

## Pain Management in Pediatric Surgery: New Horizons

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### Abstract

The pain management in pediatric surgery is a very complex and relevant problem with many clinical implications. Pain in children requires special considerations due to physical and psychological immaturity. The enhancement in pain management results in a reduction of recovery time and complications. Few studies are available in the literature focused on postoperative pain and analgesia requirements in children following surgical procedures. In the present brief review we summarize the current strategies of pain management in pediatric surgery and we envision the new hypothetical horizons in this field.

### Introduction

Pain control after surgery is a popular matter when children are involved. Since the mid-1980s, the need to improve postoperative pain control started to be a cherished problem. In the last 20 years, pediatric hospitals have implemented pain management protocols improving postoperative pain relief of patients and families' satisfaction, although pain management continued to be a problem after pediatric surgery [1-3]. Today, the importance of postoperative pain control is well recognized; pain is considered as the fifth vital sign, and needs clinical innovations in improving its care. Indeed, the enhancement in pain management results in a reduction of recovery time and complications. Pain is a complex and unsolved phenomenon, characterized by different pathophysiological changes potentially leading to relevant postoperative morbidity and can strongly affect the clinical outcome [4].

### General features of pain in children

Pain in children requires special consideration due to physical and psychological immaturity. We have few data regarding clinical features and the pathophysiology of postsurgical pain in children. In particular, few studies have focused on postoperative pain and analgesia requirements in children following surgical procedures [1-11]. For the review we used the following search criteria using PRISMA flow chart considering the last 5 years: "pediatric pain management"; "pediatric pain management guidelines"; "pediatric pain management review"; "post operative pain management in children"; "pain management in pediatric surgery". We summarized in the (Table 1) the most relevant papers published in the last 5 years (source PubMed/MedLine). None of these studies directly assessed functional limitation or provided detailed information about the type and duration of analgesia use. We were unable to identify any studies that systematically followed patients after specific surgical procedures through to full recovery. Stewart and coworkers described the clinical features (duration and severity) of postoperative pain and analgesia requirements in children after tonsillectomy, orchidopexy, or inguinal hernia repair [12]. The investigation on the different clinical and pathophysiological features of the pain related to different surgical procedure is crucial to develop new strategies in the management of pain in children. From the data available the incidence of perioperative pain in children is high [13].

### Current strategies for pain management in children

Until now, we cannot predict which patients will develop severe postoperative acute and/or persistent pain, and the standard analgesia

is chosen by considering patient personal data (weight and age) and clinical conditions. We have to consider that little data are available about how painful the pediatric surgery is, due to the difficulty of pain assessment [13]. Nevertheless, in order to stem the problem of pain evaluation in neonates, infants, and children under 4 years, physiological parameters such as increases in heart rate, respiratory rate and blood pressure with the presence of sweating, high cortisol and cortisone levels, and endorphin concentrations are measured, together with the evaluation of the facial expressions.

Considering that different receptors and neurochemicals are involved in postoperative pain pathways, pain management should be multimodal [14]. By using minor, moderately active or major analgesics, it is possible to act on the transduction of the stimulus into the electrical signal, on the transmission of the signal along the pain pathways, and on its modulation and perception, which is also modulated by cognitive, emotional and cultural factors.

Currently, the systemic multimodal approach includes different drugs, ranging from paracetamol (acetaminophen), to nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, adjuvants as ketamine and clonidine and regional anesthetics [15]. Another analgesic technique involves the On-Q pain 0pump, which allows a continuous infusion of continuous local analgesia by a catheter placed deeply in the fascial planes, without the risks associated to the epidural catheterization but with the advantage to provide similar analgesia [16].

Great advantages are associated with regional anesthesia, too. A substantial body of literature supports the safety and efficacy of performing regional anesthetic techniques in children; evidence-based literature shows that combined regional and general anesthesia in

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First author	Title	Year of publication	Journal
Chou R. et al.	Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council.	2016	J Pain
Van der Heijden MJ et al.	The Effects of Perioperative Music Interventions in Pediatric Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials	2015	Plos one
Baley K et al.	Intravenous acetaminophen and intravenous ketorolac for management of pediatric surgical pain: a literature review.	2014	AANA J
Shah RD et al.	Applications of regional anaesthesia in paediatrics.	2013	Br. J. Anaesth.
Association of Paediatric Anaesthetists of Great Britain and Ireland.	Good practice in postoperative and procedural pain management, 2nd edition.	2012	Pediatr Anaesth
Morton NS	The pain-free ward: myth or reality	2012	Pediatr. Anaesth.

Table 1: Relevant reviews published in the last 5 years.

paediatric patients can decrease hospital stay and improve outcomes [17]. Advances in ultrasonography and precise dosing regimens have facilitated widespread applications of regional anaesthetic techniques in infants, children, and adolescents. Prospective studies indicate that these techniques can be safely performed and positively impact on the outcomes of paediatric patients undergoing painful procedures and those who suffer from chronic pain [17]. In order to obtain maximum pain relief reducing the side effects as much as possible, new strategies are needed. New research about the inter individual variability of pediatric patients in terms of genetics and epigenetics and new tools (based on nanotechnology), would permit a major use of local drugs and the personalized dosage of systemic drugs. We are confident that in near future molecular analysis and nanotechnology will help the traditional medicine, towards the personalization of postoperative pain treatment and an improvement of patient's quality of life.

### Future Perspectives: From Nanotechnology to Molecular Features

One of the most important current objectives of the research in pain therapy consists in personalizing the treatments, by a multidisciplinary approach including new analgesic deliveries (based on nanotechnology) and a deeper knowledge about pharmacogenetics and epigenetics (in terms of histone changes, mRNA expression, and DNA methylation). Sprints and collaborators, already in 2012, discussed the key role of Nano medicine in the development of innovative pain management [18]. The importance of developing implantable devices for tailored local drug release, as nano-structured devices, are due to the drug release only into the targeted tissue affected by the surgery, dissolving any side effect related to the systemic release of the traditional treatments.

Several literature data demonstrated the importance of the genetic background in determining the inter-individual variability of pain sensitivity (such as *COMT*), drug pharmacodynamics (such as *OPRM1*) and pharmacokinetics (such as *CYP2D6*) in the postoperative setting [19-22]. Recent data show that modification of epigenetic processes are involved in the development of chronic pain [23,24]. Orlova and coworkers showed the modulation of microRNA in complex regional pain syndrome, and recent data demonstrated the dynamicity of microRNA due to opioids and opioid tolerance [25]. On the other hand, Dohering and coworkers observed an increase of DNA methylation in patients under chronic opioid use [26]. The same effect of opioids has been also described in the postoperative period, while a demethylating effect has been shown for the local anesthetics [27].

Shaw and Martin determined the potential of epigenetics on modulating surgery wound healing in a murin model (Shaw and Martin). Their discovery also demonstrates, once again, the importance of animal studies in pain therapy, as recent discussed by Gigliuto and

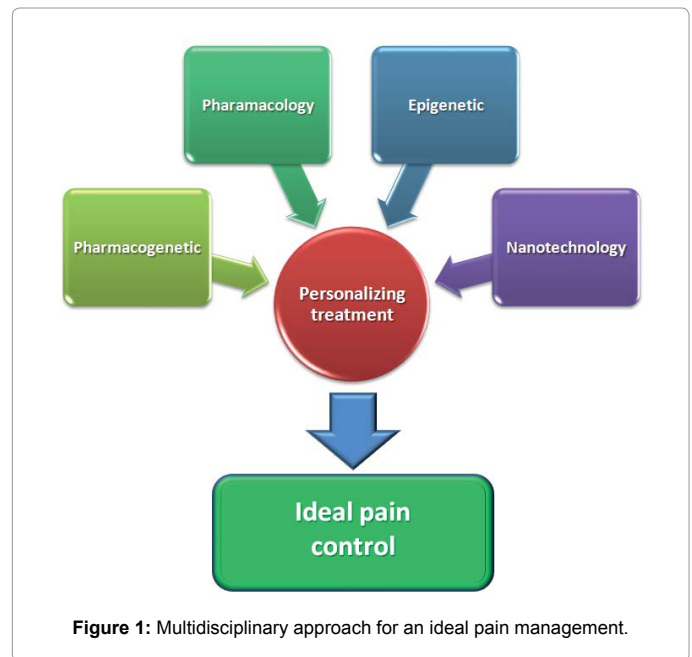


Figure 1: Multidisciplinary approach for an ideal pain management.

coworkers for big animal models [28]. We are confident that new tools and multidisciplinary approaches, in postoperative medicine, might improve pediatric patient outcome (Figure 1).

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