.^{89,93} Recently, 8–9 year follow-up of children from the same cohort found no effects on IQ or behavior (although visual analysis was not assessed).⁹⁴ In that study, morphine exposure appeared to be associated with better “executive functions” assessed by parent report. However, considering the high number of outcome measures tested and the lack of differences in teacher report or standardized assessment of executive functions, the positive association between morphine exposure and executive functions appears highly tentative. Differences in long-term outcomes of children in these two trials may reflect the substantially higher morphine dosing in the NEOPAIN trial conducted in the United States compared to Simons et al conducted in Europe.^{89,90}

The major limitation to both these trials is the (albeit understandable) use of “rescue” dosing with morphine, leading to considerable crossover between randomized arms, with as much or more morphine administered to the “placebo” group as the morphine group in both studies. This lack of equipoise rendered the result of comparisons of the randomized group membership inconclusive, and findings were only meaningful when adjusted using propensity scores to address clinical confounders related to the decision to provide morphine beyond the confines of the trials. In two longitudinal clinical cohort studies statistically adjusting for key medical confounders, Grunau and colleagues have reported no evidence of protective or adverse effects of greater morphine exposure cumulatively from birth to term equivalent age on brain development, cortisol levels, or cognitive development.^{7–10,95,96} However, higher morphine exposure was transiently associated with poorer motor development at 8 months, but not at 18 months corrected age.⁹ Moreover, in an independent cohort, higher morphine exposure across the neonatal intensive care unit stay was associated with poorer growth of the cerebellum imaged early in life and again at term equivalent age.⁹⁷ In summary, follow-up studies at school-age of children in the NEOPAIN and the European morphine trials (after adjustment with propensity scores) suggest little evidence of

major adverse relationships with psychosocial or academic functioning, although currently subtle impact on neurodevelopment cannot be ruled out.

Potential mechanism of neurologic impact—Hemodynamic effects have been identified as a contributing factor to the association between morphine and acute brain injury. Clinically significant hypotension (requiring intravenous vasopressors or fluid boluses) occurs in a large proportion of morphine-treated infants, most often following a bolus dose.^{90,98} This adverse effect appears to have minimal impact on preterm infants without pre-existing hypotension. However, in preterm infants with pre-existing hypotension, particularly those at lower gestational ages, the hemodynamic impact of morphine is more profound and may contribute to the pathophysiology of IVH.⁹⁸

The potential mechanism of a negative impact of opioids on the developing brain beyond the risks of acute injury has been explored extensively. Reduction of neuronal density and dendritic length as well as apoptosis have been observed in rodent models of early opioid exposure.^{99–102} A similar apoptotic effect on human fetal microglia and neurons *in vitro* has been observed.¹⁰³ Early opioid exposure also compromises myelination.¹⁰⁴ The cellular etiology of these apoptotic and anti-proliferative effects have been extensively explored *in vitro* and in preclinical models. Opioids act by agonism of the G-protein coupled μ -opioid receptor which produces analgesia and sedation through inhibition of ascending neural pathways in the brainstem, inhibition of neuronal firing in the dorsal horn of the spinal cord, and depression of both presynaptic and postsynaptic neuronal membrane potentials peripherally. Acute stimulation of the μ -opioid receptor decreases glutamate release reducing excitotoxic neuronal injury, potentially explaining the benefits of single, high-dose opioid administration in the surgical setting. Chronic stimulation of the μ -opioid receptor results in phosphorylation by G-protein coupled receptor kinases (Figure 3). Phosphorylation causes uncoupling of the opioid receptor from the G-protein, followed by binding of the receptor to β -arrestin. β -arrestin acts as a signal transducer, recruiting kinases including extracellular-signal-regulated kinase (Erk) to the receptor. Complexing with these kinases can lead to cytosolic retention of the receptor/ β -arrestin/Erk aggregate, inhibiting the growth promoting effects of Erk. Additionally, β -arrestin may scaffold with c-Jun N-terminal kinase (JNK) and apoptosis signal-regulating kinase (Ask), increasing the overall activity of this apoptosis promoting enzyme.¹⁰⁵ As with anesthetic exposure in the thalamus, chronic opioid exposure results in lower levels of BDNF in the hippocampus, a site with high-level Trk receptor expression.¹⁰⁶ Cumulatively, these cellular perturbations result in reduced brain growth in preclinical models of chronic opioid exposure.¹⁰⁷ Further, evidence suggests that these adverse effects on central nervous system development translate into abnormalities in later cognitive function and behavior. For example, rodents exposed to postnatal morphine exhibit persistently decreased motor activity and impaired learning ability.^{108–111} However, morphine acts differently in the brain in the presence of pain, compared to when pain is not present. For example, in neonatal rat pups exposed to pain induced with repeated inflammation of the paws, pre-emptive morphine prevented altered nociception in adulthood.^{112,113} In contrast, there is preliminary evidence that early exposure to pain or morphine may have similar adverse effects on both the structure and function of the developing brain under certain circumstances.¹¹⁴ However, in many preclinical studies, doses of inflammatory agents induce long-lasting tissue alterations that exceed the extent and duration of pain exposure in hospitalized preterm infants. Appropriate experimental models that examine effects of morphine combined with pain are needed, with paradigms and dosing that more closely fit the clinical experience of the preterm infant.

Dexmedetomidine

Clinical data—Dexmedetomidine represents an interesting potential alternative therapy for prolonged sedation of the preterm infant during mechanical ventilation. The short-term outcomes of mechanically ventilated preterm infants treated with dexmedetomidine infusion have been described in a case-control study. In this study, outcomes were compared to historical controls who received fentanyl infusion. Infants treated with dexmedetomidine required less adjunctive sedation, a shorter duration of mechanical ventilation, and had a lower incidence of culture-positive sepsis.¹¹⁵ These findings reflect the advantages of dexmedetomidine over standard sedative regimens demonstrated in randomized trials in adults.^{116–118} In the single study in preterm infants, the incidence of severe IVH or PVL did not differ between groups.¹¹⁵ No studies have reported the long-term developmental outcome of preterm infants treated with dexmedetomidine.

Potential mechanism of neurologic impact—Further studies are necessary to define the incidence of acute brain injury in preterm infants treated with dexmedetomidine. A well described adverse effect of dexmedetomidine is hypotension, which is common with bolus doses in both adult and pediatric patients.^{119,120} The incidence and degree of hypotension after bolus dosing appears to be similar to fentanyl and midazolam.^{121,122} Avoidance of bolus doses or rapid titration of dexmedetomidine attenuates this adverse effect in adults.¹²³ Prospective studies of dexmedetomidine in preterm infants must include the outcome of acute brain injury as well as continuous assessment of blood pressure, heart rate, and perfusion.

The potential neuroprotective effects of dexmedetomidine on the developing brain have been explored in preclinical models. Initial models in newborn rodents examined the impact of a single bolus dose of dexmedetomidine after ibotenate-induced brain lesions (designed to mirror the pathology of PVL in the preterm human infant). Dexmedetomidine reduced the number of damaged neurons *in vitro* and reduced the size of the lesion *in vivo*.^{124,125} Subsequent experiments confirming both *in vitro* and *in vivo* neuroprotection have been conducted in models of hypoxic-ischemic insult.¹²⁶ Dexmedetomidine is a highly selective agonist of the G-protein coupled α_2 -adrenergic receptor that provides analgesia, anxiolysis, and sedation via reduction in sympathetic outflow from the locus coeruleus and release of substance P from the dorsal horn of the spinal cord. Several potential molecular mechanisms may contribute to the neuroprotective actions of α_2 -agonists. These agents reduce glutamate release resulting in decreased excitotoxic damage.¹²⁷ Additionally, α_2 -agonists upregulate the bcl-2 protein and suppress bax expression,¹²⁸ contrasting directly with the actions of volatile anesthetics discussed earlier. In contrast to chronic opioid exposure, dexmedetomidine increases the expression of phosphorylated Erk through imidazoline receptor stimulation.¹²⁹ Specifically, Erk activation increases BDNF expression in cortical astrocytes, providing neuroprotection in the setting of excitotoxicity. Dexmedetomidine does not impact neuronal BDNF expression.¹³⁰ The molecular effects of chronic α_2 -receptor stimulation have not been explored and represent a vital need in preclinical research. The decision to pursue trials of dexmedetomidine in preterm infants must be made considering the efficacy, adverse effect profile, and potential risks and benefits of this agent with regards to neurodevelopment. When clinical trials of dexmedetomidine are undertaken in preterm infants, inclusion of advanced neuroimaging to assess brain microstructure and growth must be considered in conjunction with assessment of long-term neurodevelopmental impact.

Synopsis

Research in the developmental physiology of nociception clearly demonstrates the ability of preterm infants to perceive pain. Preclinical and clinical studies have confirmed the adverse consequences of untreated pain and stress on brain development. Based on the available

evidence, treatment is indicated for acute events ranging from minor procedural pain to major surgery as well as chronic stressful experiences including mechanical ventilation. Controversy exists concerning the safety and long-term impact of interventions commonly utilized in these situations. Sucrose has widely been implemented as standard therapy for minor procedural pain. However, the mechanism of action of this therapy has not been elucidated and long-term neurodevelopmental outcomes of preterm infants after chronic exposure is unknown, with greatest concern for infants born at the lowest gestational ages. Until the long term effects of repeated sucrose exposure have been evaluated, judicious use of sucrose should be considered, as well as utilization of alternatives such as kangaroo care and facilitated tucking for humanitarian care. Anesthetics are commonly utilized during major surgery in preterm infants. Concerning preclinical and clinical data suggest these agents may promote apoptosis and impact neurodevelopment. Ongoing studies will help define the impact of these agents, fully elucidate the mechanism of impact, and identify adjuvant therapies which may ameliorate detrimental effects. Sedation is likely indicated for preterm infants requiring invasive mechanical ventilation. However, the pharmacologic agents examined in clinical trials (benzodiazepines and opioids) may have both acute and chronic adverse neurologic impacts. Dexmedetomidine represents a promising alternative, although extensive, multidisciplinary research must be completed before widespread use in preterm infants is considered.

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Key points

- Optimal therapeutic approaches for the treatment of pain and agitation in the preterm infant have not been elucidated
- Sucrose effectively reduces behavioral responses to minor procedural pain, however the impact of repetitive dosing on long-term neurodevelopment remains unknown
- Preterm infants often receive anesthetics during surgical procedures despite concerns about the impact of this exposure on the developing brain
- Concerns about neurodevelopmental effects discourage chronic administration of opioids and benzodiazepines to preterm infants during mechanical ventilation suggesting the urgent need to explore alternative agents and non-pharmacologic management

Figure 1.
Intrinsic and extrinsic apoptotic pathways

Figure 2. Role of brain-derived neurotrophic factor in regulation of apoptosis. Arrows indicate promotion, blocked connectors indicate inhibition. *Trk*, tropomyosin receptor kinase.

Figure 3.
Potential mechanisms of opioid-induced anti-proliferative and apoptotic effects.