Analgesia for neonates

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Key points

Facial expression is the most specific and consistent pain response in neonates. The basic nociceptive connections are formed well before birth, but are immature. Neonates have increased plasticity and excitability of their developing nervous system. An understanding of the differences in drug handling by neonates necessitates alterations in dosing and frequencies of commonly used medications. Multimodal analgesia maximizes efficacy while minimizing side-effects.

The International Association for the Study of Pain defines pain as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage’. Until fairly recently, it was widely assumed that the immature nervous system of the neonate did not perceive pain in the same way as older children and adults.1 The consequence of this was that many procedures were performed with minimal or no analgesia. Later theories also held that neonates were more likely to suffer complications from the use of opioids (particularly respiratory depression) and so they were often withheld.

Assessing pain in pre-verbal infants poses difficulties as evidenced by the many validated assessment tools at our disposal (Table 1). Facial expression is the most specific and consistent pain response. Features denoting pain are a bulging brow, deep nasolabial folds, an oval-shaped mouth, screwed up eyes, and a trembling tongue. The key to successfully managing pain relief in neonates, or any other patient population, is to strive for balanced analgesia using a multimodal approach. This will maximize the benefits while minimizing the side-effects.

Pain pathways: similarities and differences

In order for pain to be perceived, there must be an intact pain pathway. This comprises sensory neurones with connecting afferent nerve to dorsal horn cells, spinal inter-neuronal connections, and connections to higher centres.2 The system must then be subject to modulatory influences, both locally and from descending inhibitory pathways. A recent work on neural connectivity has shown that there are thalamocortical connections by 12–16 weeks, maturing by 23–25 weeks post-conceptual age. In other words, all of the physical necessities for pain perception are present by 25 weeks gestation.3

The neonatal afferent pathway is composed of high-threshold Aβ and low-threshold Aβ mechanoreceptors, which respond with lower firing frequencies in comparison with adults. Whereas in adults the Aβ afferents extend into laminae III and IV of the dorsal horn, in neonates they extend dorsally into laminae I and II with C fibres. The response seen to activation of the Aβ fibres is more akin to the excitatory effects seen from Aδ and C-fibre activation in adults. In addition to these differences, the receptive fields of the dorsal horn cells and cortical somatosensory cells are larger, and therefore more likely to be excited by peripheral sensory stimulation. The excitatory side of the pain perception system is therefore functional from birth, albeit with some differences from the adult. How does this comparison hold for the inhibitory arm? Pre-term infants have a dorsal cutaneous flexor reflex that is twice as sensitive to pain as in term infants, who in turn are more sensitive than older children. The explanation for this may lie in the absence of descending inhibitory neurones, connecting supraspinal centres and dorsal horn cells. These absent circuits form part of the anti-nociceptive pathways in older children and adults. There is a functional inhibitory system which acts at the level of the spinal cord and utilizes GABAergic synapses and GABA/glycine co-synapses to reduce neuronal excitability, which is not as effective as that found in older children.

Although most of the studies in neurophysiology have been performed using animal models, there remains little doubt that pain experienced in the neonatal period will shape the sensory and motor responses shown in later life. This was admirably demonstrated in a study by Taddio and colleagues4 on human infants. They demonstrated that the behavioural responses to routine vaccination at 4–6 months of age correlated with exposure to prior painful stimuli, in this case circumcision. Uncircumcised males showed lowest pain scores, followed by those circumcised with pre-application of EMLA® cream. Those who had been circumcised but had placebo treatment exhibited highest pain scores. The actual nature of the later response, whether hypo- or

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Table 1 Pain assessment tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Physiological indicators</th>
<th>Behavioural indicators</th>
<th>Gestational age tested</th>
<th>Adjust for gestational age</th>
<th>Nature of pain assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIPP (premature infant</td>
<td>Heart rate, oxygen saturation</td>
<td>Brow bulge, eyes squeezed</td>
<td>28–40 weeks</td>
<td>Y</td>
<td>Procedural and postoperative pain</td>
</tr>
<tr>
<td>pain profile)</td>
<td>Respiratory patterns</td>
<td>facial expressions, cry, arm/leg</td>
<td></td>
<td></td>
<td>Procedural pain</td>
</tr>
<tr>
<td>NIPS (neonatal infant</td>
<td>None</td>
<td>facial muscle group</td>
<td>Preterm and term infants,</td>
<td>N</td>
<td>Acute pain</td>
</tr>
<tr>
<td>pain scale)</td>
<td></td>
<td>involvement</td>
<td>infants at 4 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NFCS (neonatal facial</td>
<td>Respiration, HR, oxygen saturation, BP</td>
<td>Posture, tone, sleep pattern, expression, colour, cry</td>
<td>Neonates</td>
<td>N</td>
<td>Acute pain</td>
</tr>
<tr>
<td>coding system)</td>
<td>CNS state, breathing, HR, mean BP</td>
<td>movement, tone, face</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PAT (pain assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tool)</td>
<td></td>
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<tr>
<td>SUN (scale for use in</td>
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<td></td>
<td></td>
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<tr>
<td>newborns)</td>
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</table>

Hyper-algesia, seems to relate to the age at which the painful state is experienced. Pre-term infants exposed to painful stimuli seem to experience hypoaesthesia later while post-term infants experience hyperalgesic responses to later pain.

Developmental pharmacology

Dosage of analgesic drugs will vary with gestational age and postnatal development. Pharmacokinetic variables change after birth and will be influenced by a number of factors.

(i) Body composition is different at birth; the neonate has high total body water content, with the largest percentage being in the extracellular space. Body fat and muscle content are lower. Ionized drugs have a greater volume of distribution and drugs that are redistributed to fat or muscle may have a prolonged duration of action.

(ii) Renal function is immature at birth with a low glomerular filtration rate and reduced renal tubular function prolonging renal drug excretion and increasing drug half-life.

(iii) Changes in plasma protein concentration and binding affect the volume of distribution of drugs. Lower drug dosages may be required with an increased amount of free drug for a given dose.

(iv) Drug uptake into liver cells is less efficient and metabolic enzyme activity is immature, resulting in the likelihood of prolonged drug action.

(v) The blood–brain barrier is immature and greater transfer of partially ionized drugs such as morphine into the brain will occur.

Analgesic strategies

Our acknowledgement of postoperative pain in the neonatal population is now undisputed; however, we are still sometimes guilty of overlooking the pain caused by supposedly minor procedures, such as heel sticks, which may have to recur frequently. Part of a successful pain management programme is forward planning, which can help to modulate the pain experience for the future. Simple strategies such as skin-to-skin contact 15 min before the procedure, and/or the use of sucrose in a variety of concentrations (up to 24%) with or without a dummy (non-nutritive sucking), may be effective in minimizing the long-term sequelae of stresses such as heel sticks or cannula insertion. Oral sucrose produces a calming effect by initiating the release of endorphins triggered by the sweet taste through receptors on the tongue. Routine practice for venepuncture has come to include application of topical local anaesthetic (LA), usually Ametop (tetra-caine) or EMLA®. There is a theoretical advantage to using an ester LA in neonates as esterases are fully functional, although care must be taken in size of site covered, and the dose used. The risk of methaemoglobinemia from the use of EMLA appears to have been exaggerated in the past, certainly in the doses used for i.v. cannulation sites.

Systemic analgesics remain the mainstay of most analgesic regimens, either in isolation or as combinations with regional LA techniques. Acetaminophen and codeine phosphate are the most frequently utilized medications and should ideally be given in combination. The use of non-steroidal anti-inflammatory agents (NSAIDs) is controversial in neonatal pain management. Neonatologists use indomethacin and ibuprofen to promote closure of the ductus arteriosus. Prostaglandins are important for the normal development of the central nervous, cardiovascular, and renal systems, and there is evidence that the genesis of these systems may be adversely affected by NSAID exposure in utero and in the neonatal period. Physiological effects of prostaglandin inhibition in neonates are sleep disruption, alterations in cerebral blood flow, decreased renal blood flow, disrupted thermoregulation, and an increased risk of pulmonary hypertension. Routine use of NSAIDs should probably be avoided at this time.

Acetaminophen

Acetaminophen has analgesic and antipyretic properties but is only weakly anti-inflammatory. Acetaminophen has a central analgesic effect mediated through activation of descending serotonergic pathways. Its main site of action may be through inhibition of prostaglandin synthesis or through an active metabolite working at cannabinoid receptors. The plasma acetaminophen concentration should be 10–20 mg ml⁻¹ to achieve antipyretic and analgesic effects. Acetaminophen metabolism is different in neonates from...
adults, the major pathway being sulphate conjugation rather than glucuronidation. The normal adult ratio of glucuronidation:sulphation (2:1) is not achieved until 12 yr of age. A small amount is metabolized via cytochrome P450 enzymes (3–10%) to a potentially hepatotoxic metabolite, N-acetyl-p-benzoquinone imine. This metabolite is neutralized by combination with hepatic glutathione, should these stores be depleted by chronic therapy or malnutrition, toxicity is more likely. The isoenzyme responsible for this process has reduced activity in neonates and may confer some degree of protection against toxicity.

Acetaminophen is available in formulations for oral, rectal, or i.v. administration. The enteral route is used whenever possible; in the neonate, rectal bioavailability is higher (approaching 100%) than in older children where absorption may be erratic. Parenteral acetaminophen is often used for the first 24 h after surgery, before conversion to oral dosing. The doses are not directly interchangeable and extra vigilance is required to avoid dosing errors. Acetaminophen can be used as a sole agent and is most often combined with codeine phosphate (Table 2).

**Codeine phosphate**

The analgesic effect of codeine comes from its conversion to morphine by the cytochrome P450 enzyme CYP2D6 mainly found in the liver. Genetic polymorphism of this enzyme leads to a significant inter-patient variability in the production of morphine that may lead to different patient responses. The activity of this enzyme is very low at birth and increases with age. This has implications for the use of codeine in neonates and infants. However, the addition of acetaminophen to codeine has been shown to improve postoperative pain relief in infants. Codeine may be administered orally, rectally, or occasionally i.m. (under anaesthesia). Absorption is rapid with both the oral and rectal routes achieving a peak plasma concentration within 1 h. It is never given i.v. due to the risk of severe hypotension, which is thought to be histamine mediated. The half-life of codeine has been shown to be increased in infants of low birth weight, and should be given with a longer interval between doses.

**Morphine**

Morphine is the most widely studied and utilized opioid. It is used both intraoperatively and after operation, either as a continuous infusion or as nurse-controlled analgesia (NCA) when a low-dose infusion is supplemented with nurse administered, programmed boluses. This allows more flexibility to accommodate periods of increased pain associated with handling. Morphine infusions are commonly used as the sole sedative/analgesic agent to facilitate controlled ventilation of neonates in intensive care.

Reduced doses of morphine are required in neonates because of an increased effect of the drug due to an immature blood–brain barrier, reduced protein binding (28% as opposed to 50% in the older child) producing a higher free drug level and a long duration of action because of immature liver metabolism and reduced renal excretion. Morphine is metabolized by hepatic pathways with the generation of inactive morphine-3-glucuronide and active morphine-6-glucuronide being produced. Approximately 20% of morphine is excreted unchanged via the renal system in neonates.

Although it had been thought that neonates were predisposed to a higher risk of respiratory depression, there is no evidence to support age-related differences in respiratory effects at equivalent plasma concentrations. Respiratory depression is unusual with plasma concentrations <20 μg litre⁻¹. Morphine exposure during the first 12 weeks of life, especially if frequent, rapidly matures opioid metabolism and may necessitate much higher dosing regimes. Dosing should always be titrated to response; some neonates may need plasma concentrations of up to 125 μg litre⁻¹ for adequate analgesia (Table 2).

The side-effects commonly seen with most opioids, for example, pruritis, vomiting, sedation, and respiratory depression, may manifest in an unpredictable way in neonates, and therefore, these infants should be nursed in an environment with extended

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**Table 2 Analgesics for neonates. PCA, post-conceptual age; NCA, nurse-controlled analgesia**

<table>
<thead>
<tr>
<th>Drug/route</th>
<th>Dose</th>
<th>Interval</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen p.o./p.r.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28–32 weeks PCA</td>
<td>15 mg kg⁻¹</td>
<td>8–12 h (max. 35 mg kg⁻¹ day⁻¹)</td>
<td>Review daily</td>
</tr>
<tr>
<td>32–53 weeks PCA</td>
<td>20 mg kg⁻¹</td>
<td>8 h (max. 60 mg kg⁻¹ day⁻¹)</td>
<td>Review daily</td>
</tr>
<tr>
<td>Acetaminophen i.v.</td>
<td>7.5 mg kg⁻¹</td>
<td>6 h (max. 30 mg kg⁻¹ day⁻¹)</td>
<td></td>
</tr>
<tr>
<td>Codeine p.o./p.r.</td>
<td>0.5–1 mg kg⁻¹</td>
<td>6 h</td>
<td></td>
</tr>
<tr>
<td>Morphine i.v.</td>
<td>25–50 μg kg⁻¹</td>
<td>4–6 h</td>
<td></td>
</tr>
<tr>
<td>Morphine NCA</td>
<td>0.2 mg kg⁻¹ in 20 ml 0.9% NaCl</td>
<td></td>
<td>Review daily</td>
</tr>
<tr>
<td></td>
<td>Background infusion: 0.5 ml h⁻¹</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Bolus dose: 0.5 ml</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Lockout: 60 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>2 mg kg⁻¹</td>
<td>Single-bolus injection</td>
<td></td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>2 mg kg⁻¹</td>
<td>Single-bolus injection</td>
<td></td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>2 mg kg⁻¹</td>
<td>Single-bolus injection</td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.2 mg kg⁻¹ h⁻¹</td>
<td>Continuous infusion</td>
<td>Maximum 48 h</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>0.2 mg kg⁻¹ h⁻¹</td>
<td>Continuous infusion</td>
<td>Maximum 48 h</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>0.2 mg kg⁻¹ h⁻¹</td>
<td>Continuous infusion</td>
<td>Maximum 48 h</td>
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</tbody>
</table>
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monitoring facilities (apnoea monitors, ECG, pulse oximetry), trained specialist staff, and access to ventilatory equipment. Other opioids such as fentanyl, alfentanil, and remifentanil are rarely used in the neonatal population other than for sedation in PICU.

Ketamine

Ketamine has been used as an analgesic in neonates, because of its non-opioid analgesic action at N-methyl-D-aspartate receptors in the spinal cord. However, laboratory research on rats has shown it to be neurotoxic to the developing brain when used in doses which exceed those used clinically, and this has resulted in reduced use of ketamine in young infants until more is known of its long-term effects.10

LA techniques

The multimodal approach to neonatal analgesia would not be complete without considering whether there is an LA technique which may complement systemic analgesia. If a more complex technique is not feasible, simple LA infiltration may provide useful analgesia. In this way, it may be possible to reduce the use of opioids with their associated side-effects. Many such techniques use a single dose administered to an anaesthetized neonate in the theatre environment. This approach reduces the risk of amide LA toxicity that may be associated with continuous infusion. Neonates handle amide LAs differently and toxicity may not manifest predictably. Whereas in adults cardiac arrest may be the first sign of LA toxicity, in neonates convulsions, arrhythmias, or respiratory arrest are more common. Pharmacokinetic differences in neonates will affect dosing and duration of treatment. A large volume of distribution reduces peak levels after single dosing, but increases the risk of accumulation with infusion. With these considerations in mind, initial doses of LA for neonates should be reduced from the adult dose (Table 2).

Many peripheral nerves are easily accessible for simple single-shot blockade, and may be performed with reliable results. Such peripheral nerve blocks include penile, ilioinguinal, and rectus sheath blocks. Advances in ultrasound visualization of neurovascular structures have facilitated blockade in younger patients and transversus abdominus plane blocks may be performed in neonates by experienced practitioners. Ultrasound has also increasingly been used to visualize the caudal and epidural space in infants, allowing the depth of the space to be accurately measured. It also allows visualization of the catheter tip, which can therefore be accurately sited at the desired spinal level. Distortion of the dura mater can be seen on injection of LA, which aids in confirming correct placement of the catheter.

Caudal epidural anaesthesia is still the most commonly performed central neuraxial block used in neonates, either as a single shot or catheter technique. A single-shot technique will reliably block dermatomes below T10 in neonates and is therefore suitable for many of the routine neonatal surgical procedures. Failure rates are low (<10%) and anatomical landmarks are easily identified. A cannula technique uses the easy passage of the sheath to help confirm correct placement, along with smooth resistance-free injection. Although additives such as clonidine or preservative-free ketamine are routinely used in older children, their use in neonates is not recommended because of a lack of evidence testifying to their long-term safety in a developing nervous system. Opioids are also not commonly added to the LA solution because of their ability to produce respiratory depression, particularly if the neonate is not planned to receive postoperative ventilatory support.

During infancy, it is possible to thread a catheter from the sacral hiatus into the thoracic or lumbar epidural space (Fig. 1). This is a relatively easy, low morbidity technique. It also allows a larger epidural catheter to be used with the advantage of decreased problems with catheter occlusion. The risk of epidural infection should not be ignored as faecal soiling may contaminate the catheter site. Serious complications are uncommon (vascular injection, haematoma, infection); more common side-effects include leg weakness and urinary retention.

The insertion of a thoracic or lumbar epidural in a neonate is made possible because of the availability of small epidural kits using a 19 G or 18 G Tuohy needle with an appropriately sized catheter. An epidural at any level is normally performed with the child anaesthetized to minimize movement during insertion. Depth of space from the skin does not correlate with age and has been found to vary between 3 and 12 mm in a large series of neonates. Loss of resistance to saline rather than air is the preferred method of identifying the space to reduce the chances of venous air embolus or patchy block. In experienced hands, the complication rate from epidurals in neonates and infants is low.11

Spinal anaesthesia is sometimes undertaken for surgery below the umbilicus in ex-premature infants whose conceptual age is <60 weeks. These infants are at major risk of postoperative apnoea if operated on under general anaesthesia, whereas the incidence is decreased when the surgery is performed under solely spinal anaesthesia. The baby is normally placed in the sitting position for the procedure, and care must be taken to ensure a clear airway. Insertion of the spinal needle should be at a level of L4–5 along a line joining the posterior iliac crests. In the UK, the most
commonly used LA is 0.5% bupivacaine as a hyperbaric or isobaric solution in a dose of 0.8 mg kg\(^{-1}\). Addition of epinephrine 1:200 000 will prolong the duration of the block by up to 35% over plain bupivacaine. Other adjuvants to increase the duration of analgesia from subarachnoid block are not commonly used in neonatal practice.

Conclusions

Our acceptance of the existence of neonatal pain and the way this may impact negatively on future pain processing has led to a structured approach to analgesic provision. We are familiar with the concept of balanced analgesia using multimodal techniques and this approach is equally suitable for use with neonates. Routine use of pain assessment tools helps us to individualize analgesic regimes. There is still scope for improvement in the management of procedural pain, which lags behind our postoperative provision.

Further reading

For further information, please see: *Good Practice in Procedural and Postoperative Pain*. Available from www.apagbi.org.uk.

Conflict of interest

None declared.

References

1. McGrath PA. In: Merskey H, Loeser JD, eds. *Children—Not Simply ‘Little Adults’*, 385–405

Please see multiple choice questions 20–23.