Developments in the treatment of postoperative pain in paediatrics

P. Busoni, A. Messeri

Pain treatment in children is a rather large and complicated topic, which has recently been further developed and enriched by interesting research studies that have been reported in the medical literature. We therefore decided to restrict this paper to postoperative pain control and the problems related to procedural pain.

The undertreatment of children who are in pain following surgery has been recognised. Inadequate treatment of neonates and babies was widespread earlier. However, the 1990s saw a change in physicians’ perceptions of neonatal pain and refinement of modern analgesic techniques for use in children [1].

The increased understanding of the neurophysiology of pain and the concept that inadequate treatment of pain can have an impact on outcome and lead to long-term behavioural changes have prompted anaesthetists to study new techniques of pain management in children. In addition, developments are currently in train in clinical pain services, with new, sophisticated analgesia delivery devices and monitoring protocols.

A multimodal approach using locoregional anaesthesia combined with opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol is now widely accepted. The emotional component of pain must also be addressed in all aspects of paediatric practice, and it must be recognised that there is a place for instinctive comforting measures, distraction techniques and new nonpharmacological treatments, all of which should be applied to complement safe and effective use of analgesic drugs.

Pharmacological analgesia

Paracetamol

Paracetamol is widely used to reduce fever and for analgesia. It acts through inhibition of cyclo-oxygenase and is thought to have an analgesic effect on NMDA receptors in the spinal chord. The pharmacodynamics of paracetamol analgesia have not yet been adequately described in humans, and the therapeutic range for analgesia is not well established. Little or no analgesia is obtained below plasma levels of 10 µg ml⁻¹. Paediatric studies using paracetamol 10 mg kg⁻¹ orally have shown no
more analgesic effect than placebo in children undergoing myringotomy [2].

Anderson et al. [3] gave each of 100 children who were scheduled for tonsillectomy paracetamol, 40 mg kg⁻¹, by the oral or the rectal route. After 50 min the plasma concentration was measured and compared with the degree of analgesia achieved. Anderson demonstrated increasing numbers of patients with satisfactory analgesia as plasma concentrations increased, with a ceiling effect at 25–30 μg ml⁻¹.

The peak analgesic effect of paracetamol is not seen until 1 h after its peak plasma concentration is reached. There is evidence for this in terms of the relationship between plasma and cerebrospinal fluid (CSF) paracetamol concentrations. The central analgesic effect is therefore attributed to the ability of paracetamol to cross the blood barrier in high concentrations [4].

The rectal and oral routes of administration are both commonly used in children. A maximum daily dose of 90 mg kg⁻¹ day⁻¹ is widely accepted as safe [5]; 60 mg kg⁻¹ day⁻¹ is recommended in neonates [6].

However, there is little published information on which dosing regimen best maintains therapeutic levels. Paracetamol is commonly given in a dose of 10–15 mg kg⁻¹ every 4 h p.o. and 15–20 mg kg⁻¹ every 4 h rectally.

In neonates the hepatic glucuronide process is not yet mature, and they are capable of forming the reactive intermediate that causes hepatocellular damage, despite a comparatively low level of cytochrome P450 system. However, the rate constant for the sulfation metabolic pathway is larger in neonates than in adults and is the most important route of metabolism.

Anderson et al. conclude that a rectal loading dose of 40 mg kg⁻¹ followed by 30 mg kg⁻¹ every 12 h by the same route or an oral loading dose of 30 mg kg⁻¹ followed by 20 mg kg⁻¹ every 8 h p.o. will achieve concentrations of 10–20 mg l⁻¹ [7]. However, high doses of paracetamol have to be used for it to be effective, and the problem of cumulative toxicity with repeated dosing has not yet been addressed in neonates. Morton [8] therefore concludes that caution is required when the current dosage maxima are applied for longer than 72 h.

**Nonsteroidal anti-inflammatory drugs**

The main benefits of NSAIDs in minor, moderate and severe pain derive from an opioid-sparing effect, and they can also be used constructively as a component in a multimodal approach to enhance the quality of analgesia by combining drugs with central and peripheral effects. However, the clinical use of NSAIDs in the perioperative period is sometimes limited for fear of upsetting haemostasis, as they inhibit thromboxane-A₂ production with a consequent decrease in platelet function. The effect of NSAIDs on clinical bleeding tendency is difficult to quantify, and generally haemostasis remains below the upper limits found in healthy patients.

Intraoperative use of rectal diclofenac (1 mg kg⁻¹) in children 1–10 years of age has been shown to provide a lower level of postoperative analgesia than 1 ml kg⁻¹ of caudal bupivacaine 0.25%, but better pain control in the late recovery phase. The incidence of side-effects is similar for diclofenac and bupivacaine group, being low after either [9].
Ketorolac is a NSAID that is effective in providing postoperative pain relief in most patients. It has been administered i.v. (0.5 mg kg$^{-1}$) and i.m. (1 mg kg$^{-1}$); it has been shown to cause a significant reduction in opioid requirements and to shorten the duration of stay in hospital with no evidence of increased bleeding [10].

**Opioids**

The use of opioids for extended surgery is well established in the paediatric population. Patient-controlled analgesia (PCA) and nurse- or parent-controlled analgesia (NCA) are opioid delivery systems that allow the patient to receive a preset amount of the opioid at preselected intervals. PCA can be used in children as young as 5–6 years of age; when children have control over their own analgesia this has considerable psychological benefits. Kerschlbaum et al. [11] report that the range of patients receiving opioids can be increased with NCA.

Recent studies have focused on the prevention of side-effects, such as postoperative nausea and vomiting (PONV), with PCA morphine [12–15]. Routine prophylactic antiemetic treatment seems to be advisable during paediatric PCA.

Tramer et al. have [12] shown that droperidol is effective in preventing PONV during adult PCA, but the use of droperidol in children still requires investigation [13]. Other antiemetic agents may be a more appropriate choice. Kokinsky et al. [14] report that a single bolus of diyrazine, a phenothiazine, when anaesthesia is induced leads to a significant reduction of vomiting. It has been demonstrated that tropisetron, a long-acting 5-hydroxytryptamine-3 receptor antagonist, can reduce vomiting during PCA in children [15].

Busoni et al. [16] have shown that dexamethasone reduces the incidence of vomiting when administered i.v. to children for common paediatric operations, and this protective effect should be studied with a view to preventing nausea during the use of PCA. During adult PCA, ketamine has been found to reduce the incidence of PONV [17]. This approach has not yet been studied in children.

Tolerance and respiratory depression are other important side-effects of opioid use. In adults, it may be safe to use ketamine to reduce tolerance [18] and respiratory depression during opioid administration [19]. These findings indicate that the inclusion of small doses of ketamine in a balanced analgesic programme may be an interesting field for future paediatric pain research.

In summary, opioids are effective, but cause side-effects; a multimodal approach to analgesia works best and offers the chance of lower doses of these agents and more rapid weaning from them.

**Nonpharmacological methods**

Recent research in paediatric pain control strongly suggests that use of relaxation, mental imagery and play can help children to control their pain. Armstrong et al. [20] have demonstrated that there is a role for play in preparation for paediatric anaesthesia. Play therapy can be an effective method of providing tangible infor-
mation about the surgical experience and simultaneously attenuating a child’s fantasies and fears about the surgery.

For Bowmer [21], play is a simple way of helping a child to deal with the painful world of hospital and to master situations that might otherwise be overwhelming. The results are rewarding in terms of happier, less anxious, children, parents and medical staff.

**Local and regional anaesthesia**

The development of locoregional anaesthesia is the result of anatomical studies and of improved understanding and safety of the local anaesthetics in use. In particular, there is increasing interest in peripheral nerve blocks achieved by way of the single-shot technique or by continuous infusion. The continuous infusion method has been developed in adult patients for orthopaedic surgery, and as yet the literature includes little information on its use in paediatric patients [22].

Ropivacaine is a widely used local anaesthetic with a wider margin of safety for paediatric patients. Ropivacaine 0.2% appears to be optimal in terms of producing adequate analgesia with an acceptable degree of motor block; the use of ropivacaine 0.3% is associated with a high incidence of motor block and minimal improvement in postoperative pain relief relative to ropivacaine 0.2% [23]. Higher concentrations of ropivacaine than 0.3% demonstrably provide a lesser degree of motor blockade than equivalent volumes and concentrations of bupivacaine [24].

When a longer duration of anaesthesia with no motor block is needed, clonidine, 2 μg kg⁻¹, or preservative-free ketamine, 0.5 mg kg⁻¹, will prolong analgesia [25, 26].

However, the main advantage of ropivacaine is its excellent safety profile. It has been successfully used in children, infants and neonates in continuous infusion through a lumbar epidural catheter, although pharmacokinetic data are limited to patients over 3 months old [27].

Levobupivacaine is a new local anaesthetic. It is a single-isomer formulation (S-[–]-enantiomer of bupivacaine) that is thought to have lower toxicity than compounds with racemic formulae. Studies in human volunteers confirm that it has a smaller arrhythmogenic, and a less negative inotropic, effect than bupivacaine [28]. In recent studies in a paediatric population, levobupivacaine has been used for peripheral and central blocks. It reduced the need for rescue analgesia, providing effective analgesia and a less intense motor block than bupivacaine [29]. The lower toxicity of bupivacaine thus gives a wider safety margin in daily clinical practice, both for single-shot administration and for continuous infusion in paediatric patients.

**Conclusions**

A lot of new and advanced methods are now available to allow paediatric anaesthetists to provide adequate pain treatment to children. The authors believe that a
multimodal approach to analgesia is the best. Local and regional anaesthesia are commonly used to treat early postoperative pain, combined with systemic drugs given in the appropriate dosages by modern delivery systems. Titration of analgesics against the results of regular reassessment of analgesia is effective. The ‘acute pain service’ is an institutional way of coordinating analgesic management and is the best way to advance the cause of ensuring comprehensive provision of safe pain control for all children.

Procedural pain is frequently encountered in children, either during an emergency or during disease management. Invasive procedures are known to be the most painful and traumatic events experienced by children. Although procedure-related pain is an acute, short-lived experience, it is accompanied by a great deal of fear and anxiety. For example, researchers have reported that bone marrow aspirations/biopsies and lumbar punctures are perceived as extremely painful by children with cancer. Previous studies have shown that children do not adapt to the discomfort associated with intrusive procedures, but experience greater levels of anxiety with repeated painful experiences. Children often experience symptoms such as depression, insomnia and anorexia before a clinic or hospital visit that will involve a procedure. The consensus among professionals caring for children with cancer supports a developmental approach to managing pain associated with procedures in children with cancer. The goal is to provide comfort and support during all procedures experienced by the child with cancer.

This overview addresses the following questions:
- What will influence the choice of therapy?
- Which procedures are included?
- Are therapeutic interventions supported by efficacy and safety data?
- Is there any evidence to support combining drugs and nonpharmacological techniques?
- How can the risk of analgesia-related complications be reduced?

**What will influence the choice of therapy?**

Many factors influence the therapy selected. These include the expected intensity and duration of pain, the age of the child at any previous unpleasant experience, whether the need results from an emergency, what the environment is like and the human resources available. Even in the case of similar procedures, therapeutic interventions sometimes vary considerably even in the same country. In a Swedish nationwide survey of pain treatment in paediatric oncology, lumbar punctures were performed under general anaesthesia in half of the institutions taking part and without general anaesthesia in the remaining centres. The expected intensity and duration of pain depends on the procedure involved and on the patient. Even a simple venous puncture can be described as the worst pain for some children. There is evidence that young children experience more distress and warrant more consideration than older children subjected to similar procedures. Safety considerations are essential when painful procedures are to be managed in remote loca-
tions. Education of nursing staff and of physicians without specialist training in anaesthesiology is a key issue in improving the safety of analgesia-sedation techniques.

**Which procedures are included?**

‘Procedural pain’ includes pain caused by many different procedures and situations. The procedures involved ranged from simple phlebotomy to invasive procedures involving serious risks should the patient move in response to the painful stimulus.

**Are therapeutic interventions supported by efficacy and safety data?**

Procedures can be divided into three categories in terms of pain and/or discomfort:

- Minor (venipuncture, Port-a-cath puncture, intravenous cannulation)
- Moderate (lumbar puncture, bone marrow aspiration)
- Major (fracture reduction, endoscopy)

For minor and moderate procedures 50% nitrous oxide and local anaesthetics, used alone or in combination, have clearly proved their effectiveness and safety. Other oral, intravenous/intramuscular agents of many chemical groups are currently in use. However, although many practitioners have anecdotal practice patterns that they believe are highly successful, the literature does not clearly support any one practice pattern over others.

**Is there any evidence to support combining drugs and nonpharmacological techniques?**

A wide range of behavioural and cognitive techniques has been found to be efficacious in helping children to cope with acute procedural pain. Many existing interventions and assessment tools are reasonably easy to use, allowing practitioners to identify the children who will be most vulnerable to pain and to reduce pain-related distress significantly in these children. However, the degree to which cognitive-behavioural management can be applied is limited in a child who is very young or has already been severely traumatised. The availability of expert practitioners is also limited in many centres.

**How can the risk of analgesia-related complications be reduced?**

Large surveys of adverse events encountered during procedural sedation have been reported in the past. In studies involving midazolam-fentanyl- and propofol-fentanyl-based regimens respiratory adverse event rates of 5–10% have been observed.
In contrast, the incidence of serious adverse events is around 1% with such agents as low-dose i.v. ketamine or nitrous oxide.

Prevention of procedural pain should be a priority for all physicians. Premixed nitrous oxide, local anaesthetics and low-dose i.v. ketamine share the same advantageous safety profile and are useful for most minor and moderately extensive procedures. The combination of hypnotics and opioids requires close monitoring and should be reserved for trained physicians. Cognitive behavioural therapies are a valuable adjunct that can be applied to reduce procedure-related distress and should be used whenever possible. Organisation and education are essential to reduce the potential hazards associated with unintentionally deep sedation. The published guidelines should be followed to minimise the incidence of severe adverse events [30].

References


