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Preoperative Norepinephrine Levels in Cerebrospinal Fluid and Plasma Correlate With Pain Intensity After Pediatric Spine Surgery

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Abstract

Purpose: Catecholamines were found to be involved in descending pain modulation and associated with perioperative pain. The purpose of the present study was to investigate the relationship between preoperative concentrations of catecholamines and postoperative pain intensity of pediatric patients.

Methods: Fifty adolescents with idiopathic scoliosis scheduled for elective spinal fusion surgery were enrolled in this prospective cohort study. Preoperative plasma and cerebrospinal fluid (CSF) samples were collected and analyzed by mass spectrometry. Pain intensity was assessed during the acute postoperative period and in the intermediate period.

Results: Preoperative plasma concentrations of norepinephrine (NE) and normetanephrine (NME), as well as the CSF concentration of NE, were significantly correlated with the presence of pain six weeks after surgery ($r = 0.48$, 0.50, and 0.50, respectively; $p < .002$). We also found that preoperative NE levels in CSF were significantly higher in patients reporting moderate to severe pain intensity than in patients with mild pain during the first day following surgery (0.268 ± 0.29 ng/mL vs. 0.121 ± 0.074 ng/mL, $p = .01$), as well as between patients reporting pain and painless patients at 6 weeks postsurgery (0.274 ± 0.282 ng/mL vs. 0.103 ± 0.046 ng/mL respectively, $U = 69.5$, $p = .002$).

Conclusions: These results support the potential role of catecholamine levels in predicting postoperative pain intensity.

Keywords: Adolescent idiopathic scoliosis; Perioperative pain; Catecholamines; Cerebrospinal fluid; Plasma

Introduction

Postoperative pain can have immediate and long-term negative consequences in almost all aspects of normal life [1,2] and can lead to the development of chronic postsurgical pain (CPSP) [3-5]. Preventing CPSP in the pediatric population becomes highly relevant as it may predispose children and adolescents to experience recurrent pain during adulthood [6-8]. The interindividual variability in pain intensity and analgesic response represents a serious challenge for effective pain management after surgery. Common analgesic strategies may not provide adequate analgesia for a significant proportion of patients when looking at individual therapeutic responses. More than half of children experience significant pain in the acute, intermediate, and long-term periods after surgery [9,10].

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The clinical challenge lies in the ability to determine which treatment is the best fit for a given patient undergoing specific surgical procedures. Pain trajectory analyses revealed that 15% of children and adolescents undergoing spinal fusion surgery experienced moderate to severe postoperative pain up to 1−2 years after surgery [11]. The postoperative pain trajectories for the first year could be identified as early as a few weeks following surgical interventions [12]. These results suggest that strategies for prevention of CPSP should be initiated early in the perioperative course, taking into account the specific clinical characteristics of each individual.

The mechanisms driving the development of CPSP and the predisposing factors of an individual to progress toward a chronic pain state are still ill defined [13]. The risk of developing CPSP is related, in part, with lower efficacy of endogenous pain inhibitory mechanisms, associated with descending serotoninergic and noradrenergic pathways [14,15]. Interestingly, dysfunction in endogenous pain inhibition has been used to predict postsurgical pain [13,16,17].

Catecholamines, such as epinephrine (EPI) and norepinephrine (NE), are key molecules of the descending monoaminergic pathways that modulate nociceptive transmission and spinal sensitization [18]. Several genotype-based studies reporting variants of catechol-*O*-methyltransferase (COMT), the enzyme responsible for the degradation of catecholamines, have suggested the potential role of catecholamine levels in predicting postoperative pain intensity, sympathetically maintained pain [19,20], as well as postoperative morphine consumption [21,22]. However, there is a paucity of information regarding the systemic and central levels of catecholamines, in addition to their regulation and relationship with postsurgical pain in children undergoing surgery. As of now, no study has reported systemic and central catecholamine concentrations and assessed their regulation in relation to perioperative pain in patients with adolescent idiopathic scoliosis (AIS).

We hypothesized that the preoperative concentration of catecholamines involved in descending pain modulation could be associated with postoperative pain intensity and morphine consumption 6 weeks after surgery. Such exploration could lead to targeted mechanisms of action for pharmacologic treatment to improve perioperative pain management. This exploratory study was designed to investigate the relationship between preoperative plasma and CSF catecholamine concentrations and postoperative pain intensity, as well as morphine consumption in a pediatric cohort of patients with AIS scheduled for elective spinal fusion surgery.

Materials and Methods

This prospective cohort study obtained ethics approval prior to the beginning of the study. This manuscript adhered to STROBE guidelines.

Study participants

Patients scheduled to undergo spinal surgery for AIS between the ages of 12 and 18 years were recruited by research assistants from the outpatient clinic of the Shriners Hospital for Children from March 2013 to February 2015. Children were excluded if they did not speak English or French, had developmental delay (eg, autism, cognitive/developmental disabilities) that would interfere with completing clinical outcome measures, and in case of major chronic medical conditions (ASA physical status III or higher before surgery). Written informed patient assent and parental consent were obtained prior to the beginning of the study.

Perioperative care

No change to standard care was required as a result of participation in this study. All patients undergoing scoliosis surgery followed the institutional perioperative anesthesia, surgical, and spinal cord monitoring protocols. The anesthesia protocol was standardized to include total intravenous anesthesia with propofol and remifentanil, ketamine, and dexamethasone. After induction, all patients received a single injection of spinal morphine (5 μg/kg). The postoperative pain management was standardized for the study purposes and included morphine and ketamine patient-controlled analgesia (PCA, bolus 1/1 mg) upon arrival to the postanesthesia care unit (PACU) with a starting bolus dose of 20 μg/kg, lockout 6 minutes and a 4 hours maximum dose up to 0.4 mg/kg. Patients received subsequent PCA dose adjustments and additional medication when necessary. The PCA data were recorded in the patients' electronic medical charts, and cumulative morphine intake was calculated per time periods. They also received oral acetaminophen 20 mg/kg every 6 hours, and all patients received standard orders for prevention of postoperative nausea and vomiting, pruritus, and constipation.

Pain measurement

Self-reported pain intensity was the main study outcome. At all time points throughout the study (preoperative, postoperative day [POD] 1, POD2, and postoperative 6-week follow-up visit), pain intensity was rated with a numeric rating scale by the patient after being asked the following question: "How much pain are you having right now if 0 is no pain at all and 10 is the worst pain ever?"

During the first 48 hours following surgery (POD1 and POD2), numeric pain rating scores were prospectively collected by the ward nurse a minimum of 10 times per day. A mean score was calculated for POD1 (starting at the time patients left the postanesthetic care unit) and POD2. For the purpose of this study, these scores were extracted from the patient's medical chart, and pain intensity was calculated with a mean of 26 ± 4 ratings per patient. Preoperative