Acute pain management in the neonate

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Abstract

Management of acute pain in the neonate is challenging and involves a multimodal approach using non-pharmacological and pharmacological techniques after pain assessment using appropriate tools. Simplicity equates to safety in these vulnerable patients.

Keywords Acute pain management; local anaesthetic; neonate; pain assessment

Royal College of Anaesthetists CPD matrix: 1D02, 3D00

Learning objectives

After reading this article you should be able to:

- understand the importance of pain assessment and chose a validated tool for use in neonates
- understand the pharmacokinetic and pharmacodynamics of analgesics in neonates
- understand appropriate multimodal interventions for pain management in neonates.

It is now widely accepted that neonates perceive and respond to pain[1] and that acute and repetitive pain experiences have long-term effects[1–3] resulting in increased sensitivity to pain and reduced pain thresholds. Male infants who had circumcision without analgesia or anaesthesia responded to immunization at age 4 and 6 months with increased behavioural pain responses and more prolonged crying when compared to a control group who received analgesia. Despite this, there is still evidence that both postoperative and particularly procedural pain is poorly treated.[1] In an effort to improve pain relief in children and neonates, guidelines from the Association of Paediatric Anaesthetists of Great Britain and Ireland concerning good practice in postoperative procedural pain management were recently published in *Paediatric Anaesthesia*.[4]

Pain assessment/measurement

Optimal pain management requires developmentally appropriate pain assessment and measurement, which can be especially difficult to perform precisely and reliably in neonates. Neonatal responses to pain vary greatly so pain assessment tools should be regarded as an aid to complex holistic assessment and management. The ideal pain scoring tool should be easy and quick to use, give reproducible results and be non-invasive. The majority of measurement tools validated in the neonatal population use observation, physiological measures and behaviours to estimate and quantify pain (see Table 1). For detailed information of validity and research on these pain assessment tools see the Royal College of Nursing pain assessment web site.[5]

Pain management interventions

Non-pharmacological interventions

A growing body of evidence supports the effectiveness of a variety of non-pharmacologic pain prevention and relief techniques using visual, tactile, auditory and taste stimuli (Box 1).

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Non-nutritive sucking (NNS) using sucrose produces a behavioural change by both endogenous opioid and non-opioid mechanisms. A Cochrane review of randomized controlled trials (RCT)[6] that monitored response to heel lance in neonates concluded that sucrose led to reduction in both physiological and behavioural indicators and significantly reduced pain score during and following the procedure. There was some evidence of a dose–response effect, but this is not conclusive and the most common concentrations of sucrose used are 9% or 30% oral solution; 0.5 ml in preterm neonates or 1 ml in term neonates. There is controversy about whether sucrose produces analgesia or simply alters behaviour[7] and there is little information concerning the safety of multiple dosing or long term use.[8]

Skin-to-skin contact, kangaroo care (KC) and swaddling (all defined as holding the neonate in an upright position 40–60 degrees with as much skin contact as possible with the parent), have also demonstrated a pain relieving action during simple procedures such as heel lance and cannulation in preterm and term neonates.[9]

Environmental changes such as changes in lighting, decreasing unnecessary handling, maintaining day and night cycles, clustering or limiting painful procedures and the use of automated lancets reduce the neonate's response to acute procedural pain.

Pharmacological interventions

Paracetamol is commonly used in the treatment of mild to moderate pain in neonates (see Table 2). Clearance is reduced in the neonate and the immature cytochrome oxidase (CYP2E1) enzyme results in a reduction of toxic metabolite production (*N*-acetyl-*p*-benzoquinone imine [NAPQI]), protecting the neonate to some extent against hepatotoxicity.[10] It can be administered orally or rectally, and intravenous (IV) paracetamol has now been licensed for neonates and infants less than 10 kg. This formulation offers increased bio-availability by avoiding first pass hepatic metabolism and is currently licensed at doses of 7.5 mg/kg, maximum 30 mg/kg/day in infants <10 kg or 1 year. The target concentration of 10 mg/litre appears similar in both children and neonates.[11]

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen have antipyretic and anti-inflammatory properties with no risk of respiratory depression or sedative side effects. As with paracetamol they have an opioid sparing effect. Current research of ibuprofen in neonates for closure of patent ductus arteriosus

Pain assessment tools use for preterm and term neonates

	Assessment criteria	Gestational age tested	Nature of pain assessed
Uni-dimensional			
NFCS (Neonatal Facial Coding System)	Facial expressions — eyes squeezed, bulging brow, open lips, taut tongue, and deepening of nasolabial.	Preterm and term neonates	Procedural
Multi-dimensional			
PIPP (Premature Infant Pain Profile)	Gestational age, heart rate, saturations, eye squeeze, behavioural state, brow bulge and nasolabial furrow.	28 — 40 weeks	Procedural and postoperative
LIDS (Liverpool Infant Distress Score)	Flexion of fingers and toes, pattern of movement, spontaneous movement, spontaneous excitability, quality of cry and sleep pattern.	Term neonates	Postoperative
CRIES (Crying, requires O_2 for saturations above 95%, increased vital signs, expression and sleeplessness.)	Cry, saturations, expression, sleep, heart rate and blood pressure.	Preterm and term neonates	Procedural and postoperative
OPS (Objective Pain Scale)	Crying, movement, agitation, body language and verbal evaluation.	Term neonate	Postoperative and procedural
CHEOPS (Children's Hospital of Eastern Ontario Pain Scale)	Calmness, physical movement, facial tension, alertness, respiratory response heart rate, blood pressure.	Preterm, term neonates and older infants	Procedural and postoperative
NIPS (Neonatal Infant Pain Scale)	State of arousal, cry, breathing, facial expression, arms and leg movement.	28—38 weeks	Procedural and acute
SUN (Scale of Use in Newborns)	CNS state, breathing, HR, mean BP, movement, tone and face.	Neonates	Acute
PAT (Pain Assessment Tool)	Respirations, HR, saturations, BP, colour, posture tone, sleep pattern and cry.	Neonates	Acute

Adapted from Royal College of Nursing. The recognition and assessment of pain in children (clinical guidelines 2009) London: RCN Publishing.

Table 1

suggests it has more effective with a lower incidence of adverse effects compared to other NSAIDs. Ibuprofen clearance is reduced in neonates with a prolonged elimination half-life of around 30 hours in both preterm and term neonates. The NSAIDs, as a group, are weakly acidic, lipophilic, and highly protein bound (e.g. ibuprofen 98.7%). Ibuprofen use may alter bilirubin binding to albumen and should be avoided in jaundiced premature neonates. Caution must be applied to dosing regime and intervals in neonates (e.g. 5 mg/kg at intervals of 12 or 24 hours) with increased vigilance for renal dysfunction and gastric bleeding.

Tramadol: systemic tramadol use in neonates and infants is limited because disposition data in young infants are not available. It is primarily metabolized into O-desmethyl tramadol (M1) by CYP2D6. The active M1 metabolite has a mu-opioid affinity approximately 200 times greater than tramadol. Tramadol clearance is reduced in premature neonates but rapidly matures to reach 84% of the mature value by 44 weeks postmenstrual age. A target concentration of 300 mcg/litre is achieved after a bolus of tramadol hydrochloride 1 mg/kg and can be maintained by infusion of tramadol hydrochloride 0.09 mg kg/h at 25 weeks, 0.14 mg kg/h at 30 weeks and 0.18 mg/kg/h at 40 weeks postmenstrual age.[12] The impact of CYP2D6 polymorphism on the variability in pharmacokinetics, metabolism and pharmacodynamics of tramadol remains to be established. It should be noted that the current licence for the use of Tramadol is 12 years and within the author's institution it is not advocated for use in children < 1 year unless discussed with the pain service.

Opioid: morphine is used for moderate to severe acute pain and is metabolized by glucuronide transferase enzymes (UGT2B7) to morphine-6- and morphine-3-glucuronides; while the ratios of these metabolites to parent drug differ to adults, the impact of this change remains speculative. Clearance is reduced in neonates with an elimination half-life of around 9 hours in preterm infants and 6.5 in term neonates. Consequently, morphine dosing must be adjusted for age to avoid respiratory depression. A typical infusion rate in non-ventilated neonates is up to a max of 5 μg/kg/h or delivered via nurse controlled analgesia (NCA) with the availability of additional bolus dose to meet individual needs (see Table 3). However, this may be increased in NICUs where closer monitoring is provided. The risk of consequences secondary to respiratory depression is reduced by continuous apnoea and saturation monitor and being nursed in a clinical area with trained nursing staff.[13]

Codeine is an oral pro-drug of morphine and has been commonly used in neonates (at doses of 0.5 mg/kg 6 hourly) but a significant proportion of neonates cannot metabolize codeine to its active

Non-pharmacological pain management in neonates

Sucrose therapy
- Considered to be the role of endogenous opioids
- 30 + RCT on single dose for procedures

Swaddling
- Stimulation of proprioceptive system
- Reduced physiological response, i.e. heart rate, saturated oxygen
- Few studies in to efficacy of this procedure

Skin to skin contact
- Stimulation of proprioceptive system
- Reduced physiological response, i.e. heart rate
- 24 + RCT on single dose for procedures

Kangaroo care
- Stimulation of proprioceptive system
- Reduced physiological response, i.e. heart rate
- Crossover RCTs, consists of preterm neonates not ventilated
- Result in reduced heart rate, crying and pain score

Massage
- Suggested to provided tactile and kinesthetic stimuli
- Modulates behaviour to pain response
- Few studies in to efficacy of this procedure

Auditory
- Affects descending pain modulation mechanism
- No RCTs, few observation studies
- Limited proven efficacy, needs more research

Environment
- Lighting, day, clustering procedures and night cycles
- Effect, reduce bodies stress response
- 42 clinical trials varied levels of evidence

Box 1

Nurse controlled analgesic program

Morphine 1 mg/kg made up to 50 ml with 10% Dextrose gives a concentration of 20 μg/kg/ml

	Term neonate
Background	5 μg/kg/h
Bolus	5–10 μg/kg
Lockout	20 min
2 h maximum	25 μg/kg/2h

Table 3

metabolite, morphine.[14] Conversely there may be the occasional neonates that is an ultra-rapid metabolizer (CYP2D6) and this can result in increased morphine production and adverse effects. Concerns of respiratory depression and death in older children given codeine after tonsillectomy have resulted in reduced use[15] of this drug and licence change to 12 years and 18 years for tonsillectomy. Therefore, is not advocated for use in neonates.

Local anaesthetic (LA) techniques

Topical local anaesthetic creams reduce acute pain from venepuncture, venous cannulation and attenuate physiological response to circumcision. EMLA® (eutectic mixture of prilocaine and lidocaine) can cause methaemaglobinaemia (increased skin absorption due to thin epidermis and increased fetal haemoglobin that has a greater sensitivity to prilocaine) and vasoconstriction, whereas AMETOP® (amethocaine gel) does not cause vasoconstriction and has a longer duration of effect.

Local anaesthetic infiltration, peripheral nerve blockade and central neuraxial blocks have an important role in the treatment of acute postoperative pain or procedures in neonates. The aims

Common analgesic used for pain management in non-ventilated neonates

Drug	Route	Dose by post conceptual age			Interval/max dose	Duration/review
Paracetamol	PO/PR	28–32 weeks	Loading	Oral 15 mg/kg^{-1} Rectal 15 mg/kg^{-1}	12 h (max, 30 mg/kg/day)	Daily – 48 h
			Maintenance	Oral 15 mg/kg^{-1} Rectal 15 mg/kg^{-1}		
		32–53 weeks	Loading	Oral 20 mg/kg^{-1} Rectal 30 mg/kg^{-1}	8 h (max 60 mg/kg/day)	Daily – 48 h
			Maintenance	Oral 20 mg/kg^{-1} Rectal 20 mg/kg^{-1}		
	IV	<10 kg or 1 year		7.5 mg/kg^{-1}	6 h (max 30 mg/kg/day)	Daily – 24 h
Ibuprofen	PO	40–44 weeks		5 mg/kg^{-1}	12–24 h	Daily – 12 h
Codeine	PO	40–44 weeks		0.5–1 mg/kg^{-1}	8 h	Daily – 24 h
	IV	Term – 44 weeks	*Loading dose*	25–50 μg/kg^{-1}	Single dose or repeat 4–6 h	Daily – 24 h
	Continuous morphine infusion concentration = Dose 1.0 mg/kg morphine made up to 50 ml with normal saline 1 ml/hr = 20 μg/kg/h	Term – 44 weeks		0.05–0.25 ml/kg/h	Continuous	Daily – 24 h

Table 2

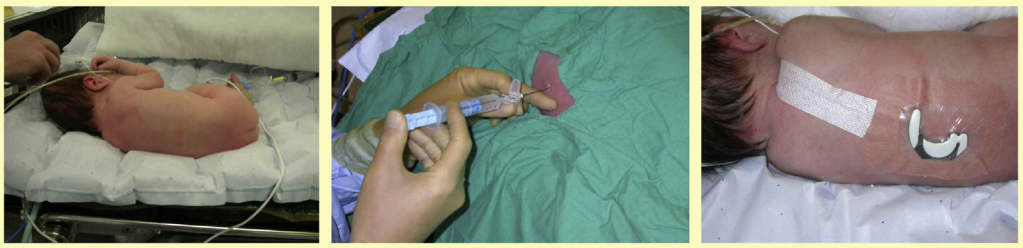

Figure 1 Insertion of an epidural in an anaesthetized neonate.

are to provide intraoperative nociceptive blockade that reduces anaesthetic requirements and residual effects of anaesthesia in the postoperative period. Postoperative analgesic requirement for opioids can be avoided or reduced lessening risks of respiratory depression and oversedation. There may be some increased risks to neonates (Figure 1) given epidural infusion analgesia, particularly in institutions where fewer than 200 epidurals per year are performed. However, large-scale audits of both central blockade and peripheral local anaesthetic techniques have demonstrated an impressive safety profile.[16] Commonly performed nerve blocks are penile block for circumcision, ilioinguinal-iliohypogastric nerve blocks for herniotomy, and intercostals blocks for chest drain insertion. Single injection caudal epidural block is very effective for sub-umbilical surgery and can provide pain relief for 6–8 hours. Additives to caudal local anaesthetic solutions such as clonidine, ketamine or opioids are not recommended in neonates.

For continuous epidural infusions there is an increased risk of local anaesthetic toxicity in neonates due to reduced hepatic clearance of amide local anaesthetic. Infusion rates should be half that of older children. Bupivacaine has been superseded by levobupivacaine or ropivacaine in many centres because these have a lower propensity to produce cardiovascular depression and seizure activity in overdose or after intravascular injection. The maximum infusion rate for all these agents is 0.25 mg/kg/h in the neonate for up to 48 hours (see Table 4).

Neonatal pain management is most effective and safe if a balanced multimodal approach is used (see Tables 5 and 6), individualized by pain assessment, in a carefully monitored environment where adverse effects can be rapidly identified and managed. ◆

Neonatal epidural infusion rates

Drug	Dose
Bupivacaine, levobupivacaine or ropivacaine Loading dose — 0.5 ml/kg (1.25 mg/kg)	0.25% (2.5 mg/ml)
Bupivacaine, levobupivacaine or ropivacaine Maintenance dose — 0.1–0.25 ml/kg/h	0.1% (1 mg/ml) (0.1–0.25 mg/kg/h)
Maximum infusion rate 0.25 mg/kg/h i.e. 0.25 ml/kg/h of 0.1% Bupivacaine, levobupivacaine or ropivacaine	

Table 4

Plan of procedural pain management in neonates

Procedure	Method of management
Venipuncture	• Use local aesthesia cream, either **Ametop** or **EMLA**. Check dose and duration of application required. • Consider non-pharmacological techniques such as 30% sucrose with NNS and KC swaddling.
Chest drain removal	• Use local aesthesia cream, either **Ametop** or **EMLA**. Check dose and duration of application required. • LA infiltration, check dose. • Consider IV morphine bolus dose (see text for dose). • Non-pharmacological techniques such as 30% sucrose with NNS and KC swaddling. • Auditory, mother voice or music.
Also assess and reassess pain to evaluate efficacy of the interventions used and adapt strategies to the neonate needs.	

Table 5

Plan of postoperative pain management in neonates

Procedure	Method of management
Formation of a colostomy	• Determine opioid history, e.g. loading dose in theatres. • If inadequate analgesia 10–50 μg/kg IV bolus as required. • Maintenance analgesia via morphine NCA (for dosing see text) and review 24 hourly. • Regular paracetamol, IV first then change to enteral as soon as possible. • Consider non-pharmacological techniques such as environment and skin to skin contact.
Repair of tracheo-oesophageal fistula	• Consider caudal epidural preoperative. Insertion in theatre environment prior to surgery (for dosing see text). • Regular paracetamol, IV first then change to enteral as soon as possible. • Consider non-pharmacological techniques such as environment, auditory (parents voice) and skin to skin contact. • Review daily and remove caudal epidural at 48 h and change to enteral or rectal analgesia.
Also assess and reassess pain to evaluate efficacy of the interventions used and adapt strategies to the neonate needs.	

Table 6

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