REVIEW ARTICLE

Neonatal pain

Suellen M. Walker

Portex Unit: Pain Research, Department of Anaesthesia and Pain Medicine, UCL Institute of Child Health, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Summary

Effective management of procedural and postoperative pain in neonates is required to minimize acute physiological and behavioral distress and may also improve acute and long-term outcomes. Painful stimuli activate nociceptive pathways, from the periphery to the cortex, in neonates and behavioral responses form the basis for validated pain assessment tools. However, there is an increasing awareness of the need to not only reduce acute behavioral responses to pain in neonates, but also to protect the developing nervous system from persistent sensitization of pain pathways and potential damaging effects of altered neural activity on central nervous system development. Analgesic requirements are influenced by age-related changes in both pharmacokinetic and pharmacodynamic response, and increasing data are available to guide safe and effective dosing with opioids and paracetamol. Regional analgesic techniques provide effective perioperative analgesia, but higher complication rates in neonates emphasize the importance of monitoring and choice of the most appropriate drug and dose. There have been significant improvements in the understanding and management of neonatal pain, but additional research evidence will further reduce the need to extrapolate data from older age groups. Translation into improved clinical care will continue to depend on an integrated approach to implementation that encompasses assessment and titration against individual response, education and training, and audit and feedback.

Introduction

Effective and safe management of procedural and postoperative pain is important for children of all ages for humanitarian reasons and to minimize acute physiological and behavioral distress. In addition, reducing pain can improve both acute and long-term outcomes and evidence to guide pediatric clinical practice is increasing (1,2). However, neonates and infants are at increased risk of experiencing moderate to severe pain during hospital care (3,4). Further, specific evidence is required to guide neonatal practice and reduce the need to extrapolate data from older age groups, but implementation of current best practice is also an ongoing challenge. Guidelines and local practice protocols are increasingly available, and although variability in uptake continues to be reported (5), improvements have also been noted; for example, with increased use of opioid analgesia for both procedural and postoperative pain in NICU (6,7) and protocols for safe administration in the ward setting (8).

Pain mechanisms in the neonatal period

Responses to painful stimuli can be demonstrated in nociceptive pathways from the periphery to the cortex in neonates, although the degree and nature of response change with age. Peripheral pain receptors (nociceptors) respond to mechanical, thermal and chemical stimuli following birth, and peripheral sensitization or primary hyperalgesia (reduced threshold and enhanced response to previously painful stimuli) develops within areas of tissue injury (9).

The spinal cord is an important site for the modulation of nociceptive input but is characterized in early development by a relative excess of excitation and

delayed development of local and descending inhibition (10–12). In addition, there are anatomical changes in the distribution of incoming sensory fibers in early development, as A-beta myelinated fibers (that respond to light touch and are restricted to laminae III-IV of the adult dorsal horn) extend into superficial laminae I-II and overlap with A-delta thin myelinated and unmyelinated C-fibers that respond to noxious stimuli (12). As a result, neonatal spinal reflex responses are more generalized, and the threshold is lower (i.e., a reflex response is evoked by a less intense stimulus). Stimulus–response relationships are still evident in human neonates, as noxious heel lance produces a greater reflex withdrawal response than touch (13). Neonatal tissue injury, such as repeated heel lance or inflammation, reduces threshold (i.e., increases sensitivity), but these effects may be minimized by analgesia (14,15).

Pain signals reach the somatosensory cortex in preterm and term neonates. Near-infrared spectroscopy (NIRS) (16,17) and electroencephalogram recordings (18) demonstrate alterations in cortical activity following heel lance for blood sampling. Postnatal age, sleep state, opioid analgesia, and previous experience can also influence the pattern, degree, and latency of response (19–21).

Acute effects and assessment of neonatal pain

Pain produces a range of physiological and behavioral responses in neonates that can be utilized in clinical assessment tools to quantify pain severity and evaluate analgesic efficacy. A range of validated tools are available for use in different practice settings (1,2,22,23), with some examples described in Table 1 (24–27). Additional measures, such as changes in stress hormones and measures of cortical activity, have been utilized in research settings (9). The adverse impact of inadequate analgesia/anesthesia on acute morbidity following neonatal surgery has long been recognized (28,29).

Long-term effects of neonatal pain

Changing levels of neural activity can alter the normal development of the central nervous system (CNS). As a result, there is increasing awareness of the need to not only reduce acute behavioral responses to neonatal pain, but also to protect from persistent sensitization of pain pathways and potential damaging effects of excess activity on brain development (9,29,30). For example, sucrose effectively reduces the acute behavioral response to painful procedures (31) but does not reduce spinal reflex response or cortical activity (13)

or prevent hyperalgesia (32) and therefore may not prevent adverse effects of repeated procedures. Comparative studies with other analgesics are required.

Neonatal surgery has been associated with alterations in future pain response. Following neonatal circumcision without analgesia, the behavioral response to immunization many months later is enhanced (33). Increased perioperative analgesic requirements were noted in infants who had also required surgery as neonates (34). More persistent changes in sensory processing were found in children 8–12 years following neonatal intensive care (35,36), and the degree of change was more marked in those who also required surgery during the neonatal period (37).

Studies in postnatal rodents allow evaluation of the effects of pain and injury at different stages of mammalian development. Age-dependent changes in response to neonatal injury have been demonstrated, with long-term alterations in sensory function that are not seen when the same injury is performed at older ages. Underlying mechanisms and modification by analgesia can also be assessed (9). Altering sensory input into the spinal cord during the neonatal period impairs normal development of both excitatory and inhibitory synaptic function (10,11). Plantar hindpaw incision, an established model of postoperative pain demonstrates differences in the acute and long-term impact of neonatal surgical injury (38–40). Prior neonatal incision effects both excitatory and inhibitory synaptic function (41–43) and increased microglial reactivity in the spinal cord (44) contributes to an enhanced degree and duration of hyperalgesia following subsequent injury. Peripheral nerve block modulates these effects (40,45), and ongoing studies will allow the evaluation of other analgesic interventions.

Adverse neurodevelopmental outcomes following neonatal intensive care are well documented (see Marlow, this edition). Increased exposure to procedural pain has been associated with poorer cognitive and motor scores (46), impairments of growth (47), reduced white matter and subcortical gray matter maturation (48), and altered corticospinal tract structure (49). In addition, poorer neurodevelopmental outcomes have been reported in surgical vs nonsurgical groups following preterm birth (50) and with surgical vs medical management of patent ductus arteriosus (PDA) and necrotizing enterocolitis (51–53). Patients with significant neonatal brain injury are often excluded, and statistical methods are used to correct for potential confounding factors. Specific contributions of pain, analgesia, and anesthesia can be difficult to determine, and respiratory disease (54) and hypotension (48,55) make independent contributions.

Table 1 Examples of neonatal pain assessment tools

Tool	Parameters	Score	Utility
Premature infant pain profile (PIPP) (24)	Gestational age, behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, nasolabial furrow	Total: 0–21 each parameter scored 0–3; ≤6 minimal pain; >12 moderate to severe pain	Procedural and postoperative pain
FLACC (25)	Face, legs, activity, cry, consolability	Total: 0–10 each parameter scored 0–2; >4 moderate pain; >7 severe pain	Procedural and postoperative pain
COMFORT scale (behavioral and physiological parameters) (26)	Alertness, calmness, respiratory distress, movement, muscle tone, facial tension, blood pressure, heart rate	Total: 8–40 each parameter scored 1–5; 17–26 adequate sedation; ≥27 inadequate sedation/analgesia	Pain and sedation in NICU
COMFORT behavior scale (27)	Alertness, calmness, respiratory response (ventilated neonate) or crying (not ventilated), movement, muscle tone, facial expression	Total: 8–30 each parameter scored 1–5; >17 moderate pain requiring intervention	Postoperative pain in NICU

Opioid analgesia

Pharmacokinetics and mechanisms

Intravenous opioid requirements during intensive care management (56) and the postoperative period (8,57) are lower in neonates than in infants and children. Pharmacokinetic parameters are influenced by age and clinical state, with decreased clearance in neonates, and additional variability following cardiac surgery and with changes in organ function and blood flow (e.g., reduced hepatic blood flow and morphine clearance with positive pressure ventilation) (58,59). A recent model based on bodyweight was able to predict clearance across all age ranges, including neonates (60). Laboratory studies also document age- and dose-dependent changes following systemic (61), epidural (62,63), or intrathecal (64) administration and allow evaluation of associated pharmacodynamic changes. Altered opioid receptor distribution and density in the dorsal root ganglion and spinal cord contribute to increased sensitivity (61,65,66) and are not solely related to changes in blood–brain barrier permeability for morphine (63) as an increased effect for the same CNS tissue concentration is present at younger ages (67).

Analgesic efficacy

Intravenous opioid infusions have an established role for perioperative analgesia in neonates (1). Protocols vary and include continuous infusions, intermittent bolus doses, or nurse-controlled analgesia (NCA) (8,57,68). NCA is delivered via the same type of pump as patient-controlled analgesia, with a prescribed bolus and dose interval, but addition of background infusions

in opioid-naïve neonates may increase the risk of respiratory depression (8,68)). Examples of local NCA protocols can be found at www.gosh.nhs.uk/health-professionals/clinical-specialties/pain-control-service-information-for-health-professionals/download-documentation/. Protocols need to be sufficiently flexible to allow for interindividual variability and titration against individual response, with regular assessment of pain score, efficacy and side-effects. Morphine and fentanyl are most often used. There is limited specific data to guide remifentanil dosing in neonates (69,70), but use in NICU for analgesia and sedation (71), perioperative analgesia (72), and intubation (73) has been reported, and the short duration of action may be advantageous for procedural pain management in NICU (74,75).

Side effects

Fear of side effects, particularly respiratory depression, has contributed to inadequate use of opioids in neonates. Large audits have demonstrated higher rates of opioid-induced respiratory depression in neonates than in older children (2.5% vs 0.27%), but long-term sequelae are rare with appropriate monitoring and management (8,68). Overall, doses did not differ between neonates with or without respiratory depression, but risk was increased by preterm birth and intercurrent comorbid conditions (8,68).

Opioid withdrawal in neonates is a significant problem following maternal opioid use during pregnancy (neonatal abstinence syndrome) and is also associated with significant neurodevelopmental impairment (76,77). However, iatrogenic opioid tolerance and withdrawal symptoms also occur in neonates, particularly with prolonged use, continuous rather than intermittent administration, and shorter acting agents such as

fentanyl (70,78,79). Assessment tools and management protocols are available (78,80).

Long-term effects of neonatal opioids

Evaluating the long-term impact of pain and analgesia in clinical cohorts is dependent on correction for clinical confounders and will also be influenced by the sensitivity of the outcome measure and age at follow-up. Following NICU, greater overall exposure to intravenous morphine was associated with poorer motor development at 8 months, but not at 18 months (46). Associations between routine use of morphine for sedation during mechanical ventilation and poor neurodevelopmental outcome (81) have not been confirmed in all analyses (55,82,83), and there is often limited data on indication (e.g., sedation, procedural, or postoperative pain), and variability in dose and duration of therapy (84). Initial follow-up of mechanically ventilated neonates at 5 years of age suggested an impairment on one component (visual analysis) of the IQ test (85), but subsequent evaluation of neuropsychological outcomes in the same population at 8–9 years reported no impairment related to neonatal morphine use (86).

Associations between exposure to general anesthesia in early life, increased levels of neuronal apoptosis (programmed cell death), and impaired neurodevelopmental outcomes have been demonstrated in a number of mammalian species (87–89). Laboratory models have also evaluated the impact of neonatal opioid exposure on neuronal apoptosis, but it is important to differentiate dose schedules associated with the development of dependence and tolerance (which may be relevant to prolonged NICU care) from perioperative analgesic dosing. Subcutaneous morphine 0.3–1.0 mg·kg^{-1} produces analgesia in neonatal rats (61). When tolerance is induced by subcutaneous morphine 10 mg·kg^{-1} bd from postnatal day P1 to P7 (90), neuronal apoptosis is increased in the cortex and amygdala, but not in regions important for memory (hippocampus) or nociceptive processing (periaqueductal gray, PAG) (91). In adult rats, repeated *intrathecal* morphine (0.03 mg·kg^{-1} bd for 7 days) produces tolerance and increases apoptosis in the spinal cord (92). However, in neonatal rodents, single doses of morphine up to 3 mg·kg^{-1} (300 times the analgesic dose of 0.01 mg·kg^{-1} at this age) did not increase apoptosis or produce any long-term impairment of spinal function, measured by sensory reflex thresholds and gait analysis (64). Whereas general anesthesia for 4 h with isoflurane, nitrous oxide, and midazolam increased cortical apoptosis in the neonatal piglet (93) and guinea pig (94), no significant increase was seen in sham control groups given fentanyl

(30 mcg·kg^{-1} bolus and 4 h infusion 15 mcg·kg^{-1}·h^{-1}). Daily subcutaneous morphine 0.5 mg·kg^{-1} from P1 to P3 or P1 to P5 did not alter levels of apoptosis in the brain. When combined with a pain stimulus (daily paw injection of formalin), this analgesic dose of morphine reduced injury-related apoptosis in the P1–P3 group, but not in the more prolonged pain group (P1–P5 formalin plus morphine) (95). Further studies are required to evaluate relationships between opioids and injury-induced apoptosis and investigate other mechanisms influencing neurodevelopmental outcomes.

Paracetamol

Pharmacokinetics and mechanisms

The pharmacokinetic profile of paracetamol in neonates has been evaluated following rectal (96), intravenous (97) and repeat IV doing over 4 days (98), and issues of neonatal dosing discussed (99). Clearance is related predominantly to weight (57% of variance), and age between postmenstrual age 28–44 weeks has minimal effect (2.2% variance) (97). A 20 mg·kg^{-1} loading and 10 mg·kg^{-1} IV dose every 6 h was predicted to achieve a serum concentration of 11 mg·L^{-1} in neonates (32–44 weeks PMA), although it was noted that safety data for this dose and drug are limited in neonates (97).

Different mechanisms contribute to the analgesic effect of paracetamol (see recent reviews (100,101)), including:

1. Prostaglandin-mediated effects, as despite the limited peripheral anti-inflammatory action compared with NSAIDs, central effects may relate to interaction with different cyclo-oxygenase sites (102).
2. The metabolite N-arachydonylphenolamine (AM404) is a ligand for the cannabinoid CB1 receptor and an uptake inhibitor of anandamide (an endogenous cannabinoid) (103).
3. Interaction with serotonergic mechanisms enhances inhibitory pathways descending from the brainstem to the spinal cord (104).
4. Effects on the spinal neurotransmitter nitric oxide.

Dose-dependent analgesic efficacy and specific spinal cord-mediated effects have been demonstrated in adult animal models (105,106), but further evaluation of dose response and mechanisms during postnatal development is warranted.

Analgesic efficacy

Analgesic efficacy of paracetamol is influenced by dose, route of administration, and type of pain stimulus. Oral

paracetamol 20 mg·kg^{-1} in neonates did not reduce the behavioral response to heel prick (107). Intravenous paracetamol (20 mg·kg^{-1} loading, 5–10 mg·kg^{-1} 6-h, and 20–40 mg·kg^{-1} per 24 h maximum) was effective for moderate pain in neonates in NICU, producing a significant trend to lower pain scores at 30 min, with a slight decrease in effect by 5–6 h (108). In the perioperative setting, multimodal analgesia with addition of paracetamol to opioid regimes can reduce opioid requirements and/or improve analgesia (109). Rectal paracetamol (30–40 mg·kg^{-1} loading and 20 mg·kg^{-1} 6–8 h) did not reduce NCA opioid requirements in neonates and infants following major surgery, although marked variability in plasma concentration following rectal dosing was noted (110). A recent study from the same group noted a significant reduction in opioid requirements in neonates and infants following major surgery with intravenous paracetamol (30 mg·kg^{-1} per day in four doses) (111). Current recommended doses for intravenous paracetamol in term neonates are 7.5 mg·kg^{-1} 6-h with a maximum daily dose of 30 mg·kg^{-1} (1) (www.rcoa.ac. uk/system/files/intravenousparacetamol.pdf). Ongoing studies and monitoring are required to further evaluate analgesic dose response and safety in neonates.

Recent case series have reported an association between use of IV paracetamol 60 mg·kg^{-1}·d^{-1} for 3–6 days and PDA closure in preterm neonates (112–114). Although significant morbidity may be associated with the alternative treatment (indomethacin/ibuprofen or surgical closure), caution with these high doses of paracetamol is also warranted, and there is no confirmed mechanism for this effect of paracetamol that allows prediction of the appropriate dose (113).

Side effects

In preterm and term neonates undergoing procedures in NICU, intravenous paracetamol 10 or 20 mg·kg^{-1} produced statistically significant but modest reductions in heart rate (average 7 b·min^{-1} at 30–120 min) and blood pressure (3 mmHg at 60 min). Changes were more marked in neonates with preexisting hypotension, suggesting impaired hemodynamics may be a relative contraindication to IV paracetamol (115).

Paracetamol overdose and hepatotoxicity has been reported in neonates (99,116,117) and infants (118). Awareness of the risk of accidental administration of milliliter rather than milligram resulting in a 10× overdose, and use of smaller intravenous paracetamol vials for neonates, has been highlighted by The UK Medicines and Healthcare Products Regulatory Agency (MHRA; www.mhra.gov.uk/Safetyinformation/Drug SafetyUpdate/CON088171).

Mechanisms of paracetamol toxicity are discussed in recent reviews (99,113). Briefly, oxidative metabolism of paracetamol (normally 5–10% vs. 50–60% glucuronidation and 25–30% sulfation) results in formation of the intermediate N-acetyl-p-benzoquinone imine (NAPQI). Although usually conjugated to glutathione and excreted in the bile, paracetamol overdose or glutathione lack results in accumulation of NAPQI and toxicity due to apoptosis and necrosis of hepatocytes. Although a reduced rate of oxidation and increased ability to replete glutathione may be protective for neonates (119), there is little data on relationships between paracetamol dose and NAPQI levels, or capacity for NAPQI detoxification in neonates, and immaturity of hepatic transporters or poor nutritional status may increase susceptibility (99,113).

Long-term effects

An epidemiologic link has been reported between paracetamol use in early life and increased risk of asthma in childhood (120,121). Others have reported that an increased number of respiratory infections, rather than paracetamol *per se*, is the important contributing factor (122,123). Differentiating association and causation is also difficult as the proportion of infants and children who receive paracetamol is high: 51% by 12 weeks of age and 97% by 2 years in a cohort with a family history of allergy (123); and over 1% before 8 weeks age and almost 95% by 4.5 years in a UK cohort (124).

Regional analgesia

Techniques and efficacy

A range of regional analgesic techniques can be effectively used in neonates (see recent reviews plus special edition of Pediatric Anesthesia January 2012) (125–127). Although analgesic efficacy has been demonstrated for many, there has been limited direct comparison of techniques or evaluation of relative benefits and risks in controlled trials in neonates (1). Dorsal penile nerve block was more effective than topical local anesthetic for circumcision performed in awake neonates (128). Ilioinguinal and rectus sheath blocks are the commonest intraoperative regional blocks for neonates (129), transversus abdominus plane (TAP) blocks are feasible (130), and local anesthetic wound infiltration is commonly performed, but additional larger studies are required to confirm benefit (131). Additional benefit may be gained if long-acting local anesthetic preparations are shown to be effective and safe in neonates (132–134).

Spinal/intrathecal, epidural, and caudal routes are utilized for neuraxial anesthesia and/or analgesia in

neonates (127,129,135,136). Potential advantages include reducing general anesthetic and opioid requirements, and case series report a reduction in the need for postoperative mechanical ventilation and specific benefit for neonates susceptible to respiratory complications (127,137).

Complications

Large series from the United Kingdom (138), Europe (129), United States (139), and Canada (140) demonstrate low complication rates following neuraxial analgesia in children, but rates are higher for central vs peripheral blocks (129). In early series, neonates were at greater risk and also had worse outcomes (141,142). Recent series have also reported higher complication rates and more pump programming errors in neonates (129,138,140), thus emphasizing the need for careful monitoring and follow-up.

Prolonged general anesthesia in neonatal rodents increases apoptosis in the spinal cord as well as the brain (143,144). This, plus the lack of systematic data evaluating spinal analgesic toxicity in early development has emphasized the need for preclinical evaluation of spinally administered drugs (127,145,146). No histological injury or increased apoptosis was found following spinal anesthesia with bupivacaine (143) or levobupivacaine (147) in neonatal rodents. Maximum tolerated doses of intrathecal morphine and clonidine (up to 300 times the analgesic dose) did not alter spinal cord histology or function (64,148). By contrast, analgesic doses of intrathecal ketamine increased apoptosis and altered long-term sensory function (149). Although no adverse effects directly related to caudal additives have been reported, there has been limited follow-up in clinical trials. As a result of adverse histological effects in both neonatal and adult animals following neuraxial delivery (150), clinical use of caudal ketamine has reduced (136,145,151).

Future directions

Significant advances continue to be made in the understanding and management of neonatal pain. Factors that may contribute to further improvements include:

1. Increased high-quality evidence from neonatal trials rather than reliance on extrapolation of doses and techniques from older age groups (1). As ethical and organizational difficulties make recruitment difficult, and samples may be small and heterogeneous, multicentre trials may be required.
2. Availability of pharmacokinetic and pharmacodynamic data from clinical and laboratory studies will continue to inform age- and injury-specific dosing (59,152).
3. Concerns regarding acute side effects have limited use of analgesia in the past, but improvements in monitoring and protocols for safe delivery have significantly improved clinical utility.
4. Additional direct comparison of analgesic techniques in neonates will further delineate the relative safety and efficacy of different drugs and techniques, particularly as the developing nervous system responds differently to pain, anesthesia, and analgesia, and potential adverse impacts on neurodevelopmental outcome may also differ (9).
5. Increased validation and use of neonatal pain assessment tools have improved clinical practice and facilitated titration of analgesia against individual response. However, these tools necessarily rely on observer assessment of behavioral and/or physiological responses as proxy measures of pain and are less specific and sensitive than assessment at older ages (23) (4). A range of neurophysiological and hormonal measures are being evaluated in research studies and may provide useful comparative data in the future.

Importantly, in addition to the above measures, improvements in clinical practice are critically dependent on implementation of current best evidence. An integrated approach is required (153), with targeted education and practice interventions, use of validated assessment tools, local protocols for analgesic administration, and regular audit and feedback, to ensure translation into improved outcomes for neonates requiring anesthesia, surgery, and intensive care.

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Conflict of interest

No conflicts of interest declared.

References

1 Association of Paediatric Anaesthetists of Great Britain and Ireland. Good practice in postoperative and procedural pain management, 2nd edition. *Pediatr Anesth* 2012; **22**(Suppl 1): 1–79.

2 Macintyre PE, Schug SA, Scott DA *et al.* Acute Pain Management: Scientific

Evidence, 3rd edn. Melbourne: ANZCA & FPM, 2010.

3 Groenewald CB, Rabbitts JA, Schroeder DR *et al*. Prevalence of moderate-severe pain in hospitalized children. *Pediatr Anesth* 2012; **22**: 661–668.

4 Stevens BJ, Harrison D, Rashotte J *et al*. Pain assessment and intensity in hospitalized children in Canada. *J Pain* 2012; **13**: 857–865.

5 Foster J, Spence K, Henderson-Smart D *et al*. Procedural pain in neonates in Australian hospitals: a survey update of practices. *J Paediatr Child Health* 2013; **49**: E35–E39.

6 Lago P, Boccuzzo G, Garetti E *et al*. Pain management during invasive procedures at Italian NICUs: has anything changed in the last five years? *J Matern Fetal Neonatal Med* 2013; **26**: 303–305.

7 Deindl P, Unterasinger L, Kappler G *et al*. Successful implementation of a neonatal pain and sedation protocol at 2 NICUs. *Pediatrics* 2013; **132**: e211–e218.

8 Howard RF, Lloyd-Thomas A, Thomas M *et al*. Nurse-controlled analgesia (NCA) following major surgery in 10,000 patients in a children's hospital. *Pediatr Anesth* 2010; **20**: 126–134.

9 Fitzgerald M, Walker SM. Infant pain management: a developmental neurobiological approach. *Nat Clin Pract Neurol* 2009; **5**: 35–50.

10 Baccei ML. Modulation of developing dorsal horn synapses by tissue injury. *Ann N Y Acad Sci* 2010; **1198**: 159–167.

11 Koch SC, Tochiki KK, Hirschberg S *et al*. C-fiber activity-dependent maturation of glycinergic inhibition in the spinal dorsal horn of the postnatal rat. *Proc Natl Acad Sci USA* 2012; **109**: 12201–12206.

12 Fitzgerald M. The development of nociceptive circuits. *Nat Rev Neurosci* 2005; **6**: 507–520.

13 Slater R, Cornelissen L, Fabrizi L *et al*. Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial. *Lancet* 2010; **376**: 1225–1232.

14 Fitzgerald M, Millard C, MacIntosh N. Hyperalgesia in premature infants. *Lancet* 1988; **1**: 292.

15 Andrews K, Fitzgerald M. Wound sensitivity as a measure of analgesic effects following surgery in human neonates and infants. *Pain* 2002; **99**: 185–195.

16 Slater R, Cantarella A, Gallella S *et al*. Cortical pain responses in human infants. *J Neurosci* 2006; **26**: 3662–3666.

17 Bartocci M, Bergqvist LL, Lagercrantz H *et al*. Pain activates cortical areas in the preterm newborn brain. *Pain* 2006; **122**: 109–117.

18 Slater R, Worley A, Fabrizi L *et al*. Evoked potentials generated by noxious stimulation in the human infant brain. *Eur J Pain* 2010; **14**: 321–326.

19 McKeever S, Johnston L, Davidson A. A review of the utility of EEG depth of anaesthesia monitors in the paediatric intensive care environment. *Intensive Crit Care Nurs* 2012; **28**: 294–303.

20 Fabrizi L, Slater R, Worley A *et al*. A shift in sensory processing that enables the developing human brain to discriminate touch from pain. *Curr Biol* 2011; **21**: 1552–1558.

21 Slater R, Fabrizi L, Worley A *et al*. Premature infants display increased noxious-evoked neuronal activity in the brain compared to healthy age-matched term-born infants. *Neuroimage* 2010; **52**: 583–589.

22 Maxwell LG, Malavolta CP & Fraga MV. Assessment of pain in the neonate. *Clin Perinatol* 2013; **40**: 457–469.

23 Royal College of Nursing. The Recognition and Assessment of Acute Pain in Children. Clinical Practice Guidelines. London: RCN, 2009.

24 Stevens B, Johnston C, Petryshen P *et al*. Premature infant pain profile: development and initial validation. *Clin J Pain* 1996; **12**: 13–22.

25 Merkel SI, Voepel-Lewis T, Shayevitz JR *et al*. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs* 1997; **23**: 293–297.

26 Ambuel B, Hamlett KW, Marx CM *et al*. Assessing distress in pediatric intensive care environments: the COMFORT scale. *J Pediatr Psychol* 1992; **17**: 95–109.

27 van Dijk M, de Boer JB, Koot HM *et al*. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. *Pain* 2000; **84**: 367–377.

28 Anand KJ, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987; **1**: 62–66.

29 Walker SM. Biological and neurodevelopmental implications of neonatal pain. *Clin Perinatol* 2013; **40**: 471–491.

30 Holsti L, Grunau RE, Shany E. Assessing pain in preterm infants in the neonatal intensive care unit: moving to a 'brain-oriented' approach. *Pain Manag* 2011; **1**: 171–179.

31 Stevens B, Yamada J, Lee GY *et al*. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev* 2013; **1**: CD001069.

32 Taddio A, Shah V, Atenafu E *et al*. Influence of repeated painful procedures and sucrose analgesia on the development of

hyperalgesia in newborn infants. *Pain* 2009; **144**: 43–48.

33 Taddio A, Katz J, Ilersich AL *et al*. Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet* 1997; **349**: 599–603.

34 Peters JW, Schouw R, Anand KJ *et al*. Does neonatal surgery lead to increased pain sensitivity in later childhood? *Pain* 2005; **114**: 444–454.

35 Hermann C, Hohmeister J, Demirakca S *et al*. Long-term alteration of pain sensitivity in school-aged children with early pain experiences. *Pain* 2006; **125**: 278–285.

36 Hohmeister J, Demirakca S, Zohsel K *et al*. Responses to pain in school-aged children with experience in a neonatal intensive care unit: cognitive aspects and maternal influences. *Eur J Pain* 2009; **13**: 94–101.

37 Walker SM, Franck LS, Fitzgerald M *et al*. Long-term impact of neonatal intensive care and surgery on somatosensory perception in children born extremely preterm. *Pain* 2009; **141**: 79–87.

38 Ririe DG, Vernon TL, Tobin JR *et al*. Age-dependent responses to thermal hyperalgesia and mechanical allodynia in a rat model of acute postoperative pain. *Anesthesiology* 2003; **99**: 443–448.

39 Ririe DG, Bremner LR, Fitzgerald M. Comparison of the immediate effects of surgical incision on dorsal horn neuronal receptive field size and responses during postnatal development. *Anesthesiology* 2008; **109**: 698–706.

40 Walker SM, Tochiki KK, Fitzgerald M. Hindpaw incision in early life increases the hyperalgesic response to repeat surgical injury: critical period and dependence on initial afferent activity. *Pain* 2009; **147**: 99–106.

41 Li J, Walker SM, Fitzgerald M *et al*. Activity-dependent modulation of glutamatergic signaling in the developing ventral dorsal horn by early tissue injury. *J Neurophysiol* 2009; **102**: 2208–2219.

42 Li J, Blankenship ML, Baccei ML. Deficits in glycinergic inhibition within adult spinal nociceptive circuits after neonatal tissue damage. *Pain* 2013; **154**: 1129–1139.

43 Li J, Baccei ML. Neonatal tissue damage facilitates nociceptive synaptic input to the developing superficial dorsal horn via NGF-dependent mechanisms. *Pain* 2011; **152**: 1846–1855.

44 Beggs S, Currie G, Salter MW *et al*. Priming of adult pain responses by neonatal pain experience: maintenance by central neuroimmune activity. *Brain* 2012; **135**: 404–417.

45 Ririe DG, Barclay D, Prout H *et al*. Preoperative sciatic nerve block decreases mechanical allodynia more in young rats: is

preemptive analgesia developmentally modulated? *Anesth Analg* 2004; **99**: 140–145.

46 Grunau RE, Whitfield MF, Petrie-Thomas J *et al*. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. *Pain* 2009; **143**: 138–146.

47 Vinall J, Miller SP, Chau V *et al*. Neonatal pain in relation to postnatal growth in infants born very preterm. *Pain* 2012; **153**: 1374–1381.

48 Brummelte S, Grunau RE, Chau V *et al*. Procedural pain and brain development in premature newborns. *Ann Neurol* 2012; **71**: 385–396.

49 Zwicker JG, Grunau RE, Adams E *et al*. Score for neonatal acute physiology-II and neonatal pain predict corticospinal tract development in premature newborns. *Pediatr Neurol* 2013; **48**: 123–129, e121.

50 Filan PM, Hunt RW, Anderson PJ *et al*. Neurologic outcomes in very preterm infants undergoing surgery. *J Pediatr* 2012; **160**: 409–414.

51 Kabra NS, Schmidt B, Roberts RS *et al*. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. *J Pediatr* 2007; **150**: 229–234, e221.

52 Rees CM, Pierro A, Eaton S. Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis. *Arch Dis Child Fetal Neonatal Ed* 2007; **92**: F193–F198.

53 Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. *Arch Pediatr Adolesc Med* 2007; **161**: 583–590.

54 Anjari M, Counsell SJ, Srinivasan L *et al*. The association of lung disease with cerebral white matter abnormalities in preterm infants. *Pediatrics* 2009; **124**: 268–276.

55 Hall RW, Kronsberg SS, Barton BA *et al*. Morphine, hypotension, and adverse outcomes among preterm neonates: who's to blame? Secondary results from the NEOPAIN trial. *Pediatrics* 2005; **115**: 1351–1359.

56 Bouwmeester NJ, Hop WC, van Dijk M *et al*. Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. *Intensive Care Med* 2003; **29**: 2009–2015.

57 Taylor J, Liley A, Anderson BJ. The relationship between age and morphine infusion rate in children. *Pediatr Anesth* 2013; **23**: 40–44.

58 Holford NH, Ma SC, Anderson BJ. Prediction of morphine dose in humans. *Pediatr Anesth* 2012; **22**: 209–222.

59 Anderson BJ. Pharmacology in the very young: anaesthetic implications. *Eur J Anaesthesiol* 2012; **29**: 261–270.

60 Wang C, Sadhavisvam S, Krekels EH *et al*. Developmental changes in morphine clearance across the entire paediatric age range are best described by a bodyweight-dependent exponent model. *Clin Drug Investig* 2013; **33**: 523–534.

61 Nandi R, Beacham D, Middleton J *et al*. The functional expression of mu opioid receptors on sensory neurons is developmentally regulated; morphine analgesia is less selective in the neonate. *Pain* 2004; **111**: 38–50.

62 Marsh D, Dickenson A, Hatch D *et al*. Epidural opioid analgesia in infant rats II: responses to carrageenan and capsaicin. *Pain* 1999; **82**: 33–38.

63 Marsh D, Dickenson A, Hatch D *et al*. Epidural opioid analgesia in infant rats I: mechanical and heat responses. *Pain* 1999; **82**: 23–32.

64 Westin BD, Walker SM, Deumens R *et al*. Validation of a preclinical spinal safety model: effects of intrathecal morphine in the neonatal rat. *Anesthesiology* 2010; **113**: 183–199.

65 Beland B, Fitzgerald M. Mu- and delta-opioid receptors are downregulated in the largest diameter primary sensory neurons during postnatal development in rats. *Pain* 2001; **90**: 143–150.

66 Rahman W, Dashwood MR, Fitzgerald M *et al*. Postnatal development of multiple opioid receptors in the spinal cord and development of spinal morphine analgesia. *Brain Res Dev Brain Res* 1998; **108**: 239–254.

67 Windh RT, Kuhn CM. Increased sensitivity to mu opiate antinociception in the neonatal rat despite weaker receptor-guanyl nucleotide binding protein coupling. *J Pharmacol Exp Ther* 1995; **273**: 1353–1360.

68 Morton NS, Errera A. APA national audit of pediatric opioid infusions. *Pediatr Anesth* 2010; **20**: 119–125.

69 Hume-Smith H, McCormack J, Montgomery C *et al*. The effect of age on the dose of remifentanil for tracheal intubation in infants and children. *Pediatr Anesth* 2010; **20**: 19–27.

70 Allegaert K, Tibboel D, van den Anker J. Pharmacological treatment of neonatal pain: in search of a new equipoise. *Semin Fetal Neonatal Med* 2013; **18**: 42–47.

71 Welzing L, Oberthuer A, Junghaenel S *et al*. Remifentanil/midazolam versus fentanyl/midazolam for analgesia and sedation of mechanically ventilated neonates and young infants: a randomized controlled trial. *Intensive Care Med* 2012; **38**: 1017–1024.

72 Sammartino M, Garra R, Sbaraglia F *et al*. Experience of remifentanil in extremely low-birth-weight babies undergoing laparotomy. *Pediatr Neonatol* 2011; **52**: 176–179.

73 Norman E, Wikstrom S, Rosen I *et al*. Premedication for intubation with morphine causes prolonged depression of electrocortical background activity in preterm infants. *Pediatr Res* 2013; **73**: 87–94.

74 Lago P, Tiozzo C, Boccuzzo G *et al*. Remifentanil for percutaneous intravenous central catheter placement in preterm infant: a randomized controlled trial. *Pediatr Anesth* 2008; **18**: 736–744.

75 Allegaert K. The clinical pharmacology of short acting analgo-sedatives in neonates. *Curr Clin Pharmacol* 2011; **6**: 222–226.

76 Hudak ML, Tan RC, Committee On Drugs *et al*. Neonatal drug withdrawal. *Pediatrics* 2012; **129**: e540–e560.

77 Cramton RE, Gruchala NE. Babies breaking bad: neonatal and iatrogenic withdrawal syndromes. *Curr Opin Pediatr* 2013; **25**: 532–542.

78 Anand KJ, Willson DF, Berger J *et al*. Tolerance and withdrawal from prolonged opioid use in critically ill children. *Pediatrics* 2010; **125**: e1208–e1225.

79 Jenkins IA, Playfor SD, Bevan C *et al*. Current United Kingdom sedation practice in pediatric intensive care. *Pediatr Anesth* 2007; **17**: 675–683.

80 Franck LS, Scoppettuolo LA, Wypij D *et al*. Validity and generalizability of the Withdrawal Assessment Tool-1 (WAT-1) for monitoring iatrogenic withdrawal syndrome in pediatric patients. *Pain* 2012; **153**: 142–148.

81 Anand KJ, Hall RW, Desai N *et al*. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEO-PAIN randomised trial. *Lancet* 2004; **363**: 1673–1682.

82 Bellu R, de Waal KA, Zanini R. Opioids for neonates receiving mechanical ventilation. *Cochrane Database Syst Rev* 2008: (1); CD004212.

83 Roze JC, Denizot S, Carbajal R *et al*. Prolonged sedation and/or analgesia and 5-year neurodevelopment outcome in very preterm infants: results from the EPIPAGE cohort. *Arch Pediatr Adolesc Med* 2008; **162**: 728–733.

84 Suarez A, Knoppert DC, Lee DS *et al*. Opioid infusions in the neonatal intensive care unit. *J Pediatr Pharmacol Ther* 2010; **15**: 142–146.

85 de Graaf J, van Lingen RA, Simons SH *et al*. Long-term effects of routine morphine infusion in mechanically ventilated neonates on children's functioning: five-year follow-up of a randomized controlled trial. *Pain* 2011; **152**: 1391–1397.

86 de Graaf J, van Lingen RA, Valkenburg AJ *et al*. Does neonatal morphine use affect neuropsychological outcomes at 8 to 9 years of age? *Pain* 2013; **154**: 449–458.

87 Jevtovic-Todorovic V, Absalom AR, Blomgren K *et al*. Anaesthetic neurotoxicity and neuroplasticity: an expert group report and statement based on the BJA Salzburg Seminar. *Br J Anaesth* 2013; **111**: 143–151.

88 Sanders RD, Hassell J, Davidson AJ *et al*. Impact of anaesthetics and surgery on neurodevelopment: an update. *Br J Anaesth* 2013; **110**(Suppl 1): i53–i72.

89 Stratmann G. Review article: neurotoxicity of anesthetic drugs in the developing brain. *Anesth Analg* 2011; **113**: 1170–1179.

90 Bajic D, Berde CB, Commons KG. Periaqueductal gray neuroplasticity following chronic morphine varies with age: role of oxidative stress. *Neuroscience* 2012; **226**: 165–177.

91 Bajic D, Commons KG, Soriano SG. Morphine-enhanced apoptosis in selective brain regions of neonatal rats. *Int J Dev Neurosci* 2013; **31**: 258–266.

92 Lim G, Wang S, Lim JA *et al*. Activity of adenylyl cyclase and protein kinase A contributes to morphine-induced spinal apoptosis. *Neurosci Lett* 2005; **389**: 104–108.

93 Rizzi S, Ori C, Jevtovic-Todorovic V. Timing versus duration: determinants of anesthesia-induced developmental apoptosis in the young mammalian brain. *Ann N Y Acad Sci* 2010; **1199**: 43–51.

94 Rizzi S, Carter LB, Ori C *et al*. Clinical anesthesia causes permanent damage to the fetal guinea pig brain. *Brain Pathol* 2008; **18**: 198–210.

95 Duhrsen L, Simons SH, Dzietko M *et al*. Effects of repetitive exposure to pain and morphine treatment on the neonatal rat brain. *Neonatology* 2013; **103**: 35–43.

96 Hansen TG, O'Brien K, Morton NS *et al*. Plasma paracetamol concentrations and pharmacokinetics following rectal administration in neonates and young infants. *Acta Anaesthesiol Scand* 1999; **43**: 855–859.

97 Allegaert K, Palmer GM, Anderson BJ. The pharmacokinetics of intravenous paracetamol in neonates: size matters most. *Arch Dis Child* 2011; **96**: 575–580.

98 Palmer GM, Atkins M, Anderson BJ *et al*. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth* 2008; **101**: 523–530.

99 Anderson BJ, Allegaert K. Intravenous neonatal paracetamol dosing: the magic of 10 days. *Pediatr Anesth* 2009; **19**: 289–295.

100 Anderson BJ. Paracetamol (Acetaminophen): mechanisms of action. *Pediatr Anesth* 2008; **18**: 915–921.

101 Smith HS. Potential analgesic mechanisms of acetaminophen. *Pain Physician* 2009; **12**: 269–280.

102 Engstrom Ruud L, Wilhelms DB, Eskilsson A *et al*. Acetaminophen reduces lipopolysaccharide-induced fever by inhibiting cyclooxygenase-2. *Neuropharmacology* 2013; **71**: 124–129.

103 Ruggieri V, Vitale G, Pini LA *et al*. Differential involvement of opioidergic and serotonergic systems in the antinociceptive activity of N-arachidonoyl-phenolamine (AM404) in the rat: comparison with paracetamol. *Naunyn Schmiedebergs Arch Pharmacol* 2008; **377**: 219–229.

104 Dogrul A, Seyrek M, Akgul EO *et al*. Systemic paracetamol-induced analgesic and antihyperalgesic effects through activation of descending serotonergic pathways involving spinal 5-HT(7) receptors. *Eur J Pharmacol* 2012; **677**: 93–101.

105 Crawley B, Saito O, Malkmus S *et al*. Acetaminophen prevents hyperalgesia in central pain cascade. *Neurosci Lett* 2008; **442**: 50–53.

106 Malmberg AB, Yaksh TL. Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. *J Pharmacol Exp Ther* 1992; **263**: 136–146.

107 Shah V, Taddio A, Ohlsson A. Randomised controlled trial of paracetamol for heel prick pain in neonates. *Arch Dis Child Fetal Neonatal Ed* 1998; **79**: F209–F211.

108 Allegaert K, Naulaers G, Vanhaesebrouck S *et al*. The paracetamol concentration-effect relation in neonates. *Pediatr Anesth* 2013; **23**: 45–50.

109 Wong I, St John-Green C, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. *Pediatr Anesth* 2013; **23**: 475–495.

110 van der Marel CD, Peters JW, Bouwmeester NJ *et al*. Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. *Br J Anaesth* 2007; **98**: 372–379.

111 Ceelie I, de Wildt SN, van Dijk M *et al*. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. *JAMA* 2013; **309**: 149–154.

112 Oncel MY, Yurttutan S, Degirmencioglu H *et al*. Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants. *Neonatology* 2013; **103**: 166–169.

113 Allegaert K, Anderson B, Simons S *et al*. Paracetamol to induce ductus arteriosus closure: is it valid? *Arch Dis Child* 2013; **98**: 462–466.

114 Oncel MY, Yurttutan S, Uras N *et al*. An alternative drug (paracetamol) in the management of patent ductus arteriosus in ibuprofen-resistant or contraindicated preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**: F94.

115 Allegaert K, Naulaers G. Haemodynamics of intravenous paracetamol in neonates. *Eur J Clin Pharmacol* 2010; **66**: 855–858.

116 Nevin DG, Shung J. Intravenous paracetamol overdose in a preterm infant during anesthesia. *Pediatr Anesth* 2010; **20**: 105–107.

117 Porta R, Sanchez L, Nicolas M *et al*. Lack of toxicity after paracetamol overdose in a extremely preterm neonate. *Eur J Clin Pharmacol* 2012; **68**: 901–902.

118 Beringer RM, Thompson JP, Parry S *et al*. Intravenous paracetamol overdose: two case reports and a change to national treatment guidelines. *Arch Dis Child* 2011; **96**: 307–308.

119 Ji P, Wang Y, Li Z *et al*. Regulatory review of acetaminophen clinical pharmacology in young pediatric patients. *J Pharm Sci* 2012; **101**: 4383–4389.

120 Etminan M, Sadatsafavi M, Jafari S, *et al*. Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. *Chest* 2009; **136**: 1316–1323.

121 Beasley R, Clayton T, Crane J *et al*. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 2008; **372**: 1039–1048.

122 Schnabel E, Heinrich J, Group LS. Respiratory tract infections and not paracetamol medication during infancy are associated with asthma development in childhood. *J Allergy Clin Immunol* 2010; **126**: 1071–1073.

123 Lowe AJ, Carlin JB, Bennett CM *et al*. Paracetamol use in early life and asthma: prospective birth cohort study. *BMJ* 2010; **341**: c4616.

124 Headley J, Northstone K. Medication administered to children from 0 to 7.5 years in the Avon Longitudinal Study of Parents and Children (ALSPAC). *Eur J Clin Pharmacol* 2007; **63**: 189–195.

125 Lonnqvist PA. Themed issue 'Pediatric Regional Anesthesia'- starting 2012 with a bang!. *Pediatr Anesth* 2012; **22**: 1–2.

126 Lonnqvist PA. Regional anaesthesia and analgesia in the neonate. *Best Pract Res Clin Anaesthesiol* 2010; **24**: 309–321.

127 Walker SM, Yaksh TL. Neuraxial analgesia in neonates and infants: a review of clinical and preclinical strategies for the development of safety and efficacy data. *Anesth Analg* 2012; **115**: 638–662.

128 Brady-Fryer B, Wiebe N, Lander JA. Pain relief for neonatal circumcision. *Cochrane Database Syst Rev* 2004: (4); CD004217.

129 Ecoffey C, Lacroix F, Giaufre E *et al*. Epidemiology and morbidity of regional anesthesia in children: a follow-up one-year prospective survey of the French-Language Society of Paediatric Anaesthesiologists (ADARPEF). *Pediatr Anesth* 2010; **20**: 1061–1069.

130 Mai CL, Young MJ, Quraishi SA. Clinical implications of the transversus abdominis plane block in pediatric anesthesia. *Pediatr Anesth* 2012; **22**: 831–840.

131 Leelanukrom R, Suraseranivongse S, Boonrukwanich V *et al*. Effect of wound infiltration with bupivacaine on postoperative analgesia in neonates and infants undergoing major abdominal surgery: a pilot randomized controlled trial. *J Anesth* 2012; **26**: 541–544.

132 Rodriguez-Navarro AJ, Berde CB, Wiedmaier G *et al*. Comparison of neosaxitoxin versus bupivacaine via port infiltration for postoperative analgesia following laparoscopic cholecystectomy: a randomized, double-blind trial. *Reg Anesth Pain Med* 2011; **36**: 103–109.

133 Roberson DP, Binshtok AM, Blasl F *et al*. Targeting of sodium channel blockers into nociceptors to produce long-duration analgesia: a systematic study and review. *Br J Pharmacol* 2011; **164**: 48–58.

134 Berde CB, Athiraman U, Yahalom B *et al*. Tetrodotoxin-bupivacaine-epinephrine combinations for prolonged local anesthesia. *Mar Drugs* 2011; **9**: 2717–2728.

135 Kokki H. Spinal blocks. *Pediatr Anesth* 2012; **22**: 56–64.

136 Johr M, Berger TM. Caudal blocks. *Pediatr Anesth* 2012; **22**: 44–50.

137 Bosenberg A. Benefits of regional anesthesia in children. *Pediatr Anesth* 2012; **22**: 10–18.

138 Llewellyn N, Moriarty A. The national pediatric epidural audit. *Pediatr Anesth* 2007; **17**: 520–533.

139 Polaner DM, Taenzer AH, Walker BJ *et al*. Pediatric Regional Anesthesia Network (PRAN): a multi-institutional study of the use and incidence of complications of pediatric regional anesthesia. *Anesth Analg* 2012; **115**: 1353–1364.

140 Wong GK, Arab AA, Chew SC *et al*. Major complications related to epidural analgesia in children: a 15-year audit of 3,152 epidurals. *Can J Anaesth* 2013; **60**: 355–363.

141 Flandin-Blety C, Barrier G. Accidents following extradural analgesia in children. The results of a retrospective study. *Pediatr Anesth* 1995; **5**: 41–46.

142 van Niekerk J, Bax-Vermeire BM, Geurts JW *et al*. Epidurography in premature infants. *Anaesthesia* 1990; **45**: 722–725.

143 Yahalom B, Athiraman U, Soriano SG *et al*. Spinal anesthesia in infant rats: development of a model and assessment of neurologic outcomes. *Anesthesiology* 2011; **114**: 1325–1335.

144 Sanders RD, Xu J, Shu Y *et al*. General anesthetics induce apoptotic neurodegeneration in the neonatal rat spinal cord. *Anesth Analg* 2008; **106**: 1708–1711.

145 Lonnqvist PA, Walker SM. Ketamine as an adjunct to caudal block in neonates and infants: is it time to re-evaluate? *Br J Anaesth* 2012; **109**: 138–140.

146 Lonnqvist PA. Adjuncts to caudal block in children–Quo vadis? *Br J Anaesth* 2005; **95**: 431–433.

147 Hamurtekin E, Fitzsimmons BL, Shubayev VI *et al*. Evaluation of spinal toxicity and long-term spinal reflex function after intrathecal levobupivacaine in the neonatal rat. *Anesthesiology* 2013; **119**: 142–155.

148 Walker SM, Grafe M, Yaksh TL. Intrathecal clonidine in the neonatal rat: dose-dependent analgesia and evaluation of spinal apoptosis and toxicity. *Anesth Analg* 2012; **115**: 450–460.

149 Walker SM, Westin BD, Deumens R *et al*. Effects of intrathecal ketamine in the neonatal rat: evaluation of apoptosis and long-term functional outcome. *Anesthesiology* 2010; **113**: 147–159.

150 Yaksh TL, Tozier N, Horais KA *et al*. Toxicology profile of N-methyl-D-aspartate antagonists delivered by intrathecal infusion in the canine model. *Anesthesiology* 2008; **108**: 938–949.

151 Eich C, Strauss J. Prompt and powerful effect of a practice guideline on caudal additives. *Pediatr Anesth* 2009; **19**: 271–272.

152 Morton NS. The pain-free ward: myth or reality. *Pediatr Anesth* 2012; **22**: 527–529.

153 Zhu LM, Stinson J, Palozzi L *et al*. Improvements in pain outcomes in a Canadian pediatric teaching hospital following implementation of a multifaceted knowledge translation initiative. *Pain Res Manag* 2012; **17**: 173–179.