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Pain after surgery in children: clinical recommendations

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Abstract

Purpose of review—To summarize recent data related to the safety and efficacy of postoperative analgesia in children that influence clinical practice recommendations.

Recent findings—Postoperative pain continues to be experienced by hospitalized children and following discharge after short stay or ambulatory surgery. Updated recommendations for post-tonsillectomy analgesia exclude codeine and suggest regular administration of paracetamol and NSAID, but evidence for the most appropriate dose and type of opioid for rescue analgesia is limited. The incidence of opioid-related respiratory depression/over-sedation in hospitalized children ranges from 0.11-0.41%, with recent large series identifying high risk groups and contributory factors that can be targeted to minimize the risk of serious or permanent harm. Data demonstrating feasibility and safety of regional analgesic techniques is increasing, but additional and procedure-specific evidence would improve technique selection and inform discussions of efficacy and safety with patients and families/carers. Persistent postsurgical pain is increasingly recognized following major surgery in adolescents. Evaluation of potential predictive factors in clinical studies, and investigation of underlying mechanisms in laboratory studies, can identify targets for both pharmacological and non-pharmacological interventions.

Summary—Recommendations for postoperative pain in children continue to evolve, with data incorporated from randomized controlled trials, case series and large audits. Management of pain following surgery in children needs to encompass not only efficacy and safety in the immediate perioperative period, but also consider pain following discharge after ambulatory surgery, and the potential risk of persistent postsurgical pain following major surgery.

Keywords

pain; children; postoperative; analgesia; opioid

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INTRODUCTION

Advances in perioperative care of children continue to be made with increasing evidence-based practice for postoperative analgesia. However, moderate to severe pain is still

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experienced by up to 40% of hospitalized children [1], and specific high risk populations or types of surgery continue to present challenges. A Medline Search of publications related to postoperative pain and analgesia in children since January 2014 identified current controversies and topics with implications for clinical recommendations. The following were chosen for inclusion in this review : pain at home; opioid-related adverse events; evidence for safety and efficacy of regional anesthesia; and persistent postsurgical pain in children and adolescents.

PAIN AT HOME

Pain at home following outpatient or short stay surgery is common and can persist for days to weeks, with associated behavioral disturbance and increased time away from school [2]. The complexity of improving pain following hospital discharge is highlighted in recent reviews, with contributory barriers including: parental factors (e.g. a tendency to under-dose or provide suboptimal analgesia despite pain, often due to fear of medication side-effects); child factors (e.g. difficulty swallowing, anxiety); medication factors (e.g. incorrect type or dosing); and system factors (e.g. inadequate information). As a result, potential interventions and strategies for improvement need to encompass education and information, regular use of appropriate pain assessment tools, and a better analgesic regimen [2,3]. In addition to pain, the impact of child and parental anxiety should be considered. Wed-based parental and children preoperative preparation strategies that address patient anxiety and parental coping are being validated and may improve access to appropriate educational materials and interventions [4,5].

Tonsillectomy and codeine

Pain after tonsillectomy is a specific concern, both in terms of the degree and duration of pain following discharge, and the limited evidence to support safe and effective management with opioids. Improvements in analgesia are required, while minimizing the risk of PONV, bleeding, and respiratory depression, particularly in patients with obstructive sleep apnea [2,6-8]. Multiple regulatory authorities warn against using codeine in children, and contra-indicate use following tonsillectomy for obstructive sleep apnea, including the US Food and Drug Administration (http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm), UK Medicines and Healthcare Products Regulatory Agency (https://www.gov.uk/drug-safety-update/codeine-for-analgesia-restricted-use-in-children-because-of-reports-of-morphine-toxicity), European Medicines Agency (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f) and the Australian Therapeutic Goods Administration (https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-5-number-2-april-2014#codeine). A program of education and changing ordersets (e.g. substituting codeine with paracetamol/ibuprofen or oxycodone, using lower doses of oxycodone or oral morphine) effectively reduced in-hospital codeine use prior to its removal from a pediatric hospital formulary [9]. Although avoiding codeine may reduce risk for some, improved recognition of high risk cases, provision of adequate analgesia with appropriate dose adjustment, and adequate monitoring and duration of hospitalization remain priorities for the care of patients with OSA [7]. Within the constraints

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of the limited evidence for efficacy and safety of alternative preparations, updated practice recommendations have been developed [8,10].

Multimodal analgesia

The lack of analgesic efficacy of codeine following adenotonsillectomy has long been an impetus to develop alternative analgesic regimens [11]. Regular dosing of paracetamol and NSAIDs with limited rescue use of alternative opioids has been suggested, but further research is required to establish the most appropriate dose and type of opioid [8,10]. Adding NSAIDs and/or paracetamol (with an appropriate dose and route) reduces post-operative opioid requirements by 30%-40% [12,13]. Following adenotonsillectomy, current clinical recommendations for combination therapy with NSAID and paracetamol [8,14] are supported by recent reports of analgesic efficacy [15,16], and reductions in opioid requirements and PONV can be achieved without increasing adverse events [17-19]. Importantly, combining paracetamol and NSAID (diclofenac) achieves similar analgesia with lower doses than required if either drug is administered alone [20].

OPIOID-RELATED ADVERSE EVENTS

Adverse drug reactions are common in hospitalized children, with incidences around 17% reported in large prospective observational studies [6]. Drugs for postoperative pain management, particularly opioids, are major contributors, however this is also influenced by the relative proportion of surgical inpatients and inclusion of reactions across a range of severities. Pruritis and postoperative nausea and vomiting were most common and it was acknowledged that these reporting is more likely when patients are being specifically monitored for side effects and followed up by specialist pain management teams [6]. The incidence of critical incidents during opioid infusions was 1.7% (58 in 3500 infusions) in a large pediatric centre [21]. Consistent with other series [22-24], drug administration or prescription errors and pump malfunction were the most common adverse events, with many ‘near misses’ detected before harm.

The reported incidence of opioid-related respiratory depression/over-sedation in hospitalized children ranges from 0.11-0.41% [21-24]. Early recognition, respiratory support and naloxone administration significantly minimizes the risk of permanent harm [6,23]. Patients at increased risk include: respiratory, hepatic and neurological comorbidites; age under one year; preterm birth; extremes of weight (underweight or obese); ENT surgery; and co-administration of other sedative/depressant drugs. A higher rate of adverse events was found in patients not managed by an Acute Pain Service [21,24]. Root cause analysis of 14 severe incidents (including 9 cases of respiratory depression/over-sedation) identified communication, training, environment/equipment, or policies and procedures as contributory factors [21]. Minimising the risk of opioid-related adverse events should not be achieved at the expense of adequate analgesia. In fact, inadequate analgesia was felt to contribute to opioid-related adverse events in cases where excessive bolus doses were subsequently given to try and control pain [21]. The importance or standardized protocols, regular monitoring, education and communication between health care teams to ensure safe and effective use of opioids has again been emphasized [21,24]. Given the wide inter-individual variability in

morphine concentration-response, that can be influenced by pharmacokinetic, pharmacodynamic and pharmacogenomic factors [25], titration against individual response remains essential in clinical care.

REGIONAL ANALGESIA

Regional anesthesia continues to be an important component of peri-operative care and analgesia for pediatric patients. Although large series demonstrate low complication rates following pediatric regional anesthesia [26], recent systematic reviews and large series highlight the need for additional high quality evidence for efficacy of both peripheral [27,28] and neuraxial [29,30] techniques. Current conclusions of systematic reviews are limited by the small number of randomized controlled trials (RCTs), relatively poor methodological quality, and significant heterogeneity and variability in design, outcome measures, interventions and treatment types [27-29]. There is a need for both procedure-specific evidence [30] as developed for adult populations [31], in addition to age-specific information [29] as outcomes (e.g. sensitivity and type of pain assessment tool, analgesic dose requirements) are influenced by age and developmental stage.

Epidural analgesia

A database review of perioperative epidural analgesia cases (n=830) reported low mean pain scores, but with wide variability across the range of ages and surgeries included [30]. Higher pain scores were found in older children, which may reflect differences in the sensitivity of pain assessment and/or the types of surgery performed. Children undergoing spine surgery with an epidural placed by the surgeon at the end of the case, had higher pain scores than those undergoing abdominal or extremity surgery, and many patients required on demand systemic opioid in addition to regional local anesthetic techniques [30]. Thoracic surgery for pectus deformity similarly produces severe post-operative pain. In a systematic review of 3 RCTs and 3 retrospective cohorts, pain scores were lower following pectus correction with epidural compared to PCA, but the degree of difference was modest and only seen at some time points [29]. In a retrospective series of children undergoing major tumour resection (majority neuroblastoma, n=40-44 per group), epidural analgesia lowered pain scores compared to a historical non-epidural group, but differences were not significant in this small uncontrolled study. However, effective epidural analgesia was also felt to reduce distress and improve satisfaction in these children who have often already undergone multiple treatments, experienced side-effects of oncology treatment such as mucositis, and may have significant previous exposure to opoids [32].

Additional procedure-specific evidence for epidural analgesia would improve technique selection and inform discussions of efficacy and safety with patients and families/carers [29]. Patient preference and institutional resources, particularly success rates and the ability to titrate and monitor thoracic epidurals, will also continue to influence choices between regional and systemic analgesia.

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Peripheral regional blocks

Use and feasibility of different regional local anesthetic blocks for perioperative analgesia continues to expand, with data from the Pediatric Regional Anesthesia Network (PRAN) providing safety information. Transversus abdominis plane (TAP) blocks (n=1994, age 2-14 years) were associated with 2 minor complications (vascular aspiration before local anesthetic injection and a peritoneal puncture) without sequelae. However, significant variability was noted in the dose of local anesthetic administered (almost 5-fold and not solely explained by patient weight), and 6.9% of children received greater than recommended doses of 2mg/kg bupivacaine [33]. No significant adverse effects were reported following placement of interscalene blocks in anesthetized (n=390) or awake (n=123) children, although the majority were performed in older children (88% 10-18 years) and the sample size is still relatively small for detecting rare events [34]. Ambulatory peripheral nerve block infusions were reported to be feasible (n=403, age 5-22 years), with low pain scores and high satisfaction in the majority [35]. However, the failure rate of 6.9% and complication rate of 14.4% (particularly leaking and catheter dislodgement) suggest further technical refinement is required.

Once feasibility and safety of these techniques has been demonstrated, there is a need for RCTs to confirm efficacy [28]. A systematic review of randomized trials (73 studies, n=5125 pediatric patients) evaluating perioperative peripheral local anesthetic blocks reported limited impact on pain score (at 4 and 24 hours) or cumulative opioid consumption [28]. Comparisons were often between different techniques or solutions, rather than ‘pure’ block versus no block, and none included a ‘sham block’. Limitations in both the quantity and quality of current evidence in pediatric populations was noted, with variability in study design, type of surgery, and outcomes, influencing the strength of the conclusions [28].

PERSISTENT POST-SURGICAL PAIN

Anesthesiologists are increasingly evaluating the impact of perioperative care on long-term patient outcomes. In pediatric practice, potential adverse effects of anesthesia on the developing brain are an important area for ongoing research [36], and there is also evidence that early life pain and surgery can produce long-term changes in sensory processing and future pain response [37]. At all ages, effective analgesic management needs to extend beyond the immediate perioperative period, to also consider pain at home following discharge (as discussed above) and the potential for more persistent postsurgical pain (PPSP). The severity and functional impact of PPSP varies, but can require management in a chronic pain clinic [38]. As the intensity of acute postoperative pain is a risk factor for the transition from acute to persistent post-surgical pain in both adults [39,40] and children [41,42], recognition of at-risk populations and potential preventive strategies is also relevant to acute peri-operative care.

Prevalence of PPSP

Retrospective cross-sectional questionnaires report variable and relatively low rates of PPSP in children [43,44], but can be influenced by both selection and recall bias. Three to 18 months following surgery (predominantly major orthopedic), 13.3% reported current pain

related to the surgery site in a phone interview (n=113; mean age 12.4 years) [45]. In a retrospective questionnaire sample with a 59% response rate, 2 of 51 children (median age 9 years) recalled pain that persisted for months and only one had current pain when assessed 2-4 years following lateral thoracotomy [46]. In a prospectively enrolled database of spinal surgery for adolescent idiopathic scoliosis (n=584, mean age 14 years), 11% reported pain at some time between 2 weeks and 2 years postoperatively. In the 6 to 24 month period, 7% reported pain with no obvious cause and over half of these were referred for further investigations, physical therapy or pain clinic review [47].

More detailed data is now available from prospective studies that assess the site and severity of pain, follow the trajectory of symptoms at multiple time points, and aim to identify predictive factors. Following major orthopaedic or general surgery (n=83, mean age 14yrs), 22% reported moderate-severe pain at 1 year. Children reporting pain (≥3 out of 10) two weeks following surgery had an increased relative risk of pain at 6 months (RR 3.3 95% CI 1.2-9) and at 12 months (RR 2.5 95%CI 0.9-7.5) [41]. Following spinal surgery for idiopathic scoliosis, the incidence of persistent pain was 22% at 6 months (n=50, mean age at surgery 14.5 years) [42], and 11-15% at 1 to 5 years (n=190, mean age at surgery 14 years) [48]. Many adolescents (35%) have moderate-severe pain prior to scoliosis surgery, but different trajectories were identified across the 2 to 5 year post-operative follow-up period: no significant pain pre- or post-operatively (12%); preoperative pain with improvement to mild/no pain (54%); short-term pain with higher levels at 1 year but subsequent improvement (18%); delayed pain with increases at 2 and 5 years (11%); and high pain preoperatively that despite initial improvement increases and remains severe at 2 and 5 years (6%) [48]. These patterns emphasize the importance of both perioperative preventive interventions and ongoing review, with referral for specialist pain management if pain becomes problematic at later time points.

Predictive factors for PPSP

Higher baseline preoperative pain, but not the degree of scoliosis or surgical factors were predictive of subsequent pain [42,48]. Reported associations between psychological measures and PPSP may offer a target for future interventions. Increased anxiety predicted acute impairment in quality of life but not pain in the 2 weeks following major thoracospinal surgery [49], but was a predictive factor for persistent pain at 6 to 12 months [41,42]. General measures of mood [42] or mental health function [48] did not predict subsequent pain. Parental responses and attitudes also need to be considered [50]. Higher catastrophizing by parents (i.e. thoughts and beliefs that an event or situation is worse than it is) was associated with increased child pain at 2 weeks [49] and persistent pain at 12 months [50]. Parental catastrophizing also influences both the child and parent memories of pain following major orthopedic or general surgery [51], thus highlighting a source of recall bias that can influence retrospective evaluation. In several series, the majority of subjects undergoing surgery were female (72% - 82%) [42,47,48], but larger samples are required to assess the specific impact of sex/gender on PPSP.

Mechanisms of PPSP

There is a need to identify both predictive factors and the underlying mechanisms of PPSP to more specifically target high risk groups with the most effective preventive strategies [39,52]. Repeated perioperative doses of gabapentin [53], but not a single preoperative dose [54], reduced opioid requirements following spinal fusion for idiopathic scoliosis, but potential effects on PPSP require further evaluation. Recent laboratory studies demonstrate long-term changes in nociceptive pathways following neonatal surgical injury in the rat, with alterations in descending modulation [55], and increases in the degree and duration of hyperalgesia when repeat surgery is performed in later life [56]. Analgesic interventions at the time of initial surgery that prevent long-term changes [55] or specifically target mechanisms underlying persistent post-incision hyperalgesia [56] may inform future clinical trials.

CONCLUSION

Evidence to guide safe and effective management of postoperative pain in children is increasing. Translation into improved clinical care requires implementation of evidence-based recommendations and quality improvement strategies. Provision of care is increasingly extending beyond the immediate perioperative period to also include pain following discharge, and potential preventive strategies for persistent postsurgical pain.

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KEY POINTS

Effective management of postoperative pain in children needs to encompass the perioperative period, pain following discharge, and the potential risk of persistent peripoperative pain.

Updated recommendations for post-tonsillectomy analgesia suggest regular administration of paracetamol and NSAID, and exclude codeine, but further evidence is required to establish the most appropriate dose and type of opioid for rescue analgesia.

Persistent postsurgical pain is being evaluated and recognized in children, with high perioperative pain, patient anxiety and parental catastrophizing predicting persistent symptoms following surgery for adolescent idiopathic scoliosis.