RESEARCH ARTICLE

Current Trends and New Strategies in Acute Postoperative Pain Management in Children

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Abstract

Acute postoperative pain in children is common. Nearly 40 percent of pediatric patients suffer from moderate to severe pain after surgery. Inadequate pain prevention and treatment has been associated with short and long-term consequences. Different treatment modalities have evolved lately, and multimodal analgesia has become the treatment of choice not only involving a pharmacological approach but also non-pharmacological approaches (eg, regional analgesia, rehabilitation, cognitive behavioral therapy, virtual reality). The aim of this article is to show current trends and strategies in the management of acute postoperative pain in children and how an inadequate treatment of it can lead to the development of chronic postsurgical pain.

Keywords: Acute postoperative pain, children, pharmacological analgesia, regional anesthesia, chronic postsurgical pain, multimodal pain management.

Introduction

In pediatric patients, optimal perioperative pain management still remains a huge challenge[1]. Experiencing pain after hospital discharge may influence adequate functional recovery in children[2]. Consequently, pain prevention and its management are considered pivotal for healthcare providers[3].

Despite a growing number of publications related to postoperative pain management, the prevalence of moderate to severe pain is still high[4] with the associated short and long-term consequences[5]. Mekonnen et al, in a recent study, showed that 40.5% of pediatric patients undergoing surgery, experienced moderate to severe pain[6]. Among predictors described in postoperative pain intensity are the following: inadequate perioperative analgesia, history of chronic pain, preoperative anxiety, type of surgery, and incision length[6-10].

Perioperative pain treatment not only involves pharmacological strategies but also nonpharmacological approaches. Acute postoperative pain management needs to be tailored to surgical procedures and types of patients. Otherwise, the chances of providing inadequate pain relief and/or the development of medication side effects are higher.

The aim of this review article is to provide current trends in regional anesthesia techniques, pharmacological treatment, and nonpharmacological approaches to treat acute postoperative pain. Finally, we consider it relevant to provide information about the current knowledge of chronic postsurgical pain and how acute postoperative pain is related to it.

Current concepts on the usage of regional anesthesia techniques for acute post-operative pain management in children

For decades, regional blocks have been part of the alternatives for managing postoperative pain. Currently, the use of regional techniques is considered a reasonable and safe alternative to deal with postoperative pain in children[11]. In this regard, recent publications from cooperative groups with large databases[12-14] have shown the positive impact of regional techniques on safety and the quality of anesthetic care of pediatric patients[15]. From those studies, it is possible to examine some features about general practice in regional anesthesia in children.

Evolution of the practice of regional anesthesia in children

Overall, there is an agreement that the usage of regional techniques in daily practice of pediatric anesthesia has increased. In general terms, about one-third of all surgical procedures in children are accompanied by some kind of regional technique[14]. During the last few decades, peripheral nerve blocks (PNB) have grown in their use representing now between 50-66% of all blocks[12, 13].

Regarding the age profile, procedures performed in patients over 3 years-old account for nearly two-thirds of all blocks, while patients between 10 and 17 years-old represent one-third and infants just one quarter of the total[12, 14]. Around 80% of all procedures are single-injection blocks and the most performed is caudal epidural. In children, about three-quarters of continuous techniques are neuraxial and that proportion almost reaches 100% in neonates[12].

Awake versus anesthetized procedures

In pediatric patients, nearly 95% of regional techniques are performed under general anesthesia or deep sedation. There is evidence suggesting that the risk of neurological complications performing nerve blocks under general anesthesia in children is comparable to the risk in awake adults[12]. In this regard, an international group of experts has issued recommendations that say that the performance of regional techniques in children under general anesthesia or deep sedation is associated with acceptable safety and should be viewed as the standard of care[16]. There is no consistent difference in terms of neurological risk between neuraxial and PNB techniques[15].

Impact of ultrasound guidance

The use of ultrasound for regional anesthesia in children has increased over the last two decades, particularly for PNB. Although the use of ultrasound has not proven to reduce relevant complications in pediatric regional anesthesia, the technique has demonstrated some benefits, such as improving success rate, reducing onset time, increasing block duration, and reducing the volume required for successful perioperative analgesia[11, 17]. Despite these benefits, the available literature shows a marked difference in the rate of usage of ultrasound between countries. In children´s hospitals in the USA, ultrasound-guided techniques have almost completely displaced landmark and nerve stimulator-assisted blocks, accounting for more than 90% of all PNB[12]. Nevertheless, data from European hospitals and, maybe more representative of general pediatric practice worldwide, has shown that ultrasound guidance is only used in nearly one-third of truncal blocks and two-thirds of upper and lower limb blocks[14]. Some of the reasons that explain these differences include the equipment availability and the lack of confidence, knowledge, or teaching centers in some countries.

Emerging blocks

Even though various types of blocks are not well described in pediatric literature, procedures used in adults can be extrapolated and applied to children[18]. In addition to the already well-known blocks, relatively new emerging techniques have gained familiarity among pediatric anesthesiologists, particularly with the use of ultrasound.

The quadratus lumborum block (QLB) has emerged as an anatomical variant of the transversus abdominal plane (TAP) block during the last decade. The key of the success of QLB is the thoracolumbar fascia which connects the anterolateral abdominal wall with the lumbar paravertebral space[19]. Benefits have been documented in pain control with QLB following colostomy closure, inguinal and lower abdominal surgeries in children, even when is compared with the TAP block and caudal anesthesia[20, 21]. Although QLB is considered safe, cases of hematoma have been reported following this block, presumably due to the injury of the lumbar arteries[22].

Since the description of the erector spinae plane (ESP) block[23], it has been extensively used in the adult population. In pediatrics, it has also been shown to be effective in a myriad of surgeries such as nephrectomy, liver transplantation, and cardiothoracic procedures, providing promising effects in terms of safety and quality of analgesia[24-27].

The pudendal nerves give motor and sensory innervation to the genital and perineal areas. It has been reported to provide longer analgesia when compared with caudal blockade and, ultrasound guidance has been successfully used to

identify the neurovascular structures in the area[28, 29].

Pharmacologic treatments

Non-opioid pharmacologic treatment

Currently, multimodal analgesia (MMA) is the recommended approach for managing acute postoperative pain[30] and is considered a key component of the enhanced recovery after surgery (ERAS) pathways[31]. Classically, MMA involves non-opioid pain medication with the aim of diminishing the use of opioids and their side effects[32]. If there is no contraindication (eg, severe liver or kidney disease) MMA strategies should include acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) as their basis. Ideally, they should be administered on a regular basis instead of as needed.

There is some evidence showing that medication such as acetaminophen, NSAIDs, dexamethasone, ketamine, clonidine, and dexmedetomidine may decrease postoperative pain and have an opioid-sparing effect in children[33].

Acetaminophen

Acetaminophen exerts its effect through different mechanisms of action such as COX-3 enzyme inhibition, cannabinoid agonist, NMDA antagonist, and the activation of descending serotonergic pathway[34]. Even though acetaminophen has been widely used, diverse studies have shown that it has a poor impact on pain control, with little effect in reducing opioid consumption vs placebo in moderate and major surgeries in children[35-37]. Nevertheless, the use of intravenous acetaminophen has been associated with positive outcomes such as faster general and oral intake recovery, higher levels of satisfaction, fewer opioid adverse effects, and a decrease in the length of the hospital stay[37, 38].

Nonsteroidal anti-inflammatory drugs

NSAIDs are commonly used to treat acute postsurgical pain in the pediatric population. Their use in the perioperative period has demonstrated adequate pain control, opioid-sparing effect[33], and a reduction in the risk of postoperative nausea and vomiting[39]. While they are widely prescribed, some concerns have emerged regarding the possible impairment of bone healing/formation in spinal fusion surgeries and the risk of bleeding after tonsillectomies. There is no solid evidence of poor bone healing/formation with the use of NSAIDs for less than 2 weeks and a recent ERAS guideline in lumbar spine fusion states that the use of NSAIDs, including selective COX-2 inhibitors, decreases pain and has an opioid-sparing effect[40]. The current evidence has shown that the use of ketorolac for controlling pain after tonsillectomy is associated with statistically more risk of post-operative bleeding[41]. However, that risk is counterbalanced by the reduction of postoperative nausea and vomiting, sedation, and respiratory depression[42].

Metamizole

The mechanism of action is not well known, but it probably involves the inhibition of central cyclooxygenases and other actions in the opioid and cannabinoid systems. Due to possible serious adverse reactions, such as agranulocytosis, its use has been the subject of debate. Nevertheless, in the last few years it has regained popularity. Metamizole has been extensively used as part of a MMA approach in the peri-operative period in children, demonstrating comparable pain relief vs NSAIDs, with very low risk of adverse reactions[43, 44]. Nevertheless, the absolute risk of agranulocytosis could not be determined with the available literature[45]. Considering this, the routine

use of metamizole cannot be recommended in pediatric patients until more adequately designed studies are conducted[45].

Gabapentinoids

These drugs have been used in the perioperative period in adults with some contradictory results[46] and literature in the pediatric population is lacking and inconclusive. Therefore, with the current evidence it is not possible to recommend their use for managing acute postoperative pain in children.

Ketamine

The use of ketamine in the perioperative period could have the potential of decreasing hyperalgesia, central sensitization, and reverse opioid tolerance[47, 48]. Nevertheless, in children, there is no consistent data to support its utility in the perioperative period[49, 50]. Despite this, there are some clinical scenarios where ketamine might be effective; a) patients at high risk of developing postsurgical neuropathic pain, b) opioid-tolerant patients, c) patients more susceptible to develop opioid related side effects and/or d) patients with previous chronic pain conditions[51, 52].

Intravenous lidocaine infusion

Only a few studies have reported the use of lidocaine in children in the perioperative period. In a recent RCT, Kaszynski et al, showed that the intraoperative use of lidocaine only had an impact in reducing the intraoperative opioid requirements in children undergoing a laparoscopic appendectomy[53].

One of the major concerns of using intravenous lidocaine, is the local anesthetic systemic toxicity (LAST). El-Deeb et al, studied 80 pediatric patients, aged 1-6 years, undergoing major abdominal surgery. Among the measured outcomes were the lidocaine plasma concentrations in patients who received a bolus of 1.5 mg/kg followed by an infusion of 1.5mg/kg/h up to 6h postoperatively. No patient reached toxic plasma levels of 5 μg/ml[54]. Even though it seems that the bolus plus infusion of lidocaine is safe in the dosages previously mentioned, a recent international consensus statement highlights that the use of intravenous lidocaine should be avoided in patients weighing < 40 kg[55].

α-2-adrenergic agonists

Among the benefits reported with the use of dexmedetomine in pediatric patients are: a) a reduction in postoperative pain, b) an opioid sparing effect and c) a decrease in emergence delirium[33, 56, 57]. However, the optimal dose and the extension of its infusion are still unclear. A recent PROSPECT guideline for tonsillectomy recommends the use of dexmedetomidine in the case that a basic analgesic regimen is contraindicated, or postoperative pain is expected to be greater than usual[58]. Regarding clonidine, a recent Cochrane review in non-ventilated infants showed that its use cannot be supported or rejected to prevent or treat postoperative pain[59].

Opioids

Opioids constitute the mainstay of the treatment of moderate to severe pain in both the adult and pediatric population[19, 60]. Nevertheless, we must be aware that opioids are the leading cause of death in Americans younger than 50 years, and adolescents and young adults are at the highest risk of prescription opioid abuse[32]. One of the reasons argued for that problem might be the over prescription in surgical patients of all ages[61]. In patients where the opioid treatment is planned, the regime should match the pain expected following

surgery and the type of patient to be treated[4].

As was mentioned, in the case of moderate to severe pain, the use of strong opioids may be recommended, and the route of administration is preferentially oral which is frequently difficult after surgery[62]. The most common intravenous opioids used in the postoperative period are hydromorphone, morphine, fentanyl, and methadone[4, 62, 63].

The US Food and Drug Administration (FDA), in 2017 issued a warning about the use of codeine and tramadol in children because of reports of ultra-rapid metabolizers and the increase in the production of active metabolites leading to respiratory depression, oversedation, and death[64]. The FDA contraindicates the use of tramadol and codeine in patients younger than 12 years[64].

Non-pharmacological multidisciplinary treatments: virtual reality

There are many non-pharmacological approaches to treat pain such as cognitive behavioral therapy, hypnosis, acupuncture, massage, music therapy and virtual reality (VR). The latter has shown to decrease pain in both adults[65] and pediatric patients[66]. A recent systematic review and meta-analysis assessing the effects of VR showed that its use reduced pain and anxiety in pediatric patients undergoing a myriad of medical procedures[66]. The use of VR in the perioperative period could be used as a tool to relieve postoperative pain and even decrease the need of pharmacological therapy.

Consequence of an improper acute pain management: Chronic postsurgical pain

Chronic postsurgical pain (CPSP) is a high priority for perioperative research. CPSP is defined as pain that develops or increases in intensity after surgery for at least 3 months, exceeding the normal healing process. The pain must be related to the surgical field, projected to the innervation territory of a nerve located in this area or referred to a dermatome[67]. Other causes of persistent pain need to be ruled out, such as infection, tumor recurrence or pain whose origin comes from pre-existing conditions[67]. Its incidence varies greatly in literature[68, 69] affecting up to 75% of adult patients[68]. Specifically in pediatric patients the median prevalence is around 20% at 12 months after major surgeries[70, 71].

CPSP is not an isolated event and is associated to prolonged recovery times, greater functional disability, school impairment, familiar and psychological distress, and economic costs[70-73].

The transition from acute to CPSP involves mechanisms at peripheral and central levels[74]. Risk factors to develop CPSP are interconnected, enhancing the probability of its occurrence. Despite a growing number of publications regarding CPSP in adults, there is still a lack of evidence related to risk factors in developing CPSP in children[69]. In a recent systematic review and meta-analysis, the risk factors in children were presurgical pain, psychological factors, and parent catastrophizing[70]. Batoz et al, in a prospective observational study, found that preoperative pain and the intensity of acute postoperative pain (VAS >30 mm) in the first 24h, were the main risk factors in developing CPSP[75]. More recently Rabbits et al, proposed a concept model to biopsychosocial mechanisms of transition from acute to CPSP in pediatric population, whose components are: 1) premorbid factors such as age, sex, genetic profile and medical factors, 2) psychosocial factors involving emotions, cognitions, behaviors and family interaction, 3) sensory processing that can

be altered leading to chronification of pain, and 4) biological factors secondary to the magnitude of surgical injury[76].

Proper identification of the population at risk of developing severe acute postoperative pain or CPSP is a key component to tailored pain management. Nevertheless, there are two main questions that remain to be resolved:

- **Can we predict the development of CPSP?** Currently, the best predictors of CPSP are the clinical risk factors[69]. Pain intensity may be determined by the activation of peripheral neurons and consequently neuroplastic changes at central levels[77]. Quantitative sensory testing (QST) is a clinical method to measure responses to sensory stimuli representing neural function or impaired pain sensitivity. Likewise, it can give some clues about central pain mechanisms and can also evaluate the efficiency of the descending inhibitory pain response through a conditioned pain modulation paradigm (CPM)[77]. Braun et al, in a recent review concluded that the preoperative use of QST has the potential to predict postoperative pain in patients undergoing elective surgery. The routine implementation of QST in the preoperative period can provide some hints regarding a more individualized perioperative pain treatment, decreasing it and enhancing the quality of life after surgery[78].
- **How can CPSP be prevented?** First, we must recognize that the literature is discouraging regarding the use of many pharmacological interventions or regional anesthesia techniques and secondly, these have been mainly evaluated in adults[68, 79]. A Cochrane review of several drugs to prevent CPSP in adults, found that only ketamine has the potential benefit of reducing its occurrence[80]. Nevertheless, this fact needs to be probed by a larger study, which is currently in progress, the ROCKet trial[81]. In the same manner, a recent systematic review and meta-analysis, despite the limited data, showed the benefit of intravenous lidocaine infusion to prevent CPSP at three months with no difference in pain intensity[82]. Even though ketamine and lidocaine have shown some benefits, it is still unclear what the optimal dose and the duration of these drugs in the perioperative period is.

  Pharmacological interventions and regional anesthesia techniques are not the only strategies to reduce CPSP. In adults, a recent systematic review of psychological treatments for the management of postsurgical pain showed that cognitive behavioral therapy-based psychological interventions reduce CPSP intensity and disability[83]. These results could be extrapolated to pediatric patients.

  According to the current literature, the prevention of CPSP not only involves pharmacological therapies, but also an early identification of preoperative, psychological, and medical factors that can be targeted. Adequate patient selection might increase the success of the preventive strategies both pharmacological and non-pharmacological. The lack of success of these preventive strategies probably resides in the absence of individualized management[84] and the lack of knowledge as to when to start them and how long they should last.

Conclusion

Optimal perioperative pain management is an essential part of care of every pediatric patient undergoing surgery. Nevertheless, we are still far from providing optimum pain management in

many pediatric surgical patients. New regional anesthetic techniques have increased in use over the years and have revolutionized current ways of managing postoperative pain. Available literature considers these techniques as effective and safe, even in patients under general anesthesia or deep sedation. It is possible to think that massive implementation of ultrasound guidance worldwide could improve the quality and safety of pediatric regional anesthesia even more. Besides these regional anesthesia techniques, there are pharmacological and nonpharmacological approaches to treat acute postoperative pain that should not be administered in an isolated fashion to boost their overall analgesic effect. Deficient postoperative analgesia has a short-term and long-term impact with the eventual development of chronic postsurgical pain. Therefore, future research is going to provide some strategies to build tailored pain management and decrease the risk of CPSP.

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