REVIEW

Pharmacological therapy for analgesia and sedation in the newborn

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Rapid advances have been made in the use of pharmacological analgesia and sedation for newborns requiring neonatal intensive care. Practical considerations for the use of systemic analgesics (opioids, non-steroidal anti-inflammatory agents, other drugs), local and topical anaesthetics, and sedative or anaesthetic agents (benzodiazepines, barbiturates, other drugs) are summarised using an evidence-based medicine approach, while avoiding mention of the underlying basic physiology or pharmacology. These developments have inspired more humane approaches to neonatal intensive care. Despite these advances, little is known about the clinical effectiveness, immediate toxicity, effects on special patient populations, or long-term effects after neonatal exposure to analgesics or sedatives. The desired or adverse effects of drug combinations, interactions with non-pharmacological interventions or use for specific conditions also remain unknown. Despite the huge gaps in our knowledge, preliminary evidence for the use of neonatal analgesia and sedation is available, but must be combined with a clear definition of clinical goals, continuous physiological monitoring, evaluation of side effects or tolerance, and consideration of long-term clinical outcomes.

Greater numbers of critically ill preterm and term neonates survive because of neonatal intensive care, although their medical care involves repeated exposure to pain resulting from invasive procedures, surgery or various diseases. Invasive procedures lead to brief episodes of acute pain,[1–3] surgery causes prolonged postoperative pain,[4] and newborn diseases produce variable types of pain.[5 6] Routine neonatal procedures are still performed often without pharmacological analgesia,[2 3] despite published guidelines for management of pain.[7 8]

Neonatal pain is physiologically disruptive and developmentally unexpected, occurring at a time when nature had designed a protective environment.[9–11] Painful stimulation elicits specific pain behaviours, activation of the somatosensory cortex,[12 13] and neuroendocrine and physiological stress responses,[14] thus altering immediate and long-term clinical outcomes in most newborns.[15–18] Repetitive pain may promote a heightened peripheral sensitivity[19–21] or dampened behavioural responses to pain[22 23] as indicators of altered development.

Studies on the prevention and management of pain in neonates should include strategies to limit the number of invasive procedures, assessments of drug efficacy and safety, dose-ranging studies to identify effective doses and minimise cumulative exposures and evaluation of various combinations of pharmacological and non-pharmacological therapies, to improve analgesia and prevent side effects.

OPIOIDS

Among the opioids, fentanyl, morphine, alfentanil and methadone seem to be used more commonly in neonates.[2 24] Adequate safety and efficacy data are not available for most opioid analgesics, owing to the lack of validated pain assessment measures and large well-designed clinical trials.

Fentanyl

Fentanyl is used frequently because of its ability to provide rapid analgesia,[25] maintain haemodynamic stability, block endocrine stress responses[26 27] and prevent pain-induced increases in pulmonary vascular resistance.[28] Fentanyl is highly lipophilic, crosses the blood–brain barrier rapidly, accumulates in fatty tissues and causes less histamine release compared with morphine. Tolerance to fentanyl develops more rapidly than tolerance to morphine,[29] requiring the escalation of doses during prolonged administration. To obtain a desired clinical effect, initial intravenous boluses of 0.5–2 μg/kg may be given every 2–5 min, followed by infusions of 0.2–2 μg/kg/h for maintained analgesia.[30–32]

One blinded randomised controlled trial (RCT) found that a single dose of fentanyl given to ventilated preterm neonates (<32 weeks, n = 22) considerably reduced pain behaviours and changes in heart rate, and increased growth hormone levels.[30] Mean fentanyl infusion rates of 0.64 μg/kg/h in ventilated infants of <34 weeks gestation and 0.75 μg/kg/h in infants of ⩾34 weeks gestation produced adequate analgesia, stable blood pressures and few adverse effects in a case–control study.[33] Infusions of fentanyl did not alter general or cerebral haemodynamics in preterm neonates.[34] Placebo-controlled RCTs in ventilated neonates found that fentanyl reduced stress hormones (catecholamines, glucocorticoids), episodes of hypoxia and behavioural stress scores, but may increase

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Abbreviations: IVH, intraventricular haemorrhage; NSAID, non-steroidal anti-inflammatory drug; PVL, periventricular leucomalacia; RCT, randomised controlled trial

ventilation requirements.[26 35] Searches of Medline (1985–2004), EMBASE (1980–2004),the Cochrane Controlled Trials Register and Pediatric Research abstracts (1990–2003) yielded only three trials of fentanyl in ventilated preterm neonates that met the inclusion criteria for a meta-analysis. These studies reported markedly lower heart rates,[26 30] behavioural stress scores[26 35] and pain scores[30] for infants receiving fentanyl versus those receiving placebo, but at 24 h, higher ventilator rates and peak inspiratory pressures were required for infants receiving fentanyl.[26]

Side effects of fentanyl include vagal bradycardia, chest wall rigidity and opioid tolerance after prolonged therapy. Despite case reports of chest wall rigidity, a prospective study of rapid fentanyl infusion showed no adverse effects on dynamic respiratory system compliance in infants.[36] Fentanyl infusions may lead to dependence, resulting in neonatal abstinence syndrome after discontinuation of the infusion. A cumulative fentanyl dose >2.5 mg/kg or therapy for >9 days was 100% predictive of opioid withdrawal.[37] Withdrawal may be prevented by reducing the dose by 25% initially, followed by 10% decreases every 4 h,[38] but this weaning schedule has not been tested empirically.

Transdermal absorption of fentanyl may provide alternative routes for patients with limited intravenous access. Apart from the management of opioid-tolerant neonates, fentanyl transdermal systems (absorption rates of 12.5, 25, 50 and 100 μg/h) have very limited application because of the high doses delivered and the greater permeability of neonatal skin.[39 40] Other concerns include gradual increases in plasma concentration, absorption rates changing due to altered skin perfusion, or ''tail-off'' in levels due to fentanyl accumulation in the subcutaneous fat below the site of application.

Morphine

Morphine reduces behavioural and hormonal responses,[41] improves ventilator synchrony,[42] alleviates postoperative pain[41 43] and sedates ventilated neonates.[44 45] In preterm neonates, morphine therapy may improve neurological outcomes,[6 46–48] decrease cerebral blood flow,[49] worsen pulmonary outcomes[50] and have questionable efficacy for acute pain.[51 52] Placebo-controlled RCTs with blinded assessments showed no differences in pain scores between placebo and morphine groups before and after tracheal suctioning or heel sticks,[48 51] possibly because of the immaturity or uncoupling of opioid receptors in the brain.[53 54]

Multiple RCTs have examined morphine use in ventilated neonates[45 46 48 55] because of its sedative effects, prolonged duration of action and less potential for tolerance.[29] Hepatic metabolism produces morphine-6-glucuronide and morphine-3-glucuronide, with biliary secretion, intestinal reabsorption and limited renal excretion, leading to longer half lives in preterm neonates.[56 57]

A meta-analysis comparing the efficacy and safety of intravenous morphine versus those of placebo in ventilated premature infants was carried out by searching Medline (1985–2004), EMBASE (1980–2004), the Cochrane Controlled Trials Register and Pediatric Research abstracts (1990–2003). Three trials[46 48 55] were eligible for inclusion (n = 1115), using pain responses as the primary outcome and the incidence of intraventricular haemorrhage (IVH), periventricular leucomalacia (PVL), mortality, days of ventilation or supplemental oxygen as secondary outcomes. All studies showed significantly lower pain scores during morphine infusion than during placebo infusions (weighted mean difference = 0.31; 95% confidence interval (CI) 0.18 to 0.44; p<0.001), but no differences were found in the incidence of IVH (relative risk (RR) 1.13; 95% CI 0.80 to 1.61), PVL (RR 0.81; 95% CI 0.51 to 1.29) or mortality (RR 1.14; 95% CI 0.81 to 1.60). More deaths occurred at younger gestational ages, with a slightly higher rate in the placebo group than in the morphine group (87% *v* 79%). Infants receiving morphine spent more days on mechanical ventilation than those receiving placebo (weighted mean difference 0.24; 95% CI 0.11 to 0.36; p<0.001), although total days on oxygen therapy did not differ between groups. Thus, morphine infusions may reduce pain and stress in mechanically ventilated neonates and may increase the number of days on ventilation, but do not alter clinical outcomes.[58]

Few studies have compared morphine and fentanyl in ventilated neonates.[29 59 60] Of these, only one randomised trial is reported, comparing infusions of fentanyl (1.5 μg/kg/h) versus morphine (20 μg/kg/h) in ventilated neonates. This study reported similar pain scores, catecholamine responses and vital signs in the two randomised groups. Decreased β-endorphin levels and a lower incidence of gastrointestinal dysmotility were seen in the fentanyl group than in the morphine group; no adverse respiratory effects or difficulties in weaning from ventilation occurred in either group.

Alfentanil

Alfentanil is a short-acting opioid, and multiple studies have examined its pharmacokinetics,[61 62] protein binding,[63] and physiological and adverse effects[64–66] in preterm and term neonates. Two RCTs have documented the efficacy of alfentanil for tracheal intubation[64] and tracheal suctioning in preterm neonates.[67] Despite promising results, trials with sufficient sample size to determine the efficacy and safety of alfentanil for preterm or term neonates have not been reported.

Methadone

A scientific rationale for the use of methadone analgesia includes specific effects on μ-opioid, δ-opioid and N-methyl D-aspartate receptors associated with potent analgesia, rapid onset of action, prolonged clinical effects, high enteral bioavailability, minimal side effects and low cost.[68] Methadone is often used for patients with opioid tolerance and withdrawal,[69 70] albeit with limited data on its safety, efficacy or pharmacokinetics in neonates.[71 72]

BENZODIAZEPINES

Midazolam and lorazepam are used extensively in neonates, but diazepam is used infrequently because of its limited metabolism in neonates (table 1). By activating γ-aminobutyric acid A-benzodiazepine receptors, they produce sedation, anxiolysis, muscle relaxation, amnesia and anticonvulsant effects, but offer little pain relief.[73] They may improve synchrony with assisted ventilation, but side effects include respiratory depression, hypotension, dependence and tolerance,[74] with occasional neuroexcitability or clonic activity resembling seizures.[75] Benzodiazepine glucuronidation uses the same metabolic pathways as bilirubin, with the potential for decreased bilirubin metabolism, especially in asphyxiated or preterm newborns. Despite extensive empirical use, relatively few studies support their use in neonates. Also, as benzodiazepines are used concomitantly with opioids, it is difficult to study their specific effects in clinical practice.

Midazolam

Midazolam is a short-acting sedative with a half life of 30–60 min, which may be prolonged in preterm and sick neonates. Despite several studies examining its use in ventilated preterm neonates,[46 76 77] a recent Cochrane report[78] noted that the results of these three RCTs could not be combined for analysis. Two studies reported increased sedation with midazolam, but one reported an increased incidence of poor neurological outcomes (IVH, PVL or death), with longer hospital stay.[46] Another study using midazolam for intubation noted side effects, causing early termination of the trial[79]; intravenous boluses of midazolam can

Table 1 Clinical use of benzodiazepines

Drug	Advantages	Disadvantages
Benzo-diazepines	Better ventilator synchrony	No pain relief
	Anti-anxiety	Arterial hypotension
	Sedation	Respiratory depression
	Hypnosis	Constipation
	Muscle relaxation	Urinary retention
	Amnesia	Myoclonus
	Anticonvulsant	Seizures
		CNS depression
		Tolerance, dependence
		May interfere with bilirubin metabolism
Midazolam	Most studied benzodiazepine	Short acting
	Quickly metabolised	Haemodynamic instability
		Changes in cerebral blood flow
Lorazepam	Longer acting	More myoclonus reported
	Better anticonvulsant	Possible accumulation with repeated doses
Diazepam		Not recommended in the neonate

CNS, central nervous system.

lead to changes in cerebral blood flow,[49 80] although long-term outcomes after neonatal midazolam therapy have not been reported.

Lorazepam

Lorazepam is also used in the intensive care nursery because of its prolonged duration of action (8–12 h) and potent anticonvulsant effects. Lorazepam was used successfully for seizure control in neonates who were refractory to phenobarbital and phenytoin, despite its potential neuronal toxicity.[81]

BARBITURATES

Barbiturates such as phenobarbital and thiopental have been used extensively in neonates for sedation and seizure control. The barbiturates are hypnotic agents with no analgesic effects and are metabolised in the liver.

Phenobarbital

Phenobarbital is the preferred therapy for seizure control in neonates. Despite unproved analgesic effects in humans and some evidence for antinociceptive effects in animals,[82] it is used during invasive procedures in neonates. Like the benzodiazepines, phenobarbital is often used in conjunction with opioids to provide sedation,[55] and for reducing excitability in the neonatal abstinence syndrome.[83] Long-term effects of seizure control with phenobarbital may delay cognitive development, but no such concerns exist for its short-term use in neonates. Antenatal phenobarbital was previously thought to protect against IVH,[84] although a recent Cochrane review did not support that contention.[85] The hypnotic and anticonvulsant effects along with its long history of use in neonates make phenobarbital an attractive adjunct for sedation in neonates, despite the side effects of respiratory depression, hypotension, tolerance and dependence.

Thiopental

Thiopental is a short-term barbiturate used primarily for anaesthetic induction. A placebo-controlled RCT showed that it prevents the blood pressure and heart rate changes associated with tracheal intubation, although clinical outcomes such as IVH or neurodevelopmental outcome were not studied.[86]

Chloral hydrate

Chloral hydrate is used commonly in neonatal intensive care when sedation is required without analgesia, such as for radiological procedures or echocardiography. It is converted to trichloroethanol and both may be metabolically active.[87] A high incidence of adverse side effects, primarily cardiorespiratory events, occurred with small doses of chloral hydrate (30 mg/kg) in ex-preterm neonates undergoing audiological testing, and were most common among infants with lower gestational ages at birth.[88] This drug should be used with caution in neonates and infants.[89]

Propofol

Propofol has gained increasing popularity as an anaesthetic agent for neonates, but with very little data to support its use in this population.[90] Although there are pharmacokinetic data on children, these data are lacking in neonates.[91] Its side effects, including respiratory depression, hypotension, bradycardia and upper airway obstruction, and prolonged use result in severe metabolic acidosis, and myocardial and hepatic failure.[91] Propofol should be used with extreme caution for invasive procedures in neonates.[92]

Ketamine

Ketamine is a dissociative anaesthetic that provides analgesia, amnesia and sedation, that has been studied extensively in older children,[93] but there have been few studies in newborns. Ketamine causes mild increases in blood pressure, heart rate and bronchodilation,[94] with minimal effects on cerebral blood flow.[95] Single doses for pain management in ventilated neonates are 0.5–2 mg/kg,[96] but continuous infusions have not been studied, except after cardiac surgery.[97] The haemodynamic effects of ketamine may be advantageous for cardiac catheterisation of neonates with congenital heart disease or pulmonary hypertension.[98 99] Animal studies suggested that ketamine causes neuronal apoptosis in the immature brain,[100] but the clinical relevance and design of these studies have been questioned.[101 102] Despite its theoretical advantages as a potent analgesic, sedative and amnestic agent, ketamine has been minimally studied in neonates; thus, it should be used mostly in approved research protocols.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are used extensively in older children and adults, but there is understandable reluctance to use them in neonates. They inhibit the cyclooxygenase enzymes (COX-1 and COX-2) responsible for converting arachidonic acid into prostaglandins, thus producing analgesic, antipyretic or anti-inflammatory effects. Adverse effects that are of particular importance to neonates include gastric erosions, leading to gastrointestinal bleeding, decreased platelet aggregation, leading to IVH, and decreased glomerular filtration, leading to renal failure.[103] The analgesic effects of NSAIDs such as indomethacin and ibuprofen have not been studied in neonates. These drugs have limited use because of their adverse effects, although they have been studied extensively for patent ductus arteriosus closure in preterm neonates.[104–106]

Acetaminophen

Acetaminophen acts primarily by inhibiting the COX enzymes in the brain and has been well studied in newborns, particularly for mild procedural pain or fever reduction after immunisations. However, it has limited efficacy for procedures such as circumcision[107] or heel prick.[108] Rectal[109–111] or intravenous formulations (propacetamol) have been studied in neonates and infants,[112] with minimal adverse effects shown clinically.[113]

LOCAL ANAESTHETICS

Local anaesthetics effectively reduce procedural pain in neonates. Injectable lidocaine and topical creams have both been studied in various neonatal populations.

Lidocaine

Injectable lidocaine belongs to the aminoacyl amide class, inhibiting axonal transmission by blocking Na^+ channels. It is 75% protein-bound in the serum, whereas other local anaesthetics such as bupivacaine and ropivacaine are 95% bound, with increased concern for potential neonatal toxicity.[114] Lidocaine solution is acidic and burns when injected; hence, slow injection is recommended as buffering is not effective. Lidocaine is used commonly for dorsal penile nerve block in neonatal circumcision, but a head-to-head comparison reported ring block to be more effective than either dorsal penile block or topical anaesthetics.[115] Lidocaine infiltration is not effective for lumbar puncture in neonates,[116] although handling, immobilisation and pain from dural puncture may over-ride the effects of local anaesthesia. Complications of therapy include case reports of seizures and changes in brain stem auditory response with lidocaine injection.[117]

Topical anaesthetics

Several topical anaesthetics have been evaluated in neonates, including a eutectic mixture of local anaesthetics cream (EMLA, Astra Pharmaceuticals, Södertälje, Sweden), a mixture of 2.5% prilocaine and lidocaine; 4% tetracaine (Ametop, Smith and Nephew, Hull, England); and 4% liposomal lidocaine (L.M.X.4 or Ela-MAX, Ferndale Labs, Ferndale, Michigan, USA). The first of these, EMLA cream, was studied extensively in neonates for procedural pain,[21 118] although newer agents have a shorter onset of action and may be more effective. For example, the pain from heel pricks, the most common skin-breaking procedure in neonates,[119] is not affected by EMLA cream.[120 121] Although multiple studies have shown its efficacy for venepuncture,[122 123] lumbar puncture[124] or immunisations,[125] it was less efficacious than sucrose for venepuncture[126] or lidocaine blocks for circumcisions.[115] Complications of topical anaesthetics include methaemoglobinaemia from the prilocaine component if EMLA cream is not applied correctly,[118 127] or transient skin reactions from various agents.[118 128] In summary, topical anaesthetics are useful for invasive procedures in neonates, but they must be used correctly and cautiously in preterm neonates.

Table 2 Recommended pharmacological therapies for common procedures

Procedure	Pharmacological therapy
Heel stick	None (sucrose 25–50% or milk)
Venous or arterial puncture	EMLA or ametope (0.5 g for 45 min)
Lumbar puncture	EMLA cream
Circumcision	Ring block or dorsal penile nerve block with lidocaine
Intubation	Not known; consider fentanyl 2 mg/kg and midazolam 0.2 mg/kg
Cardiac catheterisation or ECMO cannulation	Ketamine (2 mg/kg) and fentanyl 2 mg/kg
Tracheal suction	Not known; consider midazolam, sucrose
Mechanical ventilation	Not known; consider morphine load at 100 mg/kg (if not hypotensive and over 26 weeks gestational age) or midazolam 0.1 mg/kg with drip at 0.05 mg/kg/h or lorazepam 0.1 mg/kg every 4–6 h

ECMO, extracorporeal membrane oxygenation.

Sucrose

Oral sucrose has been used for effective analgesia in term and preterm infants.[129] Sucrose promotes calming behaviours and reduces distress associated with acute pain in animal models and humans, perhaps mediated via endogenous opioid mechanisms.[130] The efficacy of sucrose for procedural pain has been dealt with in systematic reviews,[131] but its efficacy for ongoing pain or distress[132] or postoperative pain remains questionable. Analgesic effects are present with doses as low as 0.1 ml of 24% sucrose, and other sweet-tasting liquids, such as glucose, mother's milk or saccharin, are just as effective. The administration of sucrose via a pacifier, which stimulates non-nutritive sucking, may increase its effectiveness, but very preterm infants are more likely to show immediate (gagging or choking[133]) or short-term adverse effects.[132]

CONCLUSIONS

Pharmacological therapies for neonatal analgesia and sedation have stimulated more humane approaches to neonatal intensive care procedures and monitoring.[13] Clinicians routinely use systemic analgesic agents (such as opioids, NSAIDs, acetaminophen or sucrose), sedatives or anaesthetic agents (with or without analgesic effects), or injectable or topical local anaesthetics (table 2). Different drug classes or modes of administration may be combined to optimise the efficacy and minimise the side effects. Toxicity or drug overdose resulting from repetitive use of these agents, or the enhanced vulnerability of special populations (eg, extremely premature infants or neonates with sepsis, hypotension or renal failure), must be considered to ensure their safe use. The long-term effects of untreated neonatal pain include adverse neurological outcomes, heightened response to pain, increased somatisation, hypervigilance and other adverse sequelae. Pharmacological therapies must be used in conjunction with non-pharmacological interventions such as swaddling, distraction, synchronised ventilation, clustered care and direct maternal contact (kangaroo care) if possible. Despite the great strides in research in this aspect over the past 20 years,[134] major gaps in the available scientific evidence, particularly resulting from our inability to measure pain objectively, remain the cause of the uncertainty and variability in clinical practices. Currently, we are uncertain about how to treat neonates requiring assisted ventilation or the most common painful procedures (heel sticks, tracheal suctioning, intubation), and also are uncertain about the long-term effects of untreated neonatal pain or neonatal analgesia or sedation. Clearly, a lot more work needs to be done.[135]

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