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REVIEW ARTICLE

Use of Analgesic and Sedative Drugs in the NICU: Integrating Clinical Trials and Laboratory Data

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ABSTRACT: Recent advances in neonatal intensive care include and are partly attributable to growing attention for comfort and pain control in the term and preterm infant requiring intensive care. Limitation of painful procedures is certainly possible, but most critically ill infants require unavoidable painful or stressful procedures such as intubation, mechanical ventilation, or catheterization. Many analgesics (opioids and nonsteroidal anti-inflammatory drugs) and sedatives (benzodiazepines and other anesthetic agents) are available but their use varies considerably among units. This review summarizes current experimental knowledge on the effects of sedative and analgesic drugs on brain development and reviews clinical evidence that speaks for or against the use of common analgesic and sedative drugs in the NICU but avoids any discussion of anesthesia during surgery. Risk/benefit ratios of intermittent boluses or continuous infusions for the commonly used sedative and analgesic agents are discussed in the light of clinical and experimental studies. The limitations of extrapolating experimental results from animals to humans must be considered while making practical recommendations based on the currently available evidence. **(*Pediatr Res* 67: 117–127, 2010)**

Experimental Data on the Effects of Analgesics and Sedative Drugs During Central Nervous System Development

Appropriate development of the CNS relies on the precise temporal-spatial orchestration of multifaceted molecular pathways guiding proliferation, migration, differentiation, and survival of neural cells. Interference with these finely tuned developmental mechanisms can disrupt physiologic developmental patterns, and might, ultimately, lead to permanent impairment of CNS functions. Analgesics and sedatives are potent modulators of several ionotropic and G-protein-linked receptor signaling pathways implicated in important morphogenetic events during brain development. The question of whether these drugs exert adverse effects on brain development when administered during pregnancy or in neonatal populations is of utmost importance. Experimental data describing the effects of analgesics or sedatives on the developing brain from *in vitro* (1–10) and *in vivo* (11–32) studies are summarized in Tables 1 and 2, respectively.

Opioid analgesics primarily act on μ-, δ-, and κ-types of opioid receptors on the cell surface. On agonist binding, all opioid receptor subtypes recruit inhibitory G proteins ($G_{i/o}$) to initiate the activation of multiple intracellular signaling cascades (33,34). In addition to analgesic effects, these signaling pathways are implicated in a variety of other biologic processes, including the modulation of proliferation, survival and differentiation of the neural stem cells, neurons, or glia that express opioid receptors (34).

A role for opioid receptor-mediated signaling in developmental processes is suggested by the early expression of opioid receptors in the developing rodent brain (35,36). Chronic morphine exposure during the prenatal and early postnatal periods induces significant reductions in brain volume, neuronal packing density, and dendritic growth (15). Animals subjected to such treatment show long-term impairments in learning abilities and locomotor activity (16,17). Furthermore, opioids modulate cell proliferation in germinative zones of the developing brain in a receptor-, brain region-, and cell type-specific manner (1,37–39) (see Tables 1 and 2 for specific effects). However, the role of opioid signaling in neural cell migration in the developing brain remains unknown up to date.

In contrast, opioid blockade by naltrexone leads to increases in brain size, suggesting that endogenous opioid signaling is associated with pruning during development (40). Naltrexone-induced chronic opioid blockade in the early postnatal period significantly increases dendritic arborization and the number of dendritic spines, indicating that endogenous opioids are critical regulators of neuronal differentiation and growth (41). Application of selective μ receptor agonists increases nerve growth factor (NGF)-dependent survival of embryonic chick dorsal root ganglion neurons, suggesting that growth factor-mediated neuronal survival might be modulated by opioid signaling (42). Daily morphine treatment or repetitive inflam-

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Abbreviations: COX, Cyclooxygenase

Table 1. *In vitro toxicity of sedative/analgesic drugs in the developing brain*

Drugs	Species	Results
Morphine	Mouse	Inhibition of DNA synthesis in the developing cerebellum (1)
	Rat	High dose (1 mM) inhibits neurite elongation, low concentrations (<10 nM) enhance neurite promoting activity of NGF (2)
Ketamine	Rat	Concentration-, age, and duration-dependant apoptosis (3)
		Prolonged exposition to low concentrations impairs dendritic arborization (4,5)
	Monkey	Concentration-, age-, and duration-dependant apoptosis (10)
Propofol	Rat	Concentration-, time-, and space-dependant apoptosis (6)
		Possibly irreversible lesions to GABAergic neurons (7)
		Decreased dendritic growth (8)
	Chick embryo	Growth cone collapse and neurite destruction (9)
Midazolam	Rat	No effect on dendritic growth (8)

matory pain in postnatal rats (1–7 d) lead to long-term alterations in pain threshold, locomotor behavior, and alcohol preference during adulthood, but these changes are attenuated when the two treatments are combined (43). In the adult rat brain, however, high-opioid doses induce electroencephalographic seizure activity and cell death in several brain regions (44,45).

Acetaminophen and other nonsteroidal anti-inflammatory drugs (NSAID) inhibit cyclooxygenase (COX)-1 and COX-2 enzymes expressed in the CNS and peripheral organs (46–48). COX-2 is expressed in distinct neuronal populations throughout the forebrain, and its expression in dendritic spines is dynamically regulated by NMDA-dependent synaptic activity (48,49). In rodents, COX-2 expression is relatively low during the first 2 postnatal weeks and increases markedly from the third postnatal week, coinciding with the peak of synaptogenesis (50). In patients with Rett syndrome, a severe neurodevelopmental disorder characterized by impaired dendritic differentiation (51), the intensity of somatic and dendritic COX-2 immunostaining, and the number of COX-2 immunostained neurons are significantly reduced compared with neurologically normal controls (50). Whether pharmacological blockade of COX signaling using nonsteroidal anti-inflammatory drugs can also interfere with neuronal differentiation remains unknown.

Most sedative drugs operate by ligand-gated ionotropic receptors to modulate the activity of different neurotransmitter systems (52). In addition to their roles in synaptic transmission, these neurotransmitters also act as epigenetic factors during development to control important biologic processes including progenitor cell proliferation, neuroblast migration, and neuronal differentiation (53). A delicate balance between excitatory and inhibitory signals plays a key role in the functional assembly of neuronal networks (54). Thus, the impact of sedative drugs on the development of activity-dependent neuronal networks is possible because even small changes in the relative amounts of excitation and inhibition can markedly alter neuronal processing. An increasing number of experimental observations suggest potentially adverse effects of sedative drugs on the developing brain.

Ketamine. Ketamine primarily blocks NMDA-mediated neurotransmission by binding noncompetitively to the phencyclidine (PCP)-binding site of the NMDA receptor (55). Importantly, this drug also interacts with adenosinergic, monoaminergic, cholinergic, and opioidergic signaling pathways (56,57). In rodents, duration of exposure to ketamine is critical (19,20,58), and specific brain regions are particularly vulnerable to NMDA activation during critical periods of development (59). Results on the effects of a single bolus injection are controversial (Table 1) (22–24). Using *in vitro* culture of isolated GABAergic neurons from newborn rats, Vutskits *et al.* (4,5) demonstrated that low, nonapoptogenic concentrations of ketamine interfere with dendritic arborization in these cells, potentially altering the development of neuronal networks. These rodent data were extended to primates, indicating apoptotic and necrotic cell death after prolonged ketamine exposure (24 h) on gestational d 122 and postnatal d 5 but not on postnatal d 35. Shorter ketamine exposure (3 h) did not lead to neuronal cell death in 5-d-old monkeys (25).

Benzodiazepines. Benzodiazepines selectively activate the $GABA_A$ receptor complex (60), which is functional from early developmental stages (61,62). Chronic prenatal exposure of rat fetuses to diazepam results in long-term functional deficits and atypical behavioral patterns (27,28). Exposure of 7-d-old mice to diazepam (10–30 mg/kg i.p.) induced widespread apoptosis in cortical and subcortical areas (31,63), whereas lower doses (5 mg/kg) induced apoptosis only in the laterodorsal thalamus and did not lead to behavioral or cognitive impairments later in life (24). Prolonged diazepam treatment during the prenatal and the postnatal period also induce long-lasting changes in $GABA_A$ receptors and neurosteroid levels (64–66). A single, subanesthetic dose of midazolam can induce neuroapoptosis in the cerebral cortex and basal ganglia of newborn mice (23). In newborn rats, midazolam potentiates nociceptive behavior, sensitizes cutaneous reflexes, and is devoid of any sedative effects (67). Whether neonatal exposure to midazolam also induces long-term behavioral or cognitive deficits remains unknown.

Propofol. Propofol (2,6-diisopropyl phenol) is an alkyl phenol derivative dissolved in a lipid emulsion. This drug potentiates the effect of GABA by inducing tyrosine kinase-mediated phosphorylation of the β subunits of the GABAA receptor complex (68). Despite controversy (69,70), this agent is commonly used in young children (71), including neonates (72). Toxicity of propofol for specific neurons has been shown in different *in vitro* and *in vivo* models (Table 2).

Barbiturates. Barbiturates are also potent agonists of the $GABA_A$ receptor. Exposure of 7-d-old rats to pentobarbital (20–30 mg/kg) or phenobarbital (40–100 mg/kg) for 5 h induced widespread neuronal apoptosis in the brain (31). In these experiments, neuronal death was associated with reduced expression of neurotrophins and other survival-promoting proteins in the brain (31). In contrast, single doses

Table 2. *In vivo toxicity of sedative/analgesic drugs in the developing brain*

Drugs	Species	Experimental plan	Short-term effect	Long-term effect
Morphine	Rats	Chronic exposure *in utero* and early postnatal days	Decreased brain volume, neuronal packing density, and dendritic growth (11–15)	Long-term impairments in learning abilities and motor activity (16,17)
Fentanyl	Mouse	3 injections	Exacerbation of ibotenate-induced white matter lesions (18)	
Sufentanil	Mouse	3 injections	No exacerbation of ibotenate-induced white matter lesions (18)	
Ketamine	Rats	Single dose	No adverse effect (19,20)	
		Repeated high doses (5–20 mg/kg). Repeated low doses (2.5 mg/kg)	Inconstant neuronal degeneration (19–21,59). Neuroprotective effects (21,32)	No adverse effects. Improvement of pain-induced excitotoxicity and long-term cognitive impairments (21)
	Mouse	Single dose	Inconstant neuronal apoptosis (22–24)	No gross behavioral consequences (22). Disrupted spontaneous activity and learning (24)
	Rhesus monkey	24 h continuous i.v.	Neuronal cell death inversely proportional to developmental stage (25)	
Diazepam	Rat	*In utero* chronic exposure		Altered behavior (26–28)
	Mouse	Single dose	Partial neurodegeneration (29)	No behavioral impairment (29)
Midazolam	Rat	Single dose	No increase in neuronal apoptosis (30)	
	Mouse	Single dose	Neuronal apoptosis (23)	
Propofol	Mouse	Single dose	Dose-dependent neuronal apoptosis (24)	No or minor behavioral change (24)
Thiopental	Mouse	Single dose	No neuronal apoptosis if used alone (24)	No or minor behavioral change (24)
Phenobarbital	Rat	"Plasma concentrations relevant for seizure control in humans"	Neuronal apoptosis (31)	

of thiopental (5–25 mg/kg) did not induce neurodegeneration in the CNS (24).

Combined use of sedative agents. In the NICU, children are often exposed to combinations of different analgesics and sedatives either simultaneously or sequentially, to reduce potential side effects. Most drugs have GABA-mimetic and/or NMDA antagonist properties, raising the question of whether combined use of sedative drugs has additive or synergistic neurotoxic effects (30,73). For example, coadministration of even low concentrations of ketamine and nitrous oxide synergistically enhances their neurotoxic effects (74). Sedative concentrations of midazolam and ketamine induce apoptosis in the infant mouse brain more effectively than either of these drugs alone (23). Coadministration of ketamine with propofol or thiopental also potentiates apoptotic neurodegeneration in young rodents (24). Exposure of 7-d-old rats to midazolam-nitrous oxide-isoflurane anesthesia for 6 h led to widespread neurodegeneration and this was accompanied by persistent learning deficits (30). Anesthesia-induced activation of apoptotic pathways in immature neurons implicates significant changes in the expression pattern of brain-derived neurotrophic factor (BDNF) in the brain of rat pups (75).

Extrapolation of Laboratory Results to Clinical Practice

To evaluate the clinical relevance of experimental observations claiming drug-induced neurotoxicity in the developing brain is difficult. The first critical issue concerns the extrapolation of appropriate developmental stages from different animal species to humans. For decades, it has been considered that brain development in 7-d-old mice and rats, the focus of most experimental studies, corresponds approximately to the human brain at 32–36 wk of GA (76). Recent work, however, suggests that the 7-d-old rodent brain is equivalent to the human brain at 17–20 wk of GA (77). For neuronal circuit formation, the peak synaptogenic period in humans takes place between the third trimester of pregnancy and the first few years of postnatal life (78,79), whereas, in rodents, this period is situated between the second and fourth postnatal weeks (80). Clearly, further experiments are needed to elucidate the impact of sedative drugs on the developing CNS at later stages of development.

Another related concern is that there are important developmental changes in receptor subunit composition of major neurotransmitter systems during the brain growth spurt. This strongly determines the functional modalities of neurotransmission and might fundamentally influence the impact of drugs on the developing CNS. In fact, embryonic/early postnatal $GABA_A$ receptors differ markedly from those expressed in the adult rodent brain (81–84). For example, in most brain areas, the $\alpha3$ subunits along with $\beta2$, $\beta3$, and $\gamma2$ subunits are the most prominent components of the $GABA_A$ receptor complex throughout prenatal and early postnatal development (82). Similarly, other receptor populations, such as NMDA and opioid receptors, also have developmentally regulated subunit composition or subtype expression profiles (85–87) imparting different functional properties to these receptor populations.

Furthermore, GABAergic signaling has the unique property of "ionic plasticity," which is based on short- and long-term changes in the Cl^- and HCO^{3-} ion concentrations in postsynaptic neurons. Although short-term ionic plasticity is caused by activity-dependent, channel-mediated anion shifts, long-

term ionic plasticity depends on changes in the expression patterns and kinetic regulation of molecules involved in anion homeostasis (88). During development, activation of $GABA_A$ receptors leads to neuronal depolarization because of the high intracellular Cl^- concentrations. Thus, GABA acts as an excitatory neurotransmitter during brain development. The functional switch toward the hyperpolarizing actions of this neurotransmitter is linked to the developmental expression of the K^+–Cl^- cotransporter (KCC2), actively extruding intracellular Cl^- from neurons (88). KCC2 appears during the second postnatal week in the rodent cerebral cortex (89) and from the 30th gestational week in humans (90). These data raise the intriguing possibility that exposure of premature babies to GABAergic agents would exert excitatory effects on the developing brain (67).

The possibility of interspecies differences in terms of drug effects cannot be excluded (91). In addition to rodents, however, anesthetic and subanesthetic doses of currently used anesthetics also induce apoptosis in other species such as guinea pigs (92) and monkeys (25). Another essential criticism concerns the relatively long exposure time needed to produce detectable neurotoxic effects in the majority of laboratory studies (93). From a developmental perspective, 6 h-long exposures to anesthetics in rodents would be equivalent to producing general anesthesia for 2–3 wk in the human neonate (94). However, recent results showing that even a single exposure to subanesthetic doses of anesthetics could trigger 2- to 4-fold increases in neuronal apoptosis in the mouse brain somewhat counteract these arguments (23). The rat brain may be vulnerable during specific developmental periods; in contrast, ketamine administration just before birth has beneficial effects on subsequent learning in young and adult rats (95).

New *in vitro* data indicate that short-term exposure to sedative drugs can also impair neuronal development by interfering with dendritic growth and branching without inducing cell death (4,5,8). Given the importance of neuronal dendritic architecture in appropriate information processing, one essential next step will be to determine how neuronal dendritic arborization is influenced by anesthetics. These experiments, combined with long-term assessment of behavioral outcomes after short-term sedation, would probably help us to better understand the impact of sedative drugs on CNS development.

Differences in anesthetic concentrations of drugs across different species further complicate the issue of drug-induced developmental neurotoxicity. For example, subanesthetic plasma concentrations of ketamine in humans are around 0.1–0.5 μg/mL (96,97), whereas doses of 3 mg/kg i.v. to induce anesthesia were associated with blood levels of 1–2 μg/mL (98,99). In contrast, as high as 40 mg/kg of ketamine s.c. was insufficient to produce anesthesia in young mice (23). Plasma levels of ketamine around 6 μg/mL occurred after a single s.c. dose of ketamine 20 mg/kg (20). Altogether, these data suggest that effective plasma concentrations, and probably "on-site" brain concentrations as well, are significantly higher in rodents compared with humans, raising further difficulties in the extrapolation of these experiments to human infants.

Finally, one can argue that these experimental conditions are very different from those associated with surgical anesthesia and complex perioperative management, including intensive care (93). First, based on the neuronal stimulation hypothesis (100), preoperative stress and painful stimuli during surgery can activate NMDA and other excitatory receptors in the immature brain and anesthetic drugs could thus reduce extreme degrees of neuronal excitation (101). In line with this hypothesis, clinical doses of ketamine (2.5 mg/kg) reduced cell death after inflammatory pain in the newborn rat brain (21). The average clinical situation is in contrast to experimental settings where anesthesia was administered without painful stimuli and, consequently, the effect of anesthetics on the suppression of basal neural activity was evaluated. Clearly, further experimental studies are needed to better elucidate this issue. Second, human neonates and children routinely receive nutritional support and metabolic monitoring in the perioperative period, thus minimizing the risk for hypoglycemia and impaired nutrition. In contrast, rodent pups do not suckle well after general anesthesia, resulting in a prolonged decrease in weight gain compared with nonanesthetized littermates (19). Given that the role of malnutrition in decreased brain growth and learning disabilities is well established (102,103), one cannot exclude the possibility that neurotoxic effects of anesthetics in animal studies are, at least partially, related to impaired nutrition in the perioperative period.

Existing Human Data on Neurotoxicity of Sedative Drugs Used in the NICU

Although neurotoxicity has been studied extensively in animal models, intense controversy exists about whether drugs used for sedation in the NICU cause cellular brain damage in human neonates [see previous report (73)]. The possible deleterious effects of sedative/analgesic drugs on brain development can be categorized in two groups: direct toxicity due to pharmacological effects of the drug on immature neurons and developmental pathways; indirect toxicity due to adverse events such as respiratory depression, hypotension, bradycardia, or hypoxemia potentially causing brain lesions.

No prospective clinical trial has ever addressed this issue in the newborn. Two retrospective studies evaluated the long-term effects of sedation or analgesia in preterm infants hospitalized in the NICU. The first study (104) evaluated neurologic outcome at 5–6 y in survivors from two randomized controlled trials, investigating morphine use in the early 1990s (105,106). No differences occurred between infants exposed and nonexposed to morphine, although the rates of death or disability in both groups were high (in the range of 40% for both), corresponding to commonly reported clinical outcomes in the presurfactant era. Another retrospective study compared 5-y neurodevelopmental outcomes between infants born <33 wk GA in 1997 exposed or not exposed to sedation for 7 d or more during mechanical ventilation and/or surgery (107). Although this study has limitation, after adjustment for gestational age and propensity, prolonged sedation was not associated with poor neurologic outcomes at 5 y. In term infants

suffering from hypoxic-ischemic encephalopathy, a retrospective study reported that postnatal morphine use was associated with improved outcomes, based on psychological assessments and neuroimaging studies (108). In the light of these findings, further data analyses of clinical trials examining the use of hypothermia should also investigate the effects of concomitant sedative or analgesic therapy on long-term neurodevelopmental outcomes (109–111).

Although sedative drugs might induce significant physiologic perturbations, due to depression of respiratory and circulatory systems, and that this can also be held responsible for later brain impairment, safety issues have only been studied for very few drugs in the newborn.

Opioids. In the NEOPAIN (Neurologic Outcomes and Preemptive Analgesics in Neonates) trial (112), after subgroup analysis of patients who received or did not receive open-label analgesia, continuous morphine infusion did not increase vulnerability of ventilated preterm neonates to adverse neurologic events. Those who were hypotensive before morphine therapy and those receiving doses higher than 10 μg/kg/h morphine (27–29 wk subgroup) were more likely to develop hypotension, similar to what has been reported by Simons *et al.* (113) subsequently. The use of volume expanders and vasopressor drugs was similar in the two study groups in both trials, and no relationship among morphine use, blood pressure variability, and intraventricular hemorrhage (IVH) could be determined.

Midazolam. Continuous infusion of midazolam significantly decreased blood pressures in one randomized controlled trial (114) and was related to an increase in IVH in another one (115). Midazolam decreases cerebral blood flow velocity (116). A meta-analysis concluded that midazolam should not be used routinely in ventilated preterm newborns because it prolongs length of stay in the NICU and potentially may cause harmful neurologic effects (117). For endotracheal intubation, the only randomized controlled trial evaluating midazolam combined with atropine in one arm had to be terminated early because of frequent severe adverse events in the midazolam group (118). When midazolam was combined with remifentanil in a small cohort, no major side effects were reported (119).

Barbiturates. Phenobarbital use in ventilated infants has been associated to an increase in air leaks (120) and an increased need for mechanical ventilation (121). However, ventilation strategies were not detailed in these studies, what renders interpretation of these findings difficult. Thiopental provided effective sedation for tracheal intubation but did not decrease the incidence of desaturations (122,123).

Ketamine. Systemic and cerebral hemodynamic effects of ketamine were assessed when used as analgesic therapy for central vein catheterization. No impairment of hemodynamics could be shown (124). When used for short procedures, higher doses of ketamine (2 mg/kg) reduced heart rate (125) and 5 mg/kg reduced blood pressure without impairing cardiac output (124). Studies of infants undergoing cardiac catheterization have reported respiratory complications (126) and increased blood pressure (127).

Propofol. Propofol use for tracheal intubation in premature infants caused no hemodynamic adverse events and no high-grade intracranial hemorrhages were seen on brain ultrasound performed after drug administration (72). However, other studies reported hypotension, apnea, respiratory obstruction, and transient myoclonus in infants receiving propofol (128–131).

Recommendations for Clinical Practice Based on the Best Available Evidence

Evidence from randomized controlled trials (RCT), systematic reviews, or from large observational studies was synthesized to develop practical recommendations for analgesia/sedation in different settings such as mechanical ventilation, postoperative analgesia, endotracheal intubation, or other painful procedures. Efficacy and safety issues are summarized in Table 3 for continuous analgesia/sedation and in Table 4 for intermittent analgesia/sedation. These data should be interpreted while keeping in mind that methods for assessment of prolonged pain in preterm newborns are underdeveloped (132), whereas those for acute pain are well established (133). A stepwise approach to pain management is represented in Figure 1. Proposed drug doses in different preterm populations are summarized in Table 5. The doses listed in Table 5 are extracted from the clinical studies reviewed in the text and Tables 3 and 4. Well-designed pharmacological studies are sparse in the newborn, especially in preterm infants. Most of the published data only assess pharmacokinetic issues without considering efficacy. These recommendations are therefore based on safe doses reported in published clinical trials. When several doses are reported, we selected and recommend the lowest effective doses.

Practical Recommendations for Mechanical Ventilation

Routine use of morphine or fentanyl cannot be recommended for ventilated preterm neonates because no obvious beneficial long-term effects have been proven (134). The analgesic effect is difficult to quantify as illustrated by the high rate of open-label morphine use in some trials (112). Particular caution must be exercised in the most immature infants (under 26 wk GA) or those with preexisting hypotension. Doses >10 μg/kg/h should be used with caution because of potential hemodynamic, respiratory, and neurologic adverse effects. Fentanyl is a faster-acting and shorter-lasting drug when compared with morphine but limited safety data are available (135–138) and concerns have been raised about opioid tolerance and withdrawal (139). Other derivatives of fentanyl require additional investigations.

The routine use of midazolam (117) or barbiturates (121) cannot be recommended. As a potentially harmful drug, midazolam should be prescribed with extreme caution (116,140,141). Midazolam is often used as additional treatment when analgesia is considered insufficient or as a means to decrease analgesic use but no evidence supports this practice in the neonate. Experimental data suggest, however, that midazolam lacks sedative or analgesic effects in the neonatal period (67). Moreover, combination of midazolam with opioids has been associated with hypotension, apnea, and hypoxemia in preterm infants (142).

Table 3. *Risk/benefit data for continuous analgesia and/or sedation in the newborn infant*

Drugs	Populations	Efficacy	Clinical safety data, actual or theoretical risk, and unknowns
Mechanical ventilation			
Morphine	23–32 wks GA	Pain scores inconsistently decreased (134)	Prolongation of ventilation (134) Possible hypotensive effect in the most immature infants for doses >10μg/kg/h (112,113) Rare long-term outcome available (104)
Fentanyl	26–36 wks GA	Constant significant decrease in physiological or behavioral stress or pain markers (136)	Reduced stress hormones (136) Preserved gastrointestinal motility (dose: 1 μg/kg/h) *vs* morphine (137) Increased ventilatory pressures (dose: 5 μg/kg bolus then 2 μg/kg/h) (136) No improvement in short-term outcomes (136) No assessment of long-term outcomes available
Midazolam	24 wks—term	Inconstantly improved sedation (114,115)	Worse neurological outcomes (200 μg/kg bolus then 20–60 μg/kg/h) (115) Hypotension (30 or 60 μg/kg/h) (114) Decreased cerebral blood flow velocity (200 μg/kg bolus then 200 μg/kg/h) (116)
Barbiturates	BW <1750 g	No reliable efficiency study	Increase in air leaks (2 × 10 mg/kg/12 h then 2.5 mg/kg/12 h) (120) Increased need for mechanical ventilation (121)
Postoperative analgesia			
Morphine	>35 wks BW >1500 g	Effective analgesia with same cumulative doses when used continuously or as intermittent bolus doses (143–145)	Mainly respiratory side effects (mean doses 10 μg/kg/h) (143–145). No assessment of long term outcomes
Fentanyl	>36 wks	Effective analgesia (146)	Excessive apnea if given as bolus (2 μg/kg/2 h) (146)
Acetaminophen	≥36 wks BW ≥1500 g	No effect on acute pain (147) No decrease in morphine requirements (148)	
NSAIDs	Term-aged former preterm infants	Diminished opioid use in one short descriptive study (150)	Lack of experience

BW, birth weight.

Practical Recommendations for Postoperative Analgesia

Morphine (143–145) or fentanyl (146) is effective at decreasing postoperative pain, usually recommended in continuous infusions for safety and simplicity reasons, although careful attention to dosing and respiratory monitoring is imperative. Considering current knowledge of routine use of paracetamol cannot be recommended in newborns (147,148) despite good hepatic tolerance (149). NSAIDs are an interesting alternative to opioids avoiding respiratory, hemodynamic, and digestive complications (150). However, they deserve additional investigation before they can be routinely prescribed. Routine sedation cannot be recommended for postoperative newborns.

Practical Recommendations for Endotracheal Intubation

To date, the most documented regimen associates an opioid with a muscle blocker (151). Fast-acting opioids, such as fentanyl (152–154), are probably more appropriate than morphine (155,156). Despite encouraging results, the paucity of available data for alfentanil (157) and remifentanil (119,158) imposes limitations on the use of these drugs.

Propofol certainly offers good intubating conditions and has the advantage of being a single, easy to prepare drug (72). However, complementary data should be collected before generalization of its use. Barbiturates have never been compared with opioids in a randomized trial, although thiopental provided effective sedation for tracheal intubation without decreasing episodes of desaturations (122,123). Although midazolam is widely used in clinical practice, it cannot be recommended as the drug of choice for intubation, especially when not combined with an analgesic (118).

A key question conditioning a drug's choice is what is considered the optimal time for surfactant administration? If prophylactic surfactant is given, there is usually no time or venous access for premedication before intubation in the delivery room (159). If surfactant is administered later, then the optimal use of analgesic drugs should not interfere with the planned extubation time.

Practical Recommendations for Procedural Pain Relief

The most effective method to reduce neonatal pain or discomfort is to reduce the number of procedures performed and the episodes of patient handling (160). NICUs and nurseries should develop strategies that limit handling and procedures but do not compromise the care of the infants. When

Table 4. *Clinical trials data for intermittent analgesia and/or sedation in the newborn infant*

Drugs	Populations	Efficacy	Clinical safety data, actual or theoretical risk, and unknowns
Endotracheal intubation			
Morphine	25–40 wks GA	Number of attempts inconsistently decreased. Hypoxemia episodes or duration unchanged (155,156)	Possibly inappropriate delay in the onset of action (too slow) (100 or 200 μg/kg)
Fentanyl	500–4990 g 24–42 wks GA	Rare complications, high success rate at first attempt (152–154). Addition of placebo *vs* mivacurium improves intubation conditions and tolerance (154)	No deleterious effect on general or cerebral hemodynamics (3 μg/kg) (138). No adverse effect on respiratory compliance (4 μg/kg) (135)
Fentanyl-related synthetic opioids	>28 wks GA >1000 g	Improved intubation conditions with alfentanil (157) and remifentanil (119,158)	Chest wall rigidity, frequent hypoxemia. No data available
Midazolam	Not mentioned	Trial terminated early because of frequent severe adverse events in the midazolam + atropine group (29% patients required cardiopulmonary resuscitation) (118)	Decreased mean arterial pressure and cerebral blood flow velocity (100 or 200 μg/kg) (116,140,141)
Barbiturates	>2000 g >32 wks GA	Reduction in heart rate and blood pressure (122,123)	Frequency of desaturations similar to placebo (5 or 6 mg/kg) (122,123)
Propofol	25–30 wks GA	Faster and more frequently successful intubation higher median oxygen saturations *vs* atropine/morphine/suxamethonium (72)	Questionable control group (see morphine efficacy earlier)
Ketamine	28–36 wks GA, $N = 3$	Not specifically assessed	No cerebral hemodynamic adverse effects (5 mg/kg) (124)
Other invasive procedures			
Morphine	23–32 wks GA. Mainly intubated infants	Inconsistent efficacy for heel lance procedure (165,166) Inconsistent efficacy for tracheal suction (112,115). Some efficacy for PCVC insertion (168)	Increased cerebral blood flow (50 μg/kg) (116)
Fentanyl-related synthetic opioids	29–36 wks GA <32 wks GA	Alfentanil efficient for tracheal suction but frequent thoracic rigidity (167). Remifentanil decreased pain for PICC insertion (169)	Thoracic rigidity requiring muscle blocker injection (alfentanil 20 μg/kg) (167). Same time to complete the maneuver and procedure time as placebo (169)
Acetaminophen	≥37 wks GA	No effect for heel lance (170)	Good hepatic tolerance (149)
Ketamine		Ineffective for tracheal suctioning (125)	No cerebral hemodynamic adverse effect (5 mg/kg) (124)

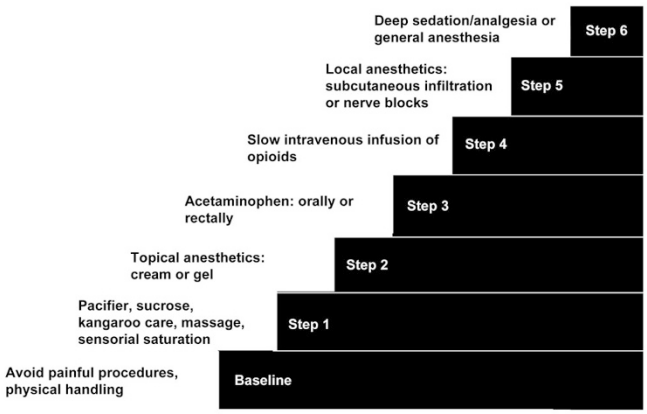

Figure 1. Stepwise approach to neonatal analgesia.

needed the use of nonpharmacological approaches, such as sucrose (161), massage (162), kangaroo care (163), or sensorial saturation (164), are currently considered safe and effective for analgesia and should be considered the first line of treatment.

Whether an opioid should be added remains controversial. Conflicting results have been reported in the use of morphine for procedures such as heel lance (165,166) or tracheal suctioning (112,115). During tracheal suctioning, alfentanil was found to be effective but induced frequent thoracic rigidity (167), whereas ketamine was found to be inappropriate (125). For percutaneous central venous catheter (PCVC) placement, morphine provided good analgesia but induced mild respiratory depression (168). Remifentanil showed promising results during PCVC insertion (169) but requires additional investigation. All other treatments (170) cannot be routinely recommended considering the current evidence.

Remaining Urgent Questions and Perspectives

Clinicians should not forget that multiple lines of evidence suggest the necessity of analgesia and sedation in infants.

Table 5. *Proposed drug doses for analgesia/sedation in the NICU (surgical anesthesia not included)*

Drug	<28 wks GA	28–32 wks GA	>32 wks GA
Morphine			
Continuous	Loading dose 5–15 μg/kg over 1 h then 5–10 μg/kg/h	Loading dose 15–25 μg/kg over 1 h then 5–15 μg/kg/h	Loading dose 25–50 μg/kg over 1 h then 5–20 μg/kg/h
Transient	5–0 μg/kg	10–30 μg/kg	20–0 μg/kg
Fentanyl			
Continuous	No available data	Optional loading dose 1–2 μg/kg over 10–20 min then 0.5–2 μg/kg/h	
Transient		0.5–2 μg/kg	
Sufentanil			
Continuous	No available data	Loading dose 0.1–0.5 μg/kg over 10–20 min then 0.05–0.2 μg/kg/h	
Transient		No available data	
Alfentanil			
Continuous		No available data	
Transient	No available data	3–10 μg/kg	
Remifentanil			
Continuous	No available data	0.03–0.5 μg/kg/min	
Transient	No available data	0.5–1 μg/kg	
Midazolam			
Continuous	Optional loading dose 50–200 μg/kg then 10–20 μg/kg/h	Optional loading dose 50–200 μg/kg then 20 to 40 μg/kg/h	Optional loading dose 50–200 μg/kg then 20–50 μg/kg/h
Transient	No available data—should not be used as a single agent for tracheal intubation		
Thiopental			
Continuous	Loading dose 1–2 mg/kg then 0.5–2.5 mg/kg/h		
Transient	No available data	1–4 mg/kg	
Propofol			
Continuous	Should not be used as continuous sedation in the neonate		
Transient	1–2.5 mg/kg, possibly repeated once		
Ketamine			
Continuous		No available data	
Transient	0.5–1 mg/kg	1–3 mg/kg	

Repetitive painful stimuli may persistently alter pain processing in humans (171), and epidemiologic studies have revealed an association between peri- and neonatal complications and behavioral/emotional problems in childhood, anxiety/depression, and even suicidal tendencies (172,173). Conversely, drug toxicity should not be underestimated and risk/benefit balance must be evaluated when prescribing analgesia or sedation for neonates. First-line treatment is the decrease in painful procedures that are still extremely frequent in the NICU (160). Nonpharmacological analgesia should be considered when moderate pain is expected. Neonatal units should establish and follow protocols indicating recommended drugs according to the expected intensity and duration of pain resulting from invasive procedures.

Basic research should focus on physiologic mechanisms involved in pain and brain development. At the same time, development of experimental models should aim at creating situations as close as possible to clinical settings, *e.g.* proper oxygenation during drug administration, optimized nutrition, and exposure of animals to painful situations as recently proposed (21).

Clinical research should focus on long-term evaluation of neurodevelopmental outcome of newborns hospitalized in NICUs with particular attention to the drugs used. Although many confounding factors (*e.g.* underlying pathologies and social conditions) are usually implicated, large population studies could provide sufficient statistical power to generate novel hypotheses. Long-term follow-up of infants included in large prospective studies on pain control would also provide precious data.

As for all clinical decisions, the risk/benefit balance should be carefully addressed when considering analgesic or sedative treatment in a neonate, using currently available data and keeping in mind the major research gaps remaining in this field.

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