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Drugs of Choice for Sedation and Analgesia in the NICU

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Synopsis

Painful procedures in the NICU are common, undertreated, and lead to adverse consequences. The most common drugs used to treat neonatal pain include the opiates, benzodiazepines, barbiturates, ketamine, propofol, acetaminophen, and local and topical anesthetics. The indications, advantages and disadvantages of the commonly used analgesic drugs are discussed. Guidance and references for drugs and dosing for specific neonatal procedures are provided.

Introduction

Before 1980, pain in the newborn period was infrequently recognized or treated[1]. The gold standard of pain assessment is self reporting which is clearly not possible in the newborn period; thus, clinicians can only measure pain indirectly. Animal and human studies have documented that neonatal pain is associated with both short and long term consequences[2,3]. Further, the enhanced survival of extremely low birthweight babies makes them more susceptible to the effects of pain and stress because of increased exposure. Indeed, one study documented that neonates under 32 weeks gestation were exposed to 10–15 painful procedures per day, and most of these procedures were untreated[4]. Unfortunately, we continue to struggle. A recent study by Carbajol et al[5] has documented the increased occurrence and lack of treatment of neonatal pain in almost 80% of newborns in intensive care!

Analgesia and sedation in Neonatal Intensive Care Unit (NICU) has been fraught with controversy because of concern over the safety of these drugs in the neonatal population, lack of adequate pharmacokinetic and -dynamic data in this population, difficulty in pain assessment, and lack of long term neurodevelopmental assessment of survivors for the pain experienced in the neonatal period[6–9]. Legitimate concern over safety has led to more governance for moderate sedation privileges for clinicians caring for neonates as well as more emphasis on obtaining consent for sedation[10], leading to roadblocks to giving sedation to neonates undergoing painful procedures. Further, individual differences and decreased morphine metabolism in younger gestational age neonates may lead to the rapid development of tolerance as well as accumulation of the drug in extremely preterm neonates[11]. Thus, the use of sedation and analgesia in the neonatal population while extremely important, must be done safely and effectively.

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Opioids

Opioids are commonly used in modern NICU's[12]. They provide procedural pain relief such as for intubation premedication[13–15], relief from chronic pain such as necrotizing enterocolitis[16] and ventilation[17–19]. Several studies and reviews have pointed to the conclusion that they should be used selectively. A recent Cochrane review found insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns[19]. The Cochrane review looked at pain scales, and overall found that a significant effect on pain was found in the treatment group. No significant effect was found in favor of the treatment group with respect to neonatal mortality, duration of ventilation, neurodevelopmental outcome, both short-term and long-term, incidence of severe intraventricular hemorrhage (IVH), any IVH, and periventricular leukomalacia (PVL). Given the likely long term adverse consequences associated with the chronic pain and stress of mechanical ventilation, it is reassuring that short term adverse effects are not more common in the opioid treated groups.

Morphine

Morphine is the most frequently used opioid analgesic in all ages, and is the most commonly used drug for analgesia in ventilated neonates[12]. Morphine has a slow onset of analgesia. Its mean onset of action is 5 minutes and the peak effect is at 15 minutes. It is metabolized in the liver into 2 active compounds, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The former is an opioid antagonist, and the latter is a potent analgesic. Preterm infants mostly produce M3G, which explains why after 3–4 days of morphine therapy, the infant develops tolerance[20]. Side-effects of morphine include hypotension in neonates with pre-existing hypotension and gestational age less than 26 weeks[21], prolonged need for assisted ventilation and increased time to reach full feeds[17,18]. Others have suggested that morphine may have a specific effect on pulmonary mechanics, possibly due to some as yet undefined direct toxicity such as histamine release and/or bronchospasm[22]. There is even controversy as to whether morphine is effective in the treatment of acute pain[23].

A randomized controlled trial conducted in the Netherlands compared the analgesic effect of morphine versus placebo infusions, for the duration of 7 days, in 150 newborns who received mechanical ventilation. The findings of the study suggested that routine morphine infusion in preterm newborns who received ventilatory support neither improved pain relief nor protected against poor neurologic outcome. The latter was defined as severe IVH, PVL, or death within 28 days [17].

The Neurologic Outcomes and Pre-emptive Analgesia in Neonates (NEOPAIN) trial included ventilated preterm neonates from 16 centers in the US and Europe. It compared the effect of morphine versus placebo infusions, following a loading dose, on the neurological outcomes of the ventilated neonates. The results suggested that continuous morphine infusion did not reduce early neurological injury in ventilated preterm neonates. The poor neurological outcome was defined as severe IVH, PVL, or death [24]. Hypotension occurred more frequently in the morphine group than the placebo group.

One study assessed the long-term outcome at 5–6 years of prematurely born children (<34 weeks of gestation) who by randomization received morphine in the neonatal period to facilitate mechanical ventilation. This study looked at children from two trials. The first one included 95 infants who were randomly assigned to receive morphine alone, pancuronium alone or both morphine and pancuronium. The second trial included 21 infants who received morphine and 20 infants who received placebo. Each child was assessed using three scales: the full scale Weschler Preschool and Primary Scale of Intelligence (WPPSI-R), the Movement ABC (Movement Assessment Battery for Children), and the Child Behavior Checklist. There were no adverse effects found on intelligence, motor function, or behavior [25].

Fentanyl

Fentanyl is an opioid analgesic that is 50–100 times more potent than morphine[26]. It is used frequently because of its ability to provide rapid analgesia [27]. It may be used as a slow intravenous push every 2 to 4 hours or as a continuous infusion. Tolerance may develop and withdrawal symptoms may occur after 5 days or more of continuous infusions[26]. In a blinded randomized controlled trial, a single dose of fentanyl given to ventilated preterm newborns significantly reduced pain behaviors and changes in heart rate. It also increased growth hormone levels [28]. In another study, fentanyl provided the same pain relief as morphine but with fewer side effects[29]. In other studies, fentanyl use resulted in lower heart rates, behavioral stress scores and pain scores as compared to placebo; however, the infants receiving fentanyl required higher ventilator rates and peak inspiratory pressures at 24 hours [30].

Fentanyl may also be used transdermally in patients with limited intravenous access. Side-effects of fentanyl include bradycardia, chest wall rigidity and opioid tolerance after prolonged therapy [27].

Methadone

Methadone is a potent analgesic with a rapid onset of action, and prolonged effect [27]. It has minimal side-effects, high enteral bioavailability and a low cost.

Other opiates

Other opiates include the short acting drugs sufentanil, alfentanil, and remifentanil. All are useful for short procedures such as intubation. Sufentanil and alfentanil are metabolized by the liver, which is immature in preterm neonates resulting in increased levels with repeated infusions, especially in preterm neonates[31]. Remifentanil on the other hand is rapidly cleared by plasma esterases and is unaffected by the maturity of the liver enzyme system, making it attractive for short neonatal surgery or other procedures when rapid recovery is anticipated [31].

Benzodiazepines

The benzodiazepines are anxiolytic drugs that have limited analgesic effect but are commonly used in NICU's to produce sedation, muscle relaxation and provide amnesia (in older patients). This class of drugs inhibits Gamma Aminobutyric Acid A (GABA_A) receptors[32]. The main complications include myoclonic jerking, excessive sedation, respiratory depression and occasional hypotension.

Midazolam

The most commonly used benzodiazepine in the NICU is midazolam. When administered with morphine, it has been shown to provide better sedation than morphine alone in ventilated patients, without adverse effects[33]. The minimal effective dose for most neonates is 200 micrograms/kg with a maintenance dose of 100 micrograms/kg/hour[34]. It can be given orally although the bioavailability is only half that of IV midazolam in neonates [35]. Intranasal midazolam has been shown to be effective for fundoscopic exams in older children, but this mode of delivery has not been tested in neonates[36]. One recent review found no apparent clinical benefit of midazolam compared to opiates in mechanically ventilated neonates[37]. Further, midazolam was associated with worse short term adverse effects (death, severe intraventricular hemorrhage, or periventricular leukomalacia) in the NOPAIN trial compared to morphine alone[38]. In summary, midazolam appears to provide sedative effects in mechanically ventilated neonates, but it should be used with caution because of reported adverse effects, particularly when used alone.

Lorazepam

Lorazepam is a longer acting benzodiazepine with a duration of action of 8–12 hours that is frequently used in preterm neonates. It is also an effective anti-convulsant for neonates refractory to phenobarbital. Unfortunately, one of its main side effects is myoclonic jerking, which mimics seizure activity[12,39]. It has been shown (along with morphine) to adhere to the tubing in patients on extra corporeal membrane oxygenation (ECMO), increasing dosing requirements by 50% in those patients[40].

Barbiturates

Barbiturates are commonly used in neonates for sedation and analgesic effects, despite a lack of evidence for pain relief[12].

Phenobarbital

Phenobarbital is usually considered the drug of choice for seizure control. Despite animal evidence for antinociception, it is often used for analgesia[41]. It is also used in conjunction with opioids for sedation[18], although there is little recent evidence that it is effective. Classically, it has been used for neonatal abstinence syndrome, but recent work by Ebner and others has demonstrated that opiates shorten the time required for treatment[42]. However, because of its anticonvulsant effects, phenobarbital is an attractive adjunct for patients with seizures.

Thiopental

Thiopental is a short acting barbiturate used for anesthetic induction. It is used sparingly in the NICU, but one randomized controlled trial showed a decreased time needed for intubation and maintenance of heart rate and blood pressure with thiopental compared to placebo during nasotracheal intubation[43].

Chloral Hydrate

Chloral hydrate is used for hypnosis when sedation but not analgesia is required for certain procedures such as magnetic resonance imaging (MRI). Apnea and bradycardia may occur in ex-preterm infants undergoing procedural sedation with doses as little as 30 mg/kg. Side effects were inversely related to gestational age[44]. The usual dose is 50–100 mg/kg, and a dose of 75 mg/kg administered orally is more efficacious but with comparable side effects (apnea, bradycardia) as a dose of 0.2 mg/kg of intravenous midazolam[45].

Ketamine

Ketamine is a dissociative anesthetic used for anesthesia, analgesia and sedation. It causes bronchodilation and mild increases in blood pressure and heart rate[46]. Cerebral blood flow is relatively unaffected with ketamine, making it an attractive choice for some unstable hypotensive neonates requiring procedures such as cannulation for ECMO[47]. Animal studies have raised concern over the neurodegenerative effects of ketamine [48,49]; however we have shown that ketamine in clinically relevant doses is neuroprotective in the presence of inflammatory pain[20]. Nevertheless, extrapolating animal to human data is problematic at best and there has been no credible evidence that ketamine is detrimental to the developing human brain in the presence of pain[50]. Clearly, more study is needed to determine safety and efficacy of this anesthetic.

Propofol

Propofol has become popular as an anesthetic agent for young children, but it has not been studied extensively in neonates[51–53]. One study compared propofol to morphine, atropine and suxamethonium for intubation and found that propofol led to shorter intubation times, higher oxygen saturations, and less trauma than the combination regimen in neonates[54]. However, propofol should be used with caution in young infants because clearance is inversely related to neonatal and postmenstrual age. Thus with intermittent bolus or continuous administration this drug can accumulate in young immature neonates, leading to toxicity[55].

Acetaminophen

Acetaminophen acts by inhibiting the COX enzymes in the brain, and it has been well studied in newborns[16]. It is useful for mild pain, in conjunction with other pain relief, or after circumcision[56].

Local anesthetics

Lidocaine

Lidocaine inhibits axonal transmission by blocking Na⁺ channels. Lidocaine is commonly used for penile blocks for circumcisions. In this circumstance, its use has demonstrated effectiveness in decreasing pain response to immunizations as long as 4 months after circumcision compared to neonates who received placebo[57]. Compared to a dorsal penile root block or eutectic mixture of local anesthetics (EMLA) cream, the ring block has been shown to be the most effective means of pain relief for circumcision[58].

Topical anesthetics

Topical anesthetics have demonstrated effectiveness for certain types of procedural pain such as venipuncture[59], lumbar puncture[60], or immunizations[61]. Complications include methemoglobinemia and transient skin rashes[62]. In preterm neonates with thin skin the concern for methemoglobinemia is accentuated.

Unfortunately, topical anesthetics have not been effective in providing pain relief for the heel prick, one of the most common skin breaking procedures, because of increased skin thickness [63]. Newer topical anesthetics include 4% tetracaine and 4% liposomal lidocaine. Although the newer agents have a shorter onset of action, they are no more effective.

Common procedures—Common neonatal procedures and advantages and disadvantages of drug therapy are summarized in Table 1.

Future directions

Non-steroidal Anti-inflammatory Drugs (NSAIDS)

NSAIDS are used extensively for pain relief in children and adults but they are mainly used for patent ductus arteriosus (PDA) closure in neonates. They act by inhibiting the cyclooxygenase enzymes (COX-1 and COX-2) responsible for converting arachidonic acid into prostaglandins, thus producing their analgesic, anti-pyretic, and anti-inflammatory effects[27]. The analgesic effects of NSAIDS have not been studied in neonates, although both ibuprofen and indomethacin have been studied for use in PDA closure. Concern over side effects of renal dysfunction, platelet adhesiveness and pulmonary hypertension, have limited their study for this indication[37,64,65]. However, ibuprofen has demonstrated beneficial effects on cerebral circulation in human studies[66] as well as beneficial effects on the development of chronic lung disease in baboon experiments[67], making it an attractive analgesic in preterm neonates.

Non-pharmacologic approaches such as acupuncture, message therapy, sucrose and music are also safe and effective[68].

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References

1. Anand KJ, Hall RW. Controversies in neonatal pain: an introduction. *Seminars in Perinatology* 2007;31(5):273–4. [PubMed: 17905180]
2. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *New England Journal of Medicine* 1987;317(21):1321–9. [PubMed: 3317037]
3. Fumagalli F, Molteni R, Racagni G, Riva MA. Stress during development: Impact on neuroplasticity and relevance to psychopathology. *Progress in Neurobiology* 2007;81(4):197–217. [PubMed: 17350153]
4. Barker DP, Rutter N. Exposure to invasive procedures in neonatal intensive care unit admissions. *Archives of Disease in Childhood Fetal & Neonatal Edition*. 1995
5. Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S. Epidemiology and treatment of painful procedures in neonates in intensive care units. *Journal of the American Medical Association* 200;300(1):60–70. [PubMed: 18594041]
6. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clinical Pharmacokinetics* 1996;31(6):423–43. [PubMed: 8968656]
7. Anand KJ, Aranda JV, Verde CB, Buckman S, Capparelli EV, Carlo W, et al. Summary proceedings from the neonatal pain-control group. *Pediatrics* 2006;117(3 Pt 2):S9–S22. [PubMed: 16777824]
8. Ranger M, Johnston CC, Anand KJ. Current controversies regarding pain assessment in neonates. *Seminars in Perinatology* 2007;31(5):283–8. [PubMed: 17905182]
9. Whitfield MF, Grunau RE. Behavior, pain perception, and the extremely low-birth weight survivor. *Clinics in Perinatology* 2000;27(2):363–79. [PubMed: 10863655]
10. Coté, Charles J., MD; Wilson, Stephen, DMD, MA, PhD. American Academy of Pediatrics, American Academy of Pediatric Dentistry. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. *Pediatrics* 2006;118(6):2587–602. [PubMed: 17142550]
11. Saarenmaa E, Neuvonen PJ, Roseberg P, Fellman V. Morphine clearance and effects in newborn infants in relation to gestational age. *Clinical Pharmacology & Therapeutics* 2000;68(2):160–6. [PubMed: 10976547]
12. Hall RW, Boyle E, Young T. Do ventilated neonates require pain management? *Seminars in Perinatology* 2007;31(5):289–97. [PubMed: 17905183]
13. Whyte S, Birrell G, Wyllie J. Premedication before intubation in UK neonatal units.[see comment]. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2000;82(1):F38–41. [PubMed: 10634840]
14. Roberts KD, Leone TA, Edwards WH, Rich WD, Finer NN. Premedication for nonemergent neonatal intubations: a randomized, controlled trial comparing atropine and fentanyl to atropine, fentanyl, and mivacurium. *Pediatrics* 2006;118(4):1583–91. [PubMed: 17015550]
15. Sarkar S, Schumacher RE, Baumgart S, Donn SM. Are newborns receiving premedication before elective intubation? *Journal of Perinatology* 2006;26(5):286–9. [PubMed: 16598295]
16. Menon G, Anand KJ, McIntosh N. Practical approach to analgesia and sedation in the neonatal intensive care unit. *Seminars in Perinatology* 1998;22(5):417–24. [PubMed: 9820566]
17. Simons SH, van Dijk M, van Lingen RA, Roofthoof D, Duivenvoorden HJ, Jongeneel N. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. *JAMA* 2003;290(18):2419–27. [PubMed: 14612478]

18. Anand KJ, Hall RW, Desai N, Shephard B, Bergqvist LL, Young TE, et al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet* 2004;363(9422):1673–82. [PubMed: 15158628][see comment]
19. Bellu R, de Waal KA, Zanini R. Opioids for neonates receiving mechanical ventilation. *Cochrane Database of Systematic Reviews* 2008;(1):CD004212.[update of *Cochrane Database Syst Rev.* 2005;(1):CD004212; PMID: 15674933]
20. Anand KJ. Pharmacological approaches to the management of pain in the neonatal intensive care unit. *Journal of Perinatology* 2007;27(Suppl 1):S4–S11. [PubMed: 17453028]
21. Hall RWKS, Barton BA, Kaiser JR, Anand KJ. Morphine, hypotension, and adverse outcomes in preterm neonates: who's to blame? *Pediatrics* 2005;115(5):1351–1359. [PubMed: 15867047]
22. Levene M. Morphine sedation in ventilated newborns: who are we treating? *Pediatrics* 2005;116(2):492–3. [PubMed: 16061608][comment]
23. Carbajal R, Lencien R, Jugie M, Paupe A, Barton BA, Anand KJ. Morphine does not provide adequate analgesia for acute procedural pain among preterm neonates. *Pediatrics* 2005;115(6):1494–500. [PubMed: 15930209]
24. Bhandari V, Bergqvist LL, Kronsberg SS, Barton BA, Anand KJ. Morphine administration and short-term pulmonary outcomes among ventilated preterm infants. *Pediatrics* 2005;116(2):352–9. [PubMed: 16061589][see comment]
25. MacGregor R, Evans D, sugden D, Gaussen T, Leven M. Outcome at 5–6 years of prematurely born children who received morphine as neonates. *Archives of Disease in Childhood Fetal & Neonatal Edition* 1998;79(1):F40–3. [PubMed: 9797623]1998 Jul
26. Mitchell A, Brooks S, Roane D. The premature infant and painful procedures. *Pain Management Nursing* 2000;1(2):58–65. [PubMed: 11706460]
27. Anand KJ, Hall RW. Pharmacological therapy for analgesia and sedation in the newborn. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2006;91(6):F448–53. [PubMed: 17056842] [erratum appears in *Arch Dis Child Fetal Neonatal Ed.* 2007 Mar;92(2):F156 Note: dosage error in text]
28. Guinsburg R, Kopelman BL, anand KJ, de Almeida MF, Peres Cde A, et al. Physiological, hormonal, and behavioral responses to a single fentanyl dose in intubated and ventilated preterm neonates. *Journal of Pediatrics* 1998;132(6):954–9. [PubMed: 9627585]
29. Saarenmaa E, Huttunen P, Leppaluoto J, Meretoja O, Fellman V. Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: A randomized trial. *Journal of Pediatrics* 1999;134(2):144–50. [PubMed: 9931520][see comment]
30. Orsini AJ, Leef KH, Costarino A, Dettorre MD, Stefano JL. Routine use of fentanyl infusions for pain and stress reduction in infants with respiratory distress syndrome. *Journal of Pediatrics* 1996;129(1):140–5. [PubMed: 8757574][see comment]
31. Berde CB, Jaksic T, Lynn AM, Maxwell LG, Soriano SG. Anesthesia and analgesia during and after surgery in neonates. *Clinical Therapeutics* 2005;27(6):900–21. [PubMed: 16117991]
32. Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clinical Pharmacokinetics* 1998;35(1):37–47. [PubMed: 9673833]
33. Arya V, Ramji S. Midazolam sedation in mechanically ventilated newborns: a double blind randomized placebo controlled trial. *Indian Pediatrics* 2001;38(9):967–72. [PubMed: 11568372][see comment]
34. Treluyer JM, Zohar S, Rey E, Hubert P, Iserin F, Jugie M, et al. Minimum effective dose of midazolam for sedation of mechanically ventilated neonates. *Journal of Clinical Pharmacy & Therapeutics* 2005;30(5):479–85. [PubMed: 16164495]
35. de Wildt SN, Kearns GL, Hop WC, Murry DJ, Abdel-Rahman SM, van den Anker JN. Pharmacokinetics and metabolism of oral midazolam in preterm infants. *British Journal of Clinical Pharmacology* 2002;53(4):390–2. [PubMed: 11966671]
36. Altintas O, Karabas VL, Demirci G, Onur I, Caglar Y. Evaluation of intranasal midazolam in refraction and fundus examination of young children with strabismus. *Journal of Pediatric Ophthalmology & Strabismus* 2005;43(6):355–9. [PubMed: 16382560]
37. Aranda JV, Carlo W, Hummel P, Thomas R, Lehr VT, Anand KJ. Analgesia and sedation during mechanical ventilation in neonates. *Clinical Therapeutics* 2005;27(6):877–99. [PubMed: 16117990]

38. Anand KJ, Baton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. *Archives of Pediatrics & Adolescent Medicine* 1999;153(4):331–8. [PubMed: 10201714][erratum appears in Arch Pediatr Adolesc Med 1999 Aug; 153(8):895]
39. Chess PR, D'Angio CT. Clonic movements following lorazepam administration in full-term infants. *Archives of Pediatrics & Adolescent Medicine* 1998;152(1):98–9. [PubMed: 9452719]
40. Bhatt-Mehrt V, Annich G. Sedative clearance during extracorporeal membrane oxygenation. *Perfusion* 2005;20(6):309–15. [PubMed: 16363315]
41. Gonzalez-Darder JM, Ortega-Alvaro A, Ruiz-Franzi I, Segura-Pastor D. Antinociceptive effects of phenobarbital in “tail-flick” test and deafferentation pain. *Anesthesia & Analgesia* 1992;75(1):81–6. [PubMed: 1616167]
42. Ebner N, Rohrmeyer K, Winklbaier B, Baewert A, Jagsch R, Peternell A, et al. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. *Drug & Alcohol Dependence* 2007;87(2–3):131–8. [PubMed: 17000060]
43. Bhutani A, Sahni R, Rastogi S, Wung JT. Randomised controlled trial of thiopental for intubation in neonates. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2000;82(1):F34–7. [PubMed: 10634839][see comment]
44. Allegaert K, Daniels H, Naulaers G, Tibboel D, Devlieger H. Pharmacodynamics of chloral hydrate in former preterm infants. *European Journal of Pediatrics* 2005;164(7):403–7. [PubMed: 15798911]
45. McCarver-May DG, Kang J, Aouthmany M, Elton R, Mowery LL, Slovis TL, et al. Comparison of chloral hydrate and midazolam for sedation of neonates for neuroimaging studies. *Journal of Pediatrics* 1996;128(4):573–6. [PubMed: 8618198][see comment]
46. Friesen RH, Henry DB. Cardiovascular changes in preterm neonates receiving isoflurane, halothane, fentanyl, and ketamine. *Anesthesiology* 1986;64(2):238–42. [PubMed: 3946810]
47. Betremieux P, Carre P, Pladys P, Roze O, Lefrancois C, Malledant Y. Doppler ultrasound assessment of the effects of ketamine on neonatal cerebral circulation. *Developmental Pharmacology & Therapeutics* 1993;20(1–2):9–13. [PubMed: 7924769]
48. Young C, Jevtovic-Todorovic V, Qin YQ, Tenkova T, Want H, Labruyere J, et al. Potential of ketamine and midazolam, individually or in combination, to induce apoptotic neurodegeneration in the infant mouse brain. *British Journal of Pharmacology* 2005;146(2):189–97. [PubMed: 15997239]
49. Olney JW, Young C, Wozniak DF, Ikonomidou C, Jevtovic-Todorovic V. Anesthesia-induced developmental neuroapoptosis. Does it happen in humans?[see comment][comment]. *Anesthesiology* 2004;101(2):273–5. [PubMed: 15277906]
50. Bhutta AT, Venkatesan AK, Rovnaghi CR, Anand KJ. Anaesthetic neurotoxicity in rodents: is the ketamine controversy real? *Acta Paediatrica* 2007;96(11):1554–6. [PubMed: 17714546]
51. Disma N, Astuto M, Rizzo G, Rosano G, Naso P, Aprile G, et al. Propofol sedation with fentanyl or midazolam during oesophagogastroduodenoscopy in children. *European Journal of Anaesthesiology* 2005;22(11):848–52. [PubMed: 16225720]
52. Rigby-Jones AE, Nolan JA, Priston MJ, Wright PM, Sneyd Jr, Wolf AR. Pharmacokinetics of propofol infusions in critically ill neonates, infants, and children in an intensive care unit. *Anesthesiology* 2002;97(6):1393–400. [PubMed: 12459664]
53. Jenkins IA, Playfor SD, Bevan C, Davis G, Wolf AR. Current United Kingdom sedation practice in pediatric intensive care. *Paediatric Anaesthesia* 2007;17(7):675–83. [PubMed: 17564650]
54. Ghanta S, Abdel-Latif ME, Lui K, Ravindranathan H, Awad J, Oei J. Propofol compared with the morphine, atropine, and suxamethonium regimen as induction agents for neonatal endotracheal intubation: a randomized, controlled trial. *Pediatrics* 2007;119(6):e1248–55. [PubMed: 17485450][see comment]
55. Allegaert K, Peeters MY, Verbesselt T, Tibboel D, Naulaers G, de Hoon JN, et al. Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. *British Journal of Anaesthesia* 2007;99(6):864–70. [PubMed: 17965417]
56. Howard CR, Howard FM, Weitzman ML. Acetaminophen analgesia in neonatal circumcision: the effect on pain. *Pediatrics* 1994;93(4):641–6. [PubMed: 8134222]

57. Taddio A, Katz J, Ilersich AL, Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet* 1997;349(9052):599–603. [PubMed: 9057731][see comment]
58. Lander J, Brady-Fryer B, Metcalfe JB, Nazarali S, Muttitt S. Comparison of ring block, dorsal penile nerve block, and topical anesthesia for neonatal circumcision: a randomized controlled trial. *JAMA* 1997;278(24):2157–62. [PubMed: 9417009][see comment]
59. Garcia OC, Reichberg S, Brion LP, Schulman M. Topical anesthesia for line insertion in very low birth weight infants. *Journal of Perinatology* 1997;17(6):477–80. [PubMed: 9447537]
60. Kaur G, Gupta P, Kumar A. A randomized trial of eutectic mixture of local anesthetics during lumbar puncture in newborns. *Archives of Pediatrics & Adolescent Medicine* 2003;157(11):1065–70. [PubMed: 14609894]
61. Gradin M, Eriksson M, Holmqvist G, Holstein A, Schollin J. Pain reduction at venipuncture in newborns: oral glucose compared with local anesthetic cream. *Pediatrics* 2002;110(6):1053–7. [PubMed: 12456899][see comment]
62. Taddio A, Stevens B, Craig K, Rastogi P, Ben-David S, Shennan A, et al. Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. *New England Journal of Medicine* 1997;336(17):1197–201. [PubMed: 9110906][see comment]
63. Larsson BA, Norman M, Bjerring P, Egekvist H, Lagercrantz H, Olsson GL. Regional variations in skin perfusion and skin thickness may contribute to varying efficacy of topical, local anaesthetics in neonates. *Paediatric Anaesthesia* 1996;6(2):107–10. [PubMed: 8846274]
64. Allegaert K, et al. The impact of ibuprofen on renal clearance in preterm infants is independent of the gestational age. *Pediatric Nephrology* 2005;20(6):740–3. [PubMed: 15785936]
65. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database of Systematic Reviews* 2008;(1):CD003481.[update of Cochrane Database Syst Rev. 2005;(4):CD003481; PMID: 16235321]
66. Naulaers G, Delanghe G, Allegaert K, Kebeer A, Cossey V, Vanhole C, et al. Ibuprofen and cerebral oxygenation and circulation. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2005;90(1):F75–6. [PubMed: 15613583]
67. McCurnin D, et al. Ibuprofen-induced patent ductus arteriosus closure: physiologic, histologic, and biochemical effects on the premature lung. *Pediatrics* 2008;121(5):945–56. [PubMed: 18450898]
68. Golianu B, Krane E, Seybold J, Almgren C, Anand KJ. Non-pharmacological techniques for pain management in neonates. *Seminars in Perinatology* 2007;31(5):318–22. [PubMed: 17905187]
69. Pereira e Silva Y, Gomez RS, Barbosa RF, Simoes E, Silva AC. Remifentanyl for sedation and analgesia in a preterm neonate with respiratory distress syndrome. *Paediatric Anaesthesia* 2005;15(11):993–6. [PubMed: 16238563][see comment]
70. Knolle E, Oehmke MJ, Gustorff B, Hellwagner K, Kress HG. Target-controlled infusion of propofol for fiberoptic intubation. *European Journal of Anaesthesiology* 2003;20(7):565–9.
71. Singh A, Girotra S, Mehta Y, Radhakrishnan S, Shrivastava S. Total intravenous anesthesia with ketamine for pediatric interventional cardiac procedures. *Journal of Cardiothoracic & Vascular Anesthesia* 2000;14(1):36–9. [PubMed: 10698390]
72. Oklu E, Bulutcu FS, Yalcin Y, Ozbek U, Cakali E, Bayindir O. Which anesthetic agent alters the hemodynamic status during pediatric catheterization? Comparison of propofol versus ketamine. *Journal of Cardiothoracic & Vascular Anesthesia* 2003;17(6):686–90. [PubMed: 14689405][see comment]
73. Bouwmeester JJ, Hop WC, van Dijk M, Anand KJ, van den Anker JN, Tibboel D. Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. *Intensive Care Medicine* 2003;29(11):2009–15. [PubMed: 12897995]
74. Simons SH, van Dijk M, Anand KS, Roofthoof D, van Lingen RA, Tibboel D. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Archives of Pediatrics & Adolescent Medicine* 2003;157(11):1058–64. [PubMed: 14609893]

Table 1

Summary of Procedures and Treatment

Procedure	Drugs	Advantages of treatment	Disadvantages of treatment	Other comments
Mechanical Ventilation [17–19,	Fentanyl (1–3 mcg/kg); morphine (0.1 mg/kg), Midazolam (0.1–0.2 mg/kg)	Improved ventilator synchrony, lower pain scores	Prolonged time on assisted ventilation, prolonged time to full feeds, increased bladder catheterization, hypotension	Use sedation as needed, not pre-emptively; Midazolam associated with adverse short term effects in NOPAIN Trial
Circumcision [58,62]	Lidocaine (1ml), EMLA	Less pain response up to 4 months post procedure	Allergic reaction, bruising at injection site	Ring block is more effective than dorsal penile nerve root block
heel lance [63]	Sucrose	Shorter crying, less changes in heart rate	None	EMLA cream is not effective
venipuncture, arterial puncture, and lumbar puncture [60,61]	Topical anesthetic (EMLA), sucrose	Lower PIPP scores, less crying	Local reaction, rare methemoglobinemia	Other non-pharmacologic treatments effective
Intubation [14,15,54,69,70]	Morphine 0.1 mg/kg, fentanyl 1–3 mcg/kg, remifentanyl 1 mg/kg, midazolam 0.2 mg/kg, propofol 2–6 mg/kg, ketamine 1 mg/kg, suxamethonium 2mg/kg	Shorter time to intubation, less trauma, less desaturation, better maintenance of vital signs	None	No accepted premedication. Opiates most common class used
More invasive procedures such as cannulation for ECMO [71,	Propofol 2–6 mg/kg, Ketamine 1 mg/kg, fentanyl 1–3 mcg/kg	Maintenance of cardiovascular stability	Questionable neurotoxicity with ketamine	Ketamine may be neuroprotective
Post surgical pain [73]	Fentanyl 1–3 mcg/kg, morphine 0.1 mg/kg, Acetaminophen 15 mg/kg	Lowered neuroendocrine response, faster recovery	Respiratory depression, hypotension with opiates	Acetaminophen for mild pain only
Endotracheal suctioning [34,74]	Midazolam 0.2 mg/kg, morphine 0.1 mg/kg, fentanyl 1–3 mcg/kg	Anxiolytic	Respiratory depression, hypotension, dependence	Usually not treated
Imaging (MRI) [45]	Chloral hydrate 50–100 mg/kg	Sedation	Respiratory depression, hypotension	Chloral hydrate provides sedation only