Postoperative analgesia in infants and children

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Over 20 yr ago, a survey reported that 40% of paediatric surgical patients experienced moderate or severe postoperative pain and that 75% had insufficient analgesia.106 Since then, a range of safe and effective techniques have been developed.

Neonatal pain perception
The structural components necessary to perceive pain are already present at about 25 weeks gestation whereas the endogenous descending inhibitory pathways are not fully developed until mid-infancy.2 4 164 Opioid and other receptors are much more widely distributed in fetuses and neonates.52 53 62 66 127 Fetuses subjected to intrauterine exchange transfusion with needle transhepatic access will show both behavioural signs of pain as well as a hormonal stress response.64 Significant pain stimulation without proper analgesia, for example circumcision, will not only cause unacceptable pain at the time of the intervention but will produce a ‘pain memory’ as illustrated by an exaggerated pain response to vaccination as long as 6 months following the circumcision.148–150 Both neonates and infants are able to mount a graded hormonal stress response to surgical interventions and adequate intra- and postoperative analgesia will not only modify the stress response but has also been shown to reduce morbidity and mortality.1 3 5 6 16 17 163 167

Successful postoperative pain management in infants and children
A pragmatic, practical approach to paediatric postoperative pain management has been developed and used in recent years in most paediatric centres. Realistic aims are to recognize pain in children, to minimize moderate and severe pain safely in all children, to prevent pain where it is predictable, to bring pain rapidly under control and to continue pain control after discharge from hospital.108 109 117 119 125

Prevention of pain whenever possible, using multi-modal analgesia, has been shown to work well for nearly all cases and can be adapted for day cases, major cases, the critically ill child, or the very young. Many acute pain services use techniques of concurrent or co-analgesia based on four classes of analgesics, namely local anaesthetics, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen (paracetamol).61 72 74 97 98 117 119 135 In particular, a local/regional analgesic technique should be used in all cases unless there is a specific reason not to and the opioid-sparing effects of local anaesthetics, NSAIDs, and acetaminophen (paracetamol) are useful. Indeed, for many day-case procedures, opioids may be omitted because combinations of the other three classes provide good pain control in most cases.88 125 Regional anaesthesia is nearly always conducted in anaesthetized children, but some high risk neonates have lower perioperative morbidity after inguinal surgery when awake spinal anaesthesia is used.91 161

An individualized pain management plan72 can be made for each child based on a cycle of assessment and documentation of the child’s pain using appropriate tools and self-reporting, with interventions linked to the assessments.30 60 63 A safety net is needed for rapid control of breakthrough pain, to monitor the efficacy of analgesia, to identify and treat adverse effects, and to ensure equipment is functioning correctly.116

In paediatric hospitals or other centres with significant numbers of paediatric surgical interventions, the establishment of a dedicated paediatric pain service is the standard of care. Where this is not possible, adult pain services often manage children with specific paediatric medical and nursing advice and expertise. In other settings substantial improvement is possible by the establishment of clinical routines and protocols for the assessment and treatment of paediatric postoperative pain. A network of nurses with a special interest in paediatric pain management can form the basis for continuous education. A well-structured protocol for postoperative analgesia with clear instructions for parents is essential following paediatric day-case surgery.118 124 125 165

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Local and regional anaesthesia

Benefits associated with the use of paediatric regional anaesthesia

Regional anaesthesia produces excellent postoperative analgesia and attenuation of the stress response in infants and children. Epidural anaesthesia can decrease the need for postoperative ventilation after tracheoesophageal fistula repair, and reduce the complications and costs following open fundoplication. Safety aspects of paediatric regional anaesthesia

A large prospective 1-yr survey of more than 24 000 paediatric regional anaesthetic blocks found an overall incidence of complications of 0.9 in 1000 blocks, with no complications of peripheral techniques. Complications were transient and half were judged to have been caused by the use of inappropriate equipment. The commonest problems with paediatric regional anaesthesia are technical: either failure to establish a block or failure of maintenance of the block. Infection, pressure area problems, peripheral nerve injury, local anaesthetic toxicity, and serious adverse effects of opioids are much rarer. A large 5-yr prospective audit of 10 000 paediatric epidural catheter techniques is currently taking place in the UK to try to establish the relative risk of these problems in modern practice.

Some simple local anaesthetic techniques for postoperative analgesia

Local anaesthetic gel topically applied to the site of circumcision, and instilled onto or infiltrated into small open wounds are simple, safe, and effective techniques. Wound perfusion can also be particularly useful for iliac crest bone graft donor sites (used for alveolar bone grafting in some techniques of cleft palate repair). Dressing perfusion by applying dilute local anaesthetic onto a foam layer adhered to. These sites can otherwise be extremely distressing to the child for a period up to 48 h.

Recent developments in regional analgesia

Descriptions of the technical aspects of regional anaesthesia and management of the child with regional block are readily available. Pharmacokinetics of local anaesthetics in infants and children have been comprehensively reviewed recently.

Spread of epidural dye

Radiological assessment of contrast injected through epidural catheters in babies (1.8–4.5 kg) after major surgery found that both the quality and extent of spread were different for every baby. Filling defects and ‘skipped’ segments were common. Spread was more extensive after 1 ml kg⁻¹ compared with 0.5 ml kg⁻¹ (mean 11.5 [3.03] vs 9.3 [3.68] segments, P=0.014) (but not twice as great) with fewer ‘skipped’ segments and greater density of dye.

Confirming the tip position of catheters threaded from the sacral hiatus

The technique of threading catheters from the sacral hiatus to position the tip at thoracic or lumbar level reported success rates of 85–96%, particularly in small children. A retrospective review of radiographs in babies younger than 6 months of age found that only 58 catheter tips were considered optimal (67%); 10 were too high (12%); and 17 were coiled at the lumbosacral level (20%). Some units use radiological screening routinely but for many others this is not feasible. An alternative approach using electrocardiography has been described. A specially devised catheter enables display of the electrocardiograph (ECG) signal from the tip and this is compared with the ECG from a surface electrode positioned at the ‘target’ segmental level. When the ECG traces are identical, the tip of the catheter is at the target level. In a descriptive study of 20 children aged 0–36 months, the authors were able to position all the tips to within two vertebral spaces of the target levels (either T4, T7, or T10). In contrast to their previous method of using stimulating epidural catheters and evaluating muscle contractions, the technique can be used after administration of neuromuscular blocking agents or epidural local anaesthetics. However, neither of the two techniques described by Tsui will exclude a catheter lying at the appropriate segmental level but in the subarachnoid space or intravascularly.

Ultrasonography-guided regional anaesthetic techniques

Ultrasonography allows real-time visualization of anatomical structures, guides the blocking procedure itself, and shows the spread of the local anaesthetic solution injected. A more rapid onset of block using less local anaesthetic solution is particularly attractive for paediatrics where most blocks are sited in anaesthetized patients. Ultrasound guidance can also be helpful for caudal and epidural blocks in infants and children as the sacrum and vertebræ are not fully ossified. Ultrasound-guided techniques have been described for infraclavicular brachial plexus blockade and lumbar plexus block in children.

Surface mapping of peripheral nerves with a nerve stimulator

Nerve mapping using a nerve stimulator is helpful for teaching peripheral nerve and plexus blocks in the upper and lower limbs, and in patients where the surface landmarks are obscure or distorted. Use of continuous peripheral nerve blocks

Continuous catheter techniques are becoming popular in children for femoral, brachial plexus, fascia iliaca, lumbar plexus, and sciatic blockade. Disposable infusion devices can be used as an alternative to standard infusion equipment.
Table 1 Suggested maximum dosages of bupivacaine, levobupivacaine, and ropivacaine in neonates and children. The same dose is recommended for each drug.

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<th>Choice of local anaesthetic solution</th>
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| A large safety study has established safe-dosing guidelines for racemic bupivacaine in children (Table 1) and this has greatly reduced the incidence of systemic toxicity. Racemic bupivacaine is gradually being replaced by ropivacaine or levobupivacaine. This change is driven by the reduced potential for systemic toxicity and the lower risk of unwanted motor blockade. There are now sufficient paediatric data to recommend either of the new agents. Rosenberg has reported non-toxic plasma concentrations of ropivacaine following a dose of up to 3 mg kg\(^{-1}\) for ilioinguinal blockade, but 3.5 mg kg\(^{-1}\) for fascia iliaca compartment blockade has been reported to cause potentially toxic plasma concentrations, namely 4–5 \(\mu\)g ml\(^{-1}\). Thus, the reduced risk of systemic toxicity should not persuade anaesthetists to exceed the previous dosing guidelines for racemic bupivacaine. For continuous epidural levobupivacaine, the use of a solution appears optimal for lower abdominal and urological surgery. For single injection caudal blockade, ropivacaine and levobupivacaine provide similar postoperative analgesia compared to racemic bupivacaine with slightly less early postoperative motor blockade, and with no discernible differences between ropivacaine and levobupivacaine. The esterase systems in tissues, plasma, and red blood cells are mature in early life, and ester local anaesthetics such as amethocaine (tetracaine) and 2-chloroprocaine are particularly applicable in neonates.

<table>
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<th>Adjuncts to local anaesthetics</th>
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| A recent systematic review of paediatric caudal adjuncts has been published. Caution is required in neonates as sedation and apnoea have been noted. In a survey of the UK members of the Association of Paediatric Anaesthesia, 58% of respondents stated that they used adjuvants with local anaesthetics for caudal epidural blockade in children to prolong the duration of analgesia without increasing side-effects such as motor blockade. The commonest were ketamine 32%, clonidine 26%, fentanyl 21%, and diamorphine 13%. Although preservative-free racemic ketamine is a very effective agent, preservative-free \(S(+)\)-ketamine is more potent and may reduce neuro-psychiatric effects. Caudally administered \(S(+)\)-ketamine (1 mg kg\(^{-1}\)) as the sole agent has even been reported to produce similar postoperative analgesia to bupivacaine 0.25% with epinephrine. The main action of adjunct ketamine is most likely mediated by actions on spinal \(N\)-methyl D-aspartate (NMDA)-receptors, as the same dose given systemically produces a much shorter duration of analgesia. When used for single injection, \(S(+)\)-ketamine has been found to be more effective in prolonging postoperative pain relief than clonidine. The combination of \(S(+)\)-ketamine 1 mg kg\(^{-1}\) and clonidine 1 \(\mu\)g kg\(^{-1}\) without the concomitant use of local anaesthetics for caudal blockade produced approximately 24 h of adequate postoperative analgesia compared with only 12 h for plain \(S(+)\)-ketamine. Adjunct clonidine in the dose range of 1–2 \(\mu\)g kg\(^{-1}\) for single injection caudal blockade will typically double the duration of analgesia compared with plain local anaesthetics, and addition of approximately 0.1 \(\mu\)g kg\(^{-1}\) h\(^{-1}\) will enhance the effect of continuous epidural blockade. Recent data suggest that the systemic effect of clonidine might be more important than the local action. The routine use of opioids as additives for postoperative analgesia has recently been critically challenged. Although there is a risk of respiratory depression, less dramatic side-effects such as itching, nausea and vomiting, urinary retention, and decrease gastrointestinal motility are more troublesome. A recent comparison of plain levobupivacaine with levobupivacaine combined with fentanyl for postoperative epidural analgesia in children, failed to show any major benefit of adjunct fentanyl. Neuraxial administration of opioids still has a place where extensive analgesia is needed, for example after spinal surgery or liver transplantation or when adequate spread of local anaesthetic blockade cannot be achieved within dosage limits. The potential benefits and risks of regional anaesthesia for paediatric cardiac surgery have recently been investigated and reviewed. Single doses of intrathecal opioids with or without local anaesthetic, or continuous spinal anaesthesia using a microcatheter technique appear particularly promising for open heart surgery, while epidural or paravertebral techniques seem to offer benefit for closed procedures. The main concern is that of local bleeding at the site of subarachnoid or epidural puncture in a heparinized child.

**Systemic analgesia**

The ranking of systemic analgesics in adults by efficacy when administered alone or in combination probably applies also to infants and children. However, the pharmacokinetics and pharmacodynamics of these agents change during early life and recent evidence has produced more logical dosing guidelines for opioids, NSAIDs, and acetaminophen (paracetamol) (Tables 2–6).

Appropriate child-friendly formulations help compliance and are now available as syrups, oral or sublingual wafers, soluble effervescent tablets, and eye drops. Metabolic pathways for many drugs are maturing in early life and indeed
**Table 2** Morphine dosing guidelines (an appropriate monitoring protocol should be used)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency relative to morphine</th>
<th>Single dose</th>
<th>Continuous infusion</th>
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<tbody>
<tr>
<td>Tramadol</td>
<td>0.1</td>
<td>1–2 mg kg⁻¹</td>
<td>1–4 μg kg⁻¹ min⁻¹ or use TCI system</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
<td>0.05–0.2 mg kg⁻¹</td>
<td>10–40 μg kg⁻¹</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>5</td>
<td>0.01–0.03 mg kg⁻¹</td>
<td>0.05–0.2 μg kg⁻¹ min⁻¹ or use TCI system</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>10</td>
<td>5–10 μg kg⁻¹</td>
<td>1–4 μg kg⁻¹ min⁻¹ or use TCI system</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50–100</td>
<td>0.5–1 μg kg⁻¹</td>
<td>0.1–0.2 μg kg⁻¹ min⁻¹</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>50–100</td>
<td>0.1–0.2 μg kg⁻¹</td>
<td>0.05–0.2 μg kg⁻¹ min⁻¹ or use TCI system</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>500–1000</td>
<td>0.025–0.05 μg kg⁻¹</td>
<td>Use TCI system</td>
</tr>
</tbody>
</table>

**Table 3** Opioids: relative potency and dosing. Appropriate monitoring and ventilatory support must be used

**Opioid techniques in children**

Morphine infusions of between 10 and 30 μg kg⁻¹ h⁻¹ provide adequate analgesia with an acceptable level of side-effects when administered with the appropriate level of monitoring.¹¹⁹ Morphine clearance in term infants greater than 1 month old is comparable with children from 1 to 17 yr old. In neonates aged 1–7 days, the clearance of morphine is one-third that of older infants and elimination half-life approximately 1.7 times longer.¹²² In appropriately selected cases, the s.c. route of administration is a useful alternative to the i.v. route.¹¹¹¹¹³ The s.c. route is contraindicated when the child is hypovolaemic or has significant ongoing fluid compartment shifts.¹⁶⁸ Patient-controlled analgesia (PCA) is now widely used in children as young as 5 yr and compares favourably with continuous morphine infusion in the older child.²⁹ A low dose background infusion is useful in the first 24 h of PCA in children, and has been shown to improve sleep pattern without increasing the adverse effects seen with higher background infusions in children and in adults.⁵⁵ Making the hand set part of a squeezable toy is highly popular with younger children. PCA opioid administration is applicable after most major surgical procedures, in sickle cell disease, in management of pain because of mucositis, and in the management of some children with chronic pain. The range of patients receiving opioids in an individually controlled manner can be increased if a nurse or parent is allowed to press the demand button within strictly set guidelines. Monitoring for such patients has to be at least as intensive as that for conventional PCA. Most regimens for nurse or parent controlled analgesia use a higher level of background infusion with a longer lockout time of around 30 min.⁷²⁹⁷⁹⁸¹⁰⁹¹¹⁷¹¹⁹ This technology can also be used in neonates where a bolus dose without a background infusion allows the nurse to titrate the child to analgesia or to anticipate painful episodes while allowing a prolonged effect from the slower clearance of morphine (Table 2).

**Other methods of opioid delivery**

Oral, sublingual, transdermal, intranasal, and rectal routes have been described and have a role in specific cases.⁷³¹⁰¹

**Other opioids**

Tramadol, oxycodone, hydromorphone, and buprenorphine may have applicability as alternatives to morphine in the postoperative period.⁵⁹¹⁰¹¹⁷¹ Pethidine (meperidine) is not recommended in children because of the adverse effects of its main metabolite, norpethidine. Fentanyl, sufentanil, alfentanil, and remifentanil may have a role after major surgery and in intensive care practice. Remifentanil is very titratable and has a context-insensitive half time with extremely rapid recovery because of esterase clearance, but transition to the postoperative phase is difficult to manage and may be complicated by acute tolerance. It may have a particular role in intraoperative stress control and in neonatal anaesthesia.⁴⁵⁴⁶¹⁰²¹³²¹³⁸ Sufentanil and fentanyl have long
context sensitive half times but give a smoother transition to maintenance analgesia. Alfentanil has a rapid onset, is titratable, and is relatively context insensitive after 90 min, with a relatively smooth transition in the postoperative phase. The potent opioids may be best delivered by target-controlled infusion devices and paediatric pharmacokinetic programmes have now been developed (Tables 3 and 4).

Non-steroidal anti-inflammatory drugs (NSAIDs)
NSAIDs are important in the treatment and prevention of mild or moderate pain in children. NSAIDs are highly effective in combination with a local or regional nerve block, particularly in day-case surgery. NSAIDs are often used in combination with opioids and the ‘opioid sparing’ effect of NSAIDs is 30–40%, as reported for adults. This produces a reduction in opioid-related adverse effects, especially ileus, bladder spasms and skeletal muscle spasms, and facilitates more rapid weaning from adverse effects, especially ileus, bladder spasms and skeletal

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose</th>
<th>Maximum daily dose</th>
<th>Dose interval</th>
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<tbody>
<tr>
<td>10–32</td>
<td>15 mg kg⁻¹</td>
<td>60 mg kg⁻¹ day⁻¹ max total 2 g</td>
<td>4–6 h</td>
</tr>
<tr>
<td>33–50</td>
<td>15 mg kg⁻¹</td>
<td>60 mg kg⁻¹ day⁻¹ max total 3 g</td>
<td>4–6 h</td>
</tr>
<tr>
<td>&gt;50</td>
<td>1 g</td>
<td>Max total 4 g</td>
<td>4–6 h</td>
</tr>
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NSAIDs and tonsillectomy
Two recent meta-analyses have considered the role of NSAIDs in post-tonsillectomy haemorrhage. NSAIDs as eye drops have found application after strabismus correction or laser surgery to the eye. Pharmacokinetic studies of NSAIDs have revealed a higher than expected dose requirement if scaled by body weight from adult doses. NSAIDs should be avoided in infants less than 6 months of age, children with aspirin or NSAID allergy, those with dehydration or hypovolaemia, children with renal or hepatic failure, or those with coagulation disorders, peptic ulcer disease or where there is a significant risk of haemorrhage. Concurrent administration of NSAIDs with anticoagulants, steroids, and nephrotoxic agents is not recommended. The most commonly reported adverse effects of NSAIDs are bleeding, followed by gastrointestinal, skin, central nervous system, pulmonary, hepatic, and renal toxic effects. Other serious side-effects have been reported, including oedema, bone marrow suppression, and Stevens–Johnson syndrome.

NSAIDs and asthma
Provocation of bronchospasm by NSAIDs is thought to be a result of a relative excess of leukotriene production. Aspirin sensitivity is present in about 2% of children with asthma and around 5% of these patients are cross-sensitive to other NSAIDs. Caution is required in those with severe eczema or multiple allergies and in those with nasal polyps. It is important to check for past exposure to NSAIDs as many asthmatic children take these agents with no adverse effects. A recent study found no change in lung function in a group of known asthmatic children given a single dose of diclofenac under controlled conditions.

NSAIDs and bone healing
Concerns have been raised by animal studies showing impaired bone healing in the presence of NSAIDs. For most orthopaedic surgery in children, the benefits of short-term perioperative use of NSAIDs outweigh the risks but limitation of use is recommended in fusion operations, limb lengthening procedures, and where bone healing has previously been difficult.

COX-2 inhibitors in paediatrics
Several COX-2 inhibitors have recently been evaluated in paediatrics, although the situation has been complicated by the withdrawal of rofecoxib from worldwide markets. Some early studies used too low a dose, and pharmacokinetic studies are now informing dosing schedules and intervals in children. The studies show equal
efficacy to other analgesic interventions with non-selective
NSAIDs or acetaminophen (paracetamol) and a morphine-
sparing effect, but trials have not been large enough to
confirm reduced adverse effects such as bleeding.84144157

Acetaminophen (paracetamol)

Acetaminophen inhibits prostaglandin synthesis in the
hypothalamus probably via inhibition of cyclooxygenase-
3,32162. This central action produces both antipyretic and
analgesic effects. Acetaminophen also reduces hyperalgesia
mediated by substance P, and reduces nitric oxide generation
involved in spinal hyperalgesia induced by substance P or
NMDA.

The analgesic potency of acetaminophen is relatively low
and its actions are dose-related; a ceiling effect is seen with
no further analgesia or antipyresis despite an increase in
dose. On its own, it can be used to treat or prevent most
mild and some moderate pain. In combination with either
NSAIDs or weak opioids, such as codeine, it can be used
to treat or prevent most moderate pain.10112 A morphine-
sparing effect has been demonstrated with higher doses in
day-cases.1090

Acetaminophen is rapidly absorbed from the small bowel,
and oral formulations in syrup, tablet or dispersible forms are
widely available and used in paediatric practice. Suppository
formulations vary somewhat in their composition and bio-
availability, with lipophilic formulations having higher
bioavailability. Absorption from the rectum is slow and
incomplete, except in neonates.14 The novel i.v. formulation
pro-paracetamol is cleaved by plasma esterases to produce
half the mass of acetaminophen. Recently, mannitol solubi-
lized paracetamol (PerfalganTM) has become available for
i.v. use. Interestingly, the higher effect site concentrations
achieved in the brain after i.v. administration may result in
higher analgesic potency. Although the site of action of acet-
aminophen is central, dosing is often based on a putative
‘therapeutic plasma concentration’ of 10–20 mg ml
–1. It is important to realize that the time to peak analgesia even
after i.v. administration is between 1 and 2 h. The time–
concentration profile of acetaminophen in cerebrospinal
fluid lags behind that in plasma, with an equilibration
half-time of around 45 min. Very few studies have tried to
relate the concentration of acetaminophen in CSF or plasma
to measurements of analgesia, particularly in children. There
is evidence that a plasma concentration of 11 µg ml
–1 or more is associated with lower pain scores. In a computer
simulation, a plasma concentration of 25 µg ml
–1 was pre-
dicted to result in good pain control in up to 60% of children
undergoing tonsillectomy.8–111415 Dosing regimens for
acetaminophen have been revised in the last few years on
the basis of age, route of administration, loading dose, main-
tenance dose, and duration of therapy to ensure a reasonable
balance between efficacy and safety. In younger infants, sick
children, and the pre-term neonate, considerable downward
dose adjustments are needed (Tables 5 and 6).

Conclusions

Moderate and severe postoperative pain can and should be
prevented or controlled safely and effectively in all children
whatever their age, severity of illness, or surgical procedure.
Continuing pain control at home after day-case surgery is
essential. The safety of analgesic therapy has improved with
the development of new drugs and fuller understanding of
their pharmacokinetics and dynamics in neonates, infants
and children, and in disease states. These developments have
been aided by technical improvements allowing more
accurate delivery of analgesia. Where complex analgesia is
needed, management by a multidisciplinary acute pain team
with paediatric expertise is the most effective approach.

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