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THERAPY IN PRACTICE

Postoperative Pain Management in Children and Infants: An Update

Christopher Brasher · Benjamin Gafsous · Sophie Dugue · Anne Thiollier · Joelle Kinderf · Yves Nivoche · Robert Grace · Souhayl Dahmani

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Abstract Many factors contribute to suboptimal pain management in children. Current evidence suggests that severe pain in children has significant long-lasting effects, even more so than in adults. In particular, recent evidence suggests a lack of optimal postoperative pain management in children, especially following ambulatory surgery. This review provides simple guidelines for the management of postoperative pain in children. It discusses the long-term effects of severe pain and how to evaluate pain in both healthy and neurologically impaired children, including neonates. Currently available treatment options are discussed with reference to the efficacy and side effects of opioid and non-opioid and regional analgesic techniques. The impact of preoperative anxiety on postoperative pain, and the efficacy of some nonpharmacological techniques such as hypnosis or distraction, are also discussed. Finally, basic organizational strategies are described, aiming to promote safer and more efficient postoperative pain management in children.

Received from the Department of Anesthesiology, Intensive Care and Pain Management, Robert Debré University Hospital.

C. Brasher · B. Gafsous · Y. Nivoche · S. Dahmani (✉)
Department of Anesthesiology, Intensive Care, Robert Debré Hospital, 48 Bd Sérurier, 75019 Paris, France
e-mail: souhayl.dahmani@rdb.aphp.fr

C. Brasher · B. Gafsous · S. Dugue · Y. Nivoche · S. Dahmani
University Paris Diderot, Paris VII. Paris Sorbonne Cité, Paris, France

S. Dugue · A. Thiollier · J. Kinderf · S. Dahmani
Department of Pain Management, Robert Debré University Hospital, Paris, France

Y. Nivoche · S. Dahmani
INSERM UMR U 676, Robert Debré University Hospital, Paris, France

R. Grace
Department of Anaesthesia, Intensive Care and Peri-operative Medicine, Cairns Hospital, Cairns, QLD, Australia

1 Introduction

Pediatric postoperative pain is treated suboptimally in many centers—too many children still experience intense pain [1, 2]. One recent study found that in the first 7 days post-tonsillectomy, up to 50 % of children experienced intense pain [1]. Sagerdhl et al. [2] found that postoperative pain was the major complaint of pediatric patients following ambulatory surgery.

Many factors contribute to inadequate pain relief in children. For example, the following factors were identified in an as yet unpublished survey performed at Robert Debré University Hospital in 2009: lack of training and experience, difficulties in quantifying pain, inadequate use of pain scales, and low expectations with respect to postoperative analgesia. Elsewhere, inter-patient variability in pain perception and analgesic requirements [3], differences in pharmacodynamics and pharmacokinetics [4, 5], age-restricted drug licensing, and a relative paucity of studies examining pediatric analgesia have also been proposed as contributing factors. The opioid-sparing effect of paracetamol is an example of the latter. It has only recently been demonstrated in children, whereas such evidence in adults has been available for years [6]. Despite these difficulties, research attests to high-quality pediatric pain relief occurring in institutions employing simple therapeutic strategies and rigorous organization [7].

The aim of this review is to provide simple guidelines for managing postoperative pain in children. The review addresses the long-term effects attributable to severe pain,

describes some currently available treatment options, and briefly addresses organizational aspects leading to improved pain management in children.

2 Part 1—the Long-Term Effects of Pain

For decades, children and infants were considered to be insensitive to pain. The pain experience was thought to be unavoidable, with the further assumption that it would be forgotten and without consequence. However, recent work has demonstrated the opposite. Current evidence suggests that severe pain in children has significant long-term effects. Research examining inflammatory pain models has observed physical cell changes and sensitization/hyperalgesia phenomena (the latter has also been observed in adults). Inflammation in rat neonates induces dorsal horn afferent nerve terminal expansion suggestive of increased pain transmission, and these changes persist into adulthood. Adult rat dorsal horns do not display this plasticity [8]. Human studies have demonstrated that neonates who experience significant pain during surgery or in critical care subsequently have more intense pain responses to noxious stimuli [9–11]. Nociceptive activation of multiple brain regions occurs up to 16 years after neonatal intensive care in preterm infants but not in controls [9]. Opioid-induced pain sensitivity has also been described in children [12–14]. These discoveries and others like them have changed perceptions about pain in childhood. More active pain management in children is being promoted in order to reduce these sensitization phenomena.

Chronic pain is another potentially significant consequence of acute pain. Chronic pain has been estimated to occur in up to 30 % of adults, with similar rates reported in children [15, 16]. High pain scores at 2 weeks post-surgery have been identified as a risk factor for having chronic pain at 1 year [16]. Common sense suggests that a reduction in acute postoperative pain may lead to a reduced incidence of chronic pain.

Given the potential for long-term sequelae, it is important that acute postoperative pain in children is optimally managed from the outset.

3 Part 2—Pain Assessment

Pain evaluation is important when managing postoperative pain in children. Analgesic treatment should be instigated and its efficacy judged as a result of formal pain evaluation. The evaluation of pain is based on two important principles. First, self-assessment of pain intensity is superior to third-party assessment; second, a consistent single tool should be used for any given patient [17–19]. Within large institutions, adherence to these principles sometimes involves substantial effort. Written pain management protocols are required along with regular training and education for surgical and pain management teams.

The appropriate pain evaluation tool is dependent on the child's age and their understanding of pain and of the tool [17]. Ideally, the most appropriate pain evaluation tool should be identified during pre-anesthetic consultation. School-age children are relatively straightforward, as they understand and are capable of choosing and using self-evaluation tools, such as the Visual Analog Scale, or one of the available, well-researched 'faces' pain scales, such as the Wong–Baker FACES® Pain Rating Scale[1] [20]. Pain assessment is more problematic in younger or neuro-cognitively delayed children, where third-party assessment tools are required. In general, third-party scores are a mix of behavioral variables, such as crying, leg or arm movements, and agitation, occasionally combined with physiological variables, such as heart rate and blood pressure. Commonly used postoperative pain scales include FLACC (Face, Legs, Activity, Cry, Consolability; Table 1) [21], CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) [22], COMFORT [23–25], and OPS (Objective Pain Scale) [26, 27]. The PPPM (Parents' Postoperative Pain Measure) scale is particularly useful for pain assessment at home following ambulatory surgery [27–29]. A short-form 10-point scale (the PPPM-SF) has been recently developed in order to simplify parents' use of this tool [30].

Other specific scales, such as NCCPC-PV (Non-communicating Children Pain Checklist—Postoperative Version) [31, 32] and the modified FLACC scale [33], have been validated for cognitively impaired children. All such scales have limitations, and third-party score variables are by definition nonspecific. However, the pain scores do decrease with analgesia and are reproducible across populations, indicating that they have genuine value in assessing pain. Sedative agents influence these scores, making pain assessment problematic when using medications such as ketamine or α2-agonists [22, 34, 35]. Furthermore, most scales have been validated for one specific age group and as such cannot be used in all children. Detailed reviews have been published on this topic [17, 18, 22]. Given the complexity and number of tools available, clear and simple protocols for each institution are desirable.

4 Part 3—Systemic Agents for Postoperative Pain Management

Many different analgesics and techniques are available to treat postoperative pain in children. Most common adult

[1] http://www.wongbakerfaces.org/.

Table 1 Face, Legs, Activity, Cry, Consolability (FLACC) scale

Criteria	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractible	Difficult to console or comfort

treatments can be translated for use in children. However, the pharmacokinetics and pharmacodynamics of medications are often modified in children, resulting in differences in comparison with adults.

4.1 Opioids

Opioids are common analgesics widely used for moderate to severe postoperative pain. These μ receptor agonists are known to be effective. Commonly used opioids include pure μ opioid agonists, such as morphine, and mixed agonist–antagonists, such as nalbuphine.

The major advantage of agonist–antagonists is their ceiling effect, theoretically producing a reduced risk of respiratory depression, pruritus, constipation, and urinary retention [36]. Agonist–antagonists are easy to use, and their doses are predictably effective. Nalbuphine is one such agonist–antagonist and is commonly used in Europe. It is usually administered as an initial bolus of 0.2 $mg \cdot kg^{-1}$, followed by continuous administration of 1 $mg \cdot kg^{-1} \cdot day^{-1}$. These doses are indicative only, and a recent study examining the intravenous pharmacokinetics in children and infants emphasized the need for age-specific dosage [37]. Nalbuphine may also be administered per rectum, although its bioavailability is decreased and variable [38]. The major limitation of nalbuphine is its analgesic ceiling effect, which may result in insufficient analgesia for patients in severe pain. Health professionals must have a low threshold for switching to more effective therapies when treatment failure occurs with mixed agonist–antagonists. A theoretical limitation of agonist–antagonists is their μ receptor antagonism subsequently decreasing the efficacy of rescue analgesia with pure μ opioid agonists. However, in a recent study, five groups of patients were given different morphine/nalbuphine admixtures, and interaction between these two drugs was found to be additive [39].

Morphine is the most commonly used μ agonist. The pharmacokinetics of morphine in children are similar to those in adults. Neonates are, however, the exception, as morphine doses need to be reduced secondary to hepatic immaturity [40–42]. Liver cytochrome enzyme function is an important factor in producing the major metabolite morphine-6-glucuronide (M6G) [43, 44]. Active morphine metabolite production and clearance are modified in the first weeks of life, with the sum effect of relative morphine and M6G accumulation [5, 44, 45] (Tables 2, 3). From infancy on, decreased M6G production compensates for reduced urinary excretion. The precise role played by M6G in morphine analgesia is debatable. Morphine pharmacokinetics do not vary greatly between patients with normal renal function. On the other hand, morphine pharmacodynamics vary greatly between patients, and no real correlation has been found between the drug dose, pain intensity, and clinical outcome [4]. To overcome this inter-patient variability, the best method of morphine administration is by patient- or nurse-controlled bolus analgesia. One difference in morphine administration in children is the frequent use of a background infusion, especially at night. A background infusion allows for improved sleep and analgesia quality without increasing side effects [7]. Regardless of whether morphine is patient controlled or nurse controlled or whether it is administered with or without a background infusion, regular monitoring of efficacy and vital signs is required. Written prescription guidelines and respiratory depression response protocols are also needed (see Protocol 1 from our institution). In one published nurse-controlled analgesia series, 1.7 % of patients experienced respiratory depression, necessitating antagonist administration [46]. Monitoring for respiratory depression is particularly important at night, as parental vigilance is diminished.

Table 2 Morphine pharmacokinetics according to patient age [5]

	V_d ($L \cdot kg^{-1}$)	$t_{½}$ (h)	CL ($mL \cdot min^{-1} \cdot kg^{-1}$)
Premature neonates	–	9.0 ± 3.4	2.2 ± 0.7
Term neonates	2.8 ± 2.6	6.5 ± 2.8	8.1 ± 3.2
Infants and children	–	2.0 ± 1.8	23.6 ± 8.5
Adults	–	2.1 ± 0.9	38 ± 5.3

CL clearance, $t_{½}$ elimination half-life, V_d volume of distribution

Protocol 1

Postoperative intravenous morphine prescription
S sedation scale with *S0* awake, *S1* intermittently asleep but easily woken, *S2* asleep, woken by verbal stimulation, *S3* asleep, woken by tactile stimulation

1. Intravenous morphine titration
Initial bolus: 100 $\mu g \cdot kg^{-1}$
Subsequent doses: 25 $\mu g \cdot kg^{-1}$ every 5–7 min to effect (VAS $\leq$ 30 mm; mild pain; EDIN $\leq$ 5 or OPS $\leq$ 3/10)
S2 sedation = stop titration
Usual total dose: 100–200 $\mu g \cdot kg^{-1}$

2. PCA protocols

a Bolus only
Bolus: 15–25 $\mu g \cdot kg^{-1}$
Refractory Period: 5–10 min
Maximum dose per 4 h: 400 $\mu g \cdot kg^{-1}$

b Background infusion + Bolus
Background infusion 10–30 $\mu g \cdot kg^{-1} \cdot h^{-1}$
Bolus: 20 $\mu g \cdot kg^{-1}$
Refractory period: 5–10 min
Maximum dose per 4 h: 400 $\mu g \cdot kg^{-1}$
To be used particularly at night and during the first 24 to 48 h post-operatively

3. Less than 3 months of age
Reduce doses by 50 %
Bolus: 10 $\mu g \cdot kg^{-1}$, with or without background infusion
Background infusion 10 $\mu g \cdot kg^{-1} 1 \cdot h^{-1}$
Maximum dose per 4 h: 200 $\mu g \cdot kg^{-1}$

4. Monitoring sedation scale dependent
S0 every 4 h
S1 hourly

5. Additional prescriptions
Laxatives prescribed immediately upon re-feeding
Pruritus: Nalbuphine 0.12 $mg \cdot kg^{-1} \cdot day^{-1}$ (10% analgesic dose), ±Hydroxyzine PRN
PONV prevention and treatment as per protocols

6. Multimodal analgesia unless contra-indicated
Paracetamol, NSAIDs Nefopam

7. Consider background infusions and bolus PCA for all spinal surgery and cerebral palsy patients

8. No background infusions and increased monitoring for patients with renal impairment

Oral opioid μ agonist formulations are available (e.g. hydromorphone, oxycodone). They represent a useful alternative to intravenous morphine. However, the fixed doses prescribed using oral preparations and the time required to judge the effect and adjust the dosage limit their usefulness in the period immediately following surgery. Furthermore, vomiting postoperatively is not uncommon and clouds the actual dose administered. The real interest in oral agents is the role they may play in pain management following discharge from hospital. However, their efficacy remains to be proven in children, and recent evidence suggests that overuse of oral opioids in the general population may ultimately limit their application [47].

A recent meta-analysis investigated the efficacy of morphine for postoperative pain in children [48]. Morphine was effective in relieving postoperative pain but no better than other analgesics such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), and regional analgesia. These findings, coupled with the potential adverse effects of hyperalgesia and tolerance recently demonstrated in children [12], have fueled efforts to identify additive and synergistic associations between opioids and non-opioid treatments, so as to reduce total opioid dosage in the postoperative period.

Codeine is a commonly prescribed opioid. It is a morphine pro-drug with an easy-to-use oral formulation making it popular for pain management following ambulatory surgery, especially in children. It is metabolized to morphine in the liver by the cytochrome P450 (CYP) isoenzyme 2D6 [49]. Codeine's safety has recently been questioned. A recent US Food and Drug Administration paper discussed the risks of codeine in ultra-rapid metabolizers [49]. Following case reports describing postoperative respiratory depression and death (most post-tonsillectomy), the European Medicines Agency restricted the use of codeine to children over 12 years of age [50]. Ultra-rapid codeine metabolizers appear to be at risk of producing more morphine than the general population, potentially leading to overdose. Another limitation of codeine use is slow metabolizers, who transform less codeine into morphine, and for whom codeine has a lesser analgesic effect [49]. These safety and efficacy concerns have led to the use of opioids other than codeine. Indeed, it has become standard practice to use other analgesic medicines such as NSAIDs or tramadol following tonsillectomy.

4.2 Non-opioid Analgesics

Non-opioid analgesics include various compounds of differing actions and efficacy. Commonly used non-opioid analgesics include paracetamol, NSAIDs, dexamethasone, tramadol, and nefopam (the latter principally in Europe).

4.2.1 Paracetamol

Paracetamol (acetaminophen) is the most commonly used non-opioid analgesic. Its mechanism of action includes

Table 3 Pharmacokinetics of morphine and its metabolite morphine-6-glucuronide (M6G) in children and adults

	Lotsch et al. (IV) [43]—in adults		Hain et al. (IV) [44]—in children	
	Morphine	M6G	Morphine	M6G
$t_{½}$ (h)	2.1 ± 0.9	1.7 ± 0.6	1.47	5.35
CL	32.7 ± 6 mL·min^{-1}·kg^{-1}	2.2 ± 0.4 mL·min^{-1}·kg^{-1}	35 mL·min^{-1}	7 mL·min^{-1}
V_d (L·kg^{-1})	1.8 ± 0.3	0.12 ± 0.02	3.6	–
C_{max} (nmol·L^{-1})	–	–	106	130

Values are displayed as mean or mean ± standard deviation

CL clearance, C_{max} maximum concentration, *IV* intravenous, $t_{½}$ elimination half-life, V_d volume of distribution

blockade of prostaglandin and substance-P production and modulation of nitric oxide production. The weight-dependent pharmacokinetics of paracetamol are relatively constant from 18 months to 18 years of age [3]. Paracetamol's most well-known adverse effect is hepatotoxicity. This is readily avoided by respecting the daily maximum dose, which varies with age and liver maturation. Most hepatotoxicity follows drug administration errors involving major overdoses in neonates and infants when paracetamol is given via the intravenous route. The daily dosages for all routes of administration are 100 mg·kg^{-1} in children, 75 mg·kg^{-1} in infants, 60 mg·kg^{-1} in term and preterm neonates older than 32 weeks post-conceptual age, and 40 mg·kg^{-1} in younger neonates [7]. Neonatal doses are heavily debated and vary internationally from 30 to 60 mg·kg^{-1}. Paracetamol alone is effective for moderate postoperative pain and is most effective when a loading dose of 25 mg·kg^{-1} is given, followed by regular 10–15 mg·kg^{-1} doses every 6 h. Paracetamol can be administered intravenously, orally, or intra-rectally. The latter is variably used, as some studies have demonstrated diminished and unpredictable bioavailability [51]. However, 40 mg·kg^{-1} of intra-rectal paracetamol has been found to be as effective as 15 mg·kg^{-1} given intravenously following adenotonsillectomy [52]. Also, both high-dose (40 mg·kg^{-1}) and low-dose (20 mg·kg^{-1}) intra-rectal paracetamol provide similar and effective analgesia following ophthalmological surgery [53], and other studies have also shown that intra-rectal paracetamol provides excellent analgesia [52, 54, 55]. As such, many institutions use it to good effect. Recent studies of paracetamol when used in association with NSAIDs have demonstrated real and significant reductions in opioid requirements postoperatively [6, 56]. Thus, opioid use should always be accompanied by paracetamol and NSAIDs, unless they are contraindicated. A number of studies have examined the bioavailability of postoperative oral paracetamol, particularly after abdominal surgery. Some evidence indicates that paracetamol absorption is similar pre- and postoperatively, even following major abdominal surgery [57]. In contrast, other studies have demonstrated a reduction in absorption during the first 12 h postoperatively [58, 59]. Thus, intravenous administration is widely recommended during the first 12–24 h post-abdominal surgery. Oral absorption is unchanged by non-gastrointestinal-tract surgery, and oral paracetamol may be prescribed immediately.

4.2.2 Nonsteroidal Anti-inflammatory Drugs

NSAIDs are cyclooxygenase (COX) inhibitors, which constrain the production of prostaglandins. NSAIDs cause renal and gastrointestinal toxicity, have antithrombotic effects, and, in animal models, delay wound and bone healing. As a consequence, selective COX-1 inhibitors have been developed, and their use is widespread among adults. However, there is a paucity of studies examining selective COX-1 inhibitors in pediatrics, and recent concerns over their adverse cardiovascular effects have limited their application in children [60]. Despite their efficacy as analgesics, the use of nonselective NSAIDs is often diminished because of concerns over their potential side effects, as outlined above [61]. However, most serious adverse events have been reported by neonatologists treating patent ductus arteriosus. These patients receive significantly higher doses of NSAIDs, and they are given for longer time periods than those encountered postoperatively [62]. Reports of serious side effects in the general pediatric population suggest incidence rates of 0.8–0.24 % [61, 63]. Thus, given NSAIDs' analgesic efficacy and opioid-sparing properties, they should be prescribed regularly, either alone or in combination with paracetamol [56, 64]. Contraindications to NSAIDs include hypovolemia, renal impairment, and active infection—and, as in adults, treatment should be limited to the first few days postoperatively. That said, excellent tolerance in pediatric populations has been reported with NSAID use for up to 3 weeks [65]. Most NSAIDs are not licensed for use in patients under 6 months of age. However, studies using NSAIDs postoperatively in neonates have demonstrated good efficacy and tolerance in this age group [66]. The pharmacokinetics of some NSAIDs differ in pediatric populations. One such example is ketoprofen. Although similar plasma concentrations have been reported using adult

administration regimens [67], one study found that higher doses of ketoprofen were required in children to achieve effective central nervous system concentrations [68].

Opinion varies about the use of NSAIDs post-adenotonsillectomy. One meta-analysis showed an increased risk of bleeding, but another did not [69, 70]. Until this issue is clarified, caution—but not necessarily prohibition—should be employed when using NSAIDs post-adenotonsillectomy. Given recent concerns over codeine use, clinicians must make their own decisions regarding the risk:benefit ratio of NSAIDs versus opiates post-adenotonsillectomy. A recent study, which demonstrated an increased risk of bleeding when dexamethasone was combined with NSAIDs post-adenotonsillectomy, has further confused the issue [71].

4.2.3 Nefopam

Nefopam is a non-opioid analgesic, whose mechanism of action is poorly understood. It is structurally unrelated to other compounds. Nefopam is widely used in adult patients in Europe. It has a demonstrated opioid-sparing effect [72] and is licensed for use in children over 16 years of age. Its use in children has been poorly studied, although off-label use is common. The usual dose is a 1–2 $mg \cdot kg^{-1}$ bolus every 6 h. Continuous infusions appear to be associated with higher rates of parasympathomimetic side effects, such as diaphoresis and tachycardia. Although nefopam is effective in treating postoperative pain in adults, it can currently only be recommended for use in older children.

4.2.4 Tramadol

Tramadol is a synthetic analog of codeine, which acts via μ, κ, and δ opioid receptors and by inhibiting norepinephrine and serotonin reuptake [73]. Tramadol is metabolized in the liver with production of a potent metabolite, O-desmethyl-tramadol. Tramadol's liver metabolism is dependent on CYP2D6 (the same enzyme responsible for codeine's transformation to morphine). Tramadol is less potent than morphine or codeine. However, the absence of described respiratory depression makes tramadol a good alternative to codeine. Tramadol may be administered orally or intravenously. The optimal dosage is 2 $mg \cdot kg^{-1}$ up to a maximum of four times daily. High rates of nausea and vomiting may limit tramadol's use.

4.2.5 Anti-hyperalgesic Compounds

The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine is the best known analgesic in this class. Ketamine has recently undergone a resurgence of use in adults. However, results in children have been less encouraging, with a recent meta-analysis showing that ketamine provides no additional benefit when used with opioids or as an adjuvant to regional analgesia [35]. In children, higher doses of ketamine are probably required for opioid sparing than in adults [35]. One study of various ketamine doses up to 1 $mg \cdot kg^{-1}$ showed no reduction in morphine consumption post-tonsillectomy [74]. These studies suggest that, in children at least, ketamine has no adjuvant role to play when used with opioids.

Gabapentin is another anti-hyperalgesic agent. Like ketamine, gabapentin is commonly used in adults, but, to date, little research has been performed in children. In one study of major spinal surgery in children, gabapentin was found to reduce postoperative pain and to have a morphine-sparing effect [75]. Further research is required, but use of gabapentin in children for postoperative pain management appears promising.

4.2.6 Dexamethasone

Inflammation plays an important role in the genesis of postoperative pain. Dexamethasone has been used for the prevention of postoperative nausea and vomiting for some time. Subsequent studies have focused on dexamethasone's analgesic properties [71]. In adults, modest but significant reductions in postoperative pain and opioid consumption have been demonstrated with dexamethasone [76]. Pediatric studies following circumcision and adenotonsillectomy have also demonstrated improved pain control and reduced agitation with intravenous or intramuscular dexamethasone [77, 78]. Given these findings, dexamethasone is widely employed as an adjuvant in the treatment of postoperative pain in children.

4.2.7 Alpha 2 Agonists—Clonidine and Dexmedetomidine

Alpha 2 agonists demonstrate hypnotic and analgesic properties. Clonidine is widely used as an adjuvant to prolong and potentiate regional analgesia. Its sedative properties may also be exploited as premedication. A recent meta-analysis has demonstrated that premedication with clonidine leads to a decrease in postoperative pain [79]. Dexmedetomidine has also been used as a hypnotic and anesthetic agent during surgery, and for sedation during pediatric imaging, noninvasive procedures, and intensive care [34, 80]. A recent meta-analysis found that dexmedetomidine has the same efficacy as opioids for managing pain post-adenotonsillectomy [81]. Intraoperative dexmedetomidine has been found to produce anesthesia that is more hemodynamically stable, reduce postoperative opioid consumption, and increases the opioid-free interval when given with volatile anesthetics for adenotonsillectomy in patients with obstructive sleep apnea

[82, 83]. However, the longer recovery time makes its use in ambulatory patients potentially problematic [83]. If this finding can be reproduced, dexmedetomidine may prove to be another useful analgesic in the management of postoperative pain in children.

5 Part 4—Regional Analgesia

Regional analgesia has increased enormously in popularity for the management of postoperative pain in children. This expansion is in part due to the problems of respiratory depression, nausea, tolerance, and hyperalgesia associated with opioids, but is also due to the expansion of ultrasound-guided regional analgesia (USGRA). USGRA results in fewer block failures and decreased total doses of local anesthetic [84, 85]. Most if not all studies comparing regional and systemic analgesia have found that regional analgesia is superior in reducing postoperative pain, hastening recovery, and reducing intraoperative blood loss [48, 86].

Regional analgesia can be provided by local, peripheral, or central blockade. Direct infiltration of local anesthetic into the wound has the advantage of being a simple and inexpensive method, although it is of uncertain benefit. Studies of efficacy have yielded variable results, and few studies have been performed in children [87, 88]. In adults, intra-peritoneal injection of local anesthetics during laparoscopic abdominal surgery has been shown to provide analgesia and an opioid-sparing effect [89].

Intrathecal and epidural blockade can be used to manage postoperative pain in children. Caudal analgesia is relatively specific to pediatrics, widely practiced, and probably effective [90]. Most 'adult' peripheral blocks may be performed in children, although they are usually performed under anesthesia to ensure immobility. Studies of block safety in anesthetized children have not demonstrated any increased risk of nerve injury, compared with blocks performed in awake adults [91, 92]. Older children may accept and tolerate blocks performed awake when they are given adequate explanation and premedication. Limb plexus blocks and abdominal or thoracic wall blocks, such as the transversus abdominis plane (TAP) or the ilioinguinal-iliohypogastric block, are also commonly performed [7].

The preferred local anesthetics are ropivacaine 0.1 % and levo-bupivacaine 0.125 % because of their relatively long-lasting effect, theoretically lower systemic complication rates, and low incidence of motor blockade at these concentrations [7].

Clinicians are generally well aware of the risk of cardiac and neurotoxicity when using local anesthetics. The systemic toxicity of local anesthetics is dependent on the free plasma concentration. Free plasma concentrations may be elevated in children because of decreased clearance as a consequence of hepatic and renal immaturity, or because of decreased binding by plasma proteins. Consequently, clinicians must have an appropriate level of respect for maximum recommended doses when using local anesthetics in children [93] (Table 4). Intralipid, used to manage systemic toxicity, must also be available. Although most cases and studies concerning intralipid have involved adults, its efficacy during resuscitation for local anesthetic toxicity has also been reported in children and infants [94]. The maximum systemic concentration of local anesthetic after regional anesthesia is dependent upon the site of injection. In adults, epidural and intercostal blocks result in more rapid absorption of local anesthetics and higher systemic concentrations than lower or upper limb blocks, and there is no reason to suppose that this does not occur similarly in children [95, 96]. The use of adjuvants, such as opioids [97], ketamine [64, 97, 98], or clonidine [34, 97, 99, 100], that decrease the total dose of local anesthetics and prolong their duration of action is to be encouraged.

The choice between single-shot or continuous infusion must be made when using regional anesthesia. Single-shot injection is simpler and is generally reserved for surgery of short duration with less prolonged postoperative pain. As such, single-shot techniques are well suited to ambulatory surgery. Commonly performed single-shot blocks include ilioinguinal-iliohypogastric, TAP, penile, para-umbilical, upper and lower limb plexus and caudal blocks, and single-shot spinal analgesia [7]. Continuous regional analgesia with local anesthetics with or without adjuvants is performed via epidural, trunk, or limb catheter insertion. Patient- or nurse-controlled boluses of local anesthetics (and adjuvants) is standard with or without a background infusion.

Simple precautions need to be taken when performing regional anesthesia. An aseptic environment must be maintained, particularly when a continuous infusion catheter is inserted. Coagulation disorders need to be excluded before blockade in proximity to vessels and nerves and, in particular, before neuraxial blockade, where the complications of coagulopathy may be catastrophic. Epidural and spinal analgesia can impair sympathetic blood pressure autoregulation and are to be avoided in situations of hemodynamic instability. Finally, attention should be paid to recovery of motor and urinary function after neuraxial or lower limb blocks, particularly during ambulatory surgery.

Herniorrhaphy in former preterm infants is a specific and common situation where regional anesthesia should be considered. These patients are at high risk of postoperative apnea following general anesthesia [101, 102]. Spinal anesthesia—alone or combined with volatile anesthesia and regional analgesia—is desirable in this setting. Stand-alone spinal anesthesia is often preferred in infants

Table 4 Maximal doses of common local anesthetics [93]

Local anesthetic	Single injection ($mg \cdot kg^{-1}$)	Continuous infusion [age >6 months] ($mg \cdot kg^{-1} \cdot h^{-1}$)	Continuous infusion [age <6 months] ($mg \cdot kg^{-1} \cdot h^{-1}$)
Levo-bupivacaine	3	0.4	0.2
Ropivacaine	3	0.4	0.2
Lidocaine	5	1.6	0.8
Lidocaine with epinephrine	7		

weighing less than 5 kg. It is usually performed in the sitting position, with an intrathecal injection of 0.75–1 $mL \cdot kg^{-1}$ of hyperbaric ('heavy') 0.5 % bupivacaine [102]. The block duration is limited to around 45 min, and the spinal anesthesia is only performed once the surgeon and nursing staff are fully prepared. Bilateral hernias in this setting are often problematic because of the increased operating time [101]. One published alternative is awake caudal anesthesia, using 1.2 $mL \cdot kg^{-1}$ of levobupivacaine or ropivacaine [103].

6 Part 5—Nonpharmacological Pain Management

There is a growing trend toward the use of nonpharmacological techniques to supplement analgesia in children. The nonpharmacological approach to postoperative pain relies primarily upon a reduction in the level of perioperative anxiety. A substantial amount of research has been performed on preoperative predictors of anxiety in children and its prevention. Psychological factors have been found to influence pain intensity and analgesic requirements [14]. The influence of the child–parent interaction and parental anxiety on children's pain perception has been well demonstrated. Many successful strategies have been found to reduce anxiety, including anesthetic induction with decreased sensory stimuli, music therapy, distraction and hypnosis, clown doctors, child life specialists, acupressure, video preparation immediately prior to induction, and general information for parents. Parental presence during induction may be beneficial but is less effective when parental anxiety levels are increased, as parent-to-child transmission of anxiety may be a problem. Kain et al. evaluated a family-based preparation named the ADVANCE strategy and found that it decreased preoperative anxiety and postoperative pain [104]. The strategy consists of providing parents with information on how to reduce their child's anxiety, and techniques to distract children while they are in the waiting area and during induction of anesthesia. Calm children and calm parents trained in coping strategies may well result in time saved and reduced analgesic and sedative consumption.

In addition to family-centered anxiety prevention, some authors have proposed hypnosis as a means to prevent or assist in the treatment of postoperative or procedural pain. Studies have found that preoperative hypnosis decreases perioperative anxiety and shortens the hospital stay in surgical patients [105]. Similar results were found when hypnosis was used during the postoperative period, where a significant effect on postoperative pain was observed [105]. The advantage of hypnosis in children is that they are very receptive to suggestion. However, training in hypnosis is costly, and the procedure itself takes time. Nonpharmacological pain management may initially seem time consuming and costly, but these strategies cannot be ignored by departments attempting to improve pediatric pain management.

7 Part 6—Organization of an Effective Pediatric Pain Management Service

Limited data are available on the intensity of postoperative pain in children. Typically, postoperative pain is greatest in the first 2 days after surgery, with a progressive decline thereafter, although some studies have reported that severe pain may last up to 7 days [2]. Thus, postoperative pain management tends to focus upon this initial period, adapting to residual pain thereafter.

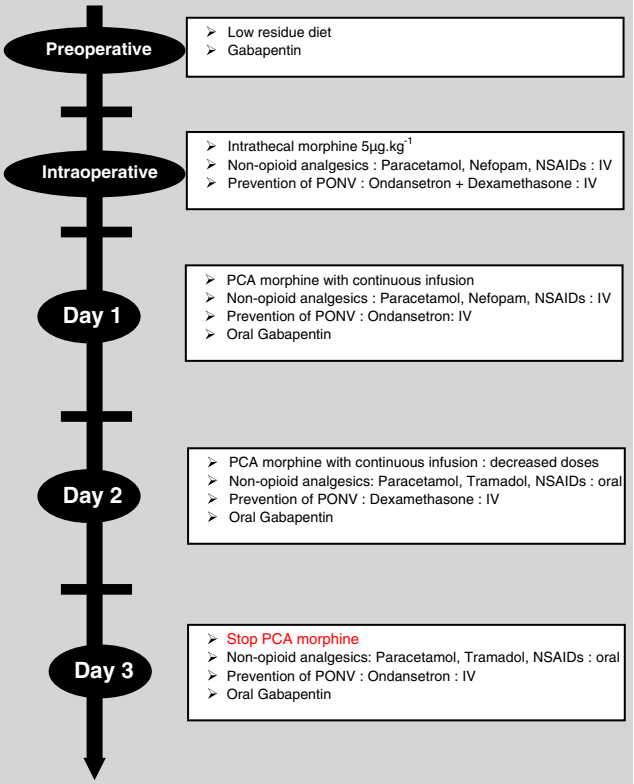
A general regimen for pain management is to administer non-opioid analgesics and regional analgesia approximately 1 h before the end of surgery and to commence opioid analgesia on arrival in the postoperative care unit. The duration of opioid analgesia and regional analgesia is usually limited to 48–72 h. This minimizes the risks of opioid sensitization and infectious complications from catheters used in regional blocks. Intravenous analgesic administration is generally preferred, although, as discussed earlier, there is mounting evidence to support the oral route, particularly in non-abdominal surgery.

Optimal postoperative pain relief is best achieved with regional analgesia and thus, wherever possible, nerve blockade should be considered. Because of the variability and unpredictable nature of postoperative pain, both opioids and regional analgesia should be titrated to need, using patient- or nurse-controlled analgesia. The pain management plan must not be restricted to the first postoperative day. Health professionals must ensure adequate pain

management following discharge, including parental education and an adequate medication supply. The management of pediatric postoperative pain post-discharge remains an ongoing challenge for physicians as ambulatory surgery increases in caseload and complexity. Undermanaged pain at home increases the risk of developing chronic pain states [16]. Pain relief at home can be achieved by systemic and regional analgesia. Recent evidence has suggested that regional analgesia at home is both safe and efficacious, especially following orthopedic surgery [100, 106, 107]. In order to illustrate these concepts, the example of spinal surgery from our institution is presented (Protocol 2).

Protocol 2

Perioperative pain management for spine surgery. *IV* intravenous, *NSAIDs* non-steroidal anti-inflammatory drugs, *PCA* patient-controlled analgesia, *PONV* postoperative nausea and vomiting



One of the most important factors in managing postoperative pain is institutional organization. The first factor to consider is physician involvement. Most patients have input from a variety of staff. Surgeons, anesthesiologists, nurses, and other staff may communicate differing views on pain management. Consequently, one of the most practical ways to cope with multiple inputs and opinions is to establish written pain protocols and procedures for all clinicians to follow. Alternatively, a dedicated pain management team can provide efficient, consistent, and effective postoperative pain management [108].

The second point to consider is ongoing professional education, especially with respect to nursing involvement in opioid administration and regional analgesia. Both opioids and local anesthetics have relatively narrow therapeutic indices and side effects that may require rapid emergency responses. In addition, both techniques may rely on nurse administration and, as such, nursing education is very important. Anesthesiologists require training too, especially in suitable regional techniques and the use of ultrasound. Systems should be put in place to allow long-term follow-up and treatment of postoperative pain at home, especially following ambulatory surgery. Nurse phone calls post-discharge are a common approach to this problem. Finally, a dedicated 'academic' team is required. Keeping up to date with the literature, translating advances in pain management into daily practice, and communicating with staff members about relevant advances in the field are the core duties of this team.

8 Conclusion

Postoperative pain management in children remains suboptimal in many centers. Current research suggests that, over and above immediate distress, severe pain may lead to abnormal pain responses such as hyperalgesia and chronic pain states. Generally speaking, optimal pain management in children requires a multimodal approach. Wherever possible, regional analgesia should be employed with a combination of systemic agents rather than relying on a single drug. Best practice suggests that opioids should not be administered alone. Adjuvant medications have been shown to reduce opioid requirements, and concerns regarding NSAID use in children may be overstated. Hospitals are complex institutions with large numbers of staff. Ongoing education and clear protocols for managing postoperative pain in children will improve services. The presence of a dedicated pain management team is ideal.

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Conflict of interest C.Brasher, B. Gafsou, S. Duge, A. Thiollier, J. Kinderf, Y. Nivoche, R. Grace, and S. Dahmani declare no conflicts of interest.

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