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Low-Dose Versus High-Dose Postoperative Naloxone Infusion Combined With Patient-Controlled Analgesia for Adolescent Idiopathic Scoliosis Surgery: A Randomized Controlled Trial

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Abstract

Study Design: Randomized controlled trial.
Objectives: The aim of this prospective randomized clinical trial was to compare low (0.5 μg/kg/h) and high (2.5 μg/kg/h) dose naloxone infusion on the time to tolerate liquids and meals after surgery, patient-controlled analgesia (PCA) opioid requirements, nausea and pruritus ratings, and hospital length of stay.
Summary of Background Data: Adolescents undergoing posterior spinal fusion often receive PCA after surgery and may experience common opioid-associated side effects, including nausea and pruritus. Low-dose naloxone infusion has been shown to reduce the incidence of pruritus and nausea while preserving analgesia, although an ideal dose has not been determined. Less is known about the potential for naloxone to improve bowel function after surgery.
Methods: Eighty-four patients (age 10–21 years) were randomly allocated to receive low- or high-dose naloxone infusion postoperatively. Surgical anesthetic consisted of propofol and opioid infusion with intrathecal morphine (10–15 μg/kg) at the conclusion of surgery. A visual analog scale (VAS) was used to rate nausea and pruritus.
Results: The groups had similar time to oral liquid intake after surgery and transition from PCA to oral pain medication. The VAS scores for pruritus and nausea were also similar, as was the need to treat these side effects. Morphine equivalents were similar between groups on postoperative day (POD) 0 and 1. On POD 2, the high-dose infusion group had significantly greater PCA bolus use (1.41±0.9 vs. 1.04±0.6; $p < .05$), although pain scores did not differ significantly. Hospital length of stay was similar for the two groups.
Conclusion: High-dose naloxone infusion was associated with similar rates of opioid side effects as low-dose. Increased PCA use noted on POD 2 may represent partial reversal of opioid analgesia in the high-dose naloxone group.
Level of Evidence: Level 1.

Keywords: Patient-controlled analgesia; Spinal fusion; Scoliosis; Adolescent; Narcotic antagonists; Pain

Introduction

Posterior spinal fusion and instrumentation (PSF-I) for adolescent idiopathic scoliosis (AIS) is typically performed when curves progress beyond 50°. The surgical procedure consists of extensive muscle dissection, bone resection and placement of instrumentation with subsequent need for several days of hospitalization. Adequate pain control is a cornerstone of quality care during recuperation, initially with intravenous opioids administered by patient-controlled analgesia (PCA) until transition to oral pain medication is possible. Unfortunately, opioid-induced side effects such as nausea and pruritus are common, occurring in more than 70% of patients [1]. The use of intravenous naloxone, a mu-opioid receptor antagonist, has been shown to reduce the incidence of opioid-induced pruritus and nausea while

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preserving analgesia when given in combination with PCA in pediatric patients after several types of surgical procedures, including PSF-I. However, naloxone doses reported for this application are quite heterogeneous, ranging 10-fold from 0.25 to 3 μg/kg/min [1-3]. In addition to nausea and pruritus, opioids can slow gastrointestinal transit time and even contribute to the formation of ileus, which is reported in 0.43% to 2% of PSF-I patients [4,5]. In patients receiving chronic opioid therapy, oral naloxone has been shown to improve gastrointestinal (GI) function, albeit at the expense of partial analgesic reversal, likely owing to the relatively large oral doses required to overcome first-pass metabolism [6,7]. Naloxone given by the oral route is problematic in the postoperative setting given that oral intake can be limited, and reversal of analgesia is unacceptable. For these reasons, oral naloxone has not been studied in the postoperative setting. Studies to date regarding intravenous naloxone have shown reduction in pruritus and nausea but have not addressed putative effects on GI function such as constipation and the ability to eat or drink after surgery. Improvement in time to resumption of oral intake could reduce hospital length of stay and related costs.

We designed a double-blind, prospective, randomized controlled trial comparing 0.5 μg/kg/h versus 2.5 μg/kg/h naloxone intravenous infusion. To simplify nomenclature, the 0.5 μg/kg/h and 2.5 μg/kg/h groups were designated "low" and "high" dose, respectively. As naloxone infusion is considered standard therapy at our institution, we did not provide a placebo control group. Our primary outcome variable was time to successful oral intake of liquids. Secondary outcomes included length of stay, time required to transition to oral pain medication, opioid PCA usage, nausea, emesis, and constipation.

Methods

The study was approved by the institutional review board or our institution, and written informed consent was obtained from the legal guardian as well as assent from the patient as appropriate. Patients presenting to orthopedic clinic between November 2011 and May 2015 for idiopathic scoliosis, age 10–21 years, English speaking, and in whom PSF-I was the planned surgical procedure were approached regarding participation in the study. Exclusion criteria included inability to understand PCA instructions and/or inability to push PCA button independently, allergies to morphine, hydromorphone, fentanyl, naloxone, or diphenhydramine, chronic opioid therapy (>2 months), and non-English speaking. It was explained to the patient and family how nausea, pruritus, and other side effects would be evaluated and treated as part of the consent process. The trial was conducted between November 2011 and May 2015 and was registered at ClinicalTrials.gov NCT01531439 prior to enrollment.

Anesthetic technique in the operating room was not strictly per protocol but was performed according to a multidisciplinary guideline previously developed for PSF-I at our institution. Briefly, a propofol infusion in combination with opioid infusion served as the primary anesthetic during the surgery. Intrathecal morphine (10–15 μg/kg) was administered at the end of the surgical procedure. Patients were then taken to either the postanesthesia care unit and subsequently to the orthopedic ward of the hospital or directly to the pediatric intensive care unit and subsequently to the ward room. Initiation of the study protocol in the form of a blinded naloxone infusion (low-dose group 0.5 μg/kg/h or high-dose group 2.5 μg/kg/h) was started when the patient arrived either in the postanesthesia care unit or pediatric intensive care unit. Randomization was accomplished by the hospital investigational drug study pharmacy such that either 10 μg/mL (low-dose group) or 50 μg/mL (high-dose group) of naloxone was provided in a 60-mL syringe and the rate was calculated by the prescribing physician using patient weight such that the infusion rate would be the same regardless of group assignment but would deliver naloxone at either 0.5 μg/kg/h or 2.5 μg/kg/h due to the difference in concentration. The patient, family, all health care personnel including bedside nurse, anesthesia pain team physician, pain team nurse, and study investigators were blinded as to group allocation. Blinding was continued for the analysis of data as well. After surgery, hydromorphone PCA was started with initial settings consisting of 4-μg/kg demand dose with an 8-minute lockout and a bolus dose of 8 μg/kg as needed up to twice in a four-hour period. A continuous infusion of hydromorphone was added at 4 μg/kg/h if deemed appropriate by the acute pain service physician. The PCA was maintained until the patient was tolerating solid foods, at which point oral pain medication was initiated by the orthopedic service.

Nausea and pruritus symptoms were treated according to a standard protocol. Specifically, ondansetron 0.1 mg/kg was given every 6 hours (maximum 4 mg) as needed for nausea and emesis. Diphenhydramine 0.5 mg/kg was given every 4 hours as needed for pruritus or nausea (maximum 50 mg). Naloxone bolus of 1 μg/kg could be given every hour as needed for nausea/vomiting, pruritus, or documented urinary retention. If nausea and pruritus symptoms persisted despite maximal treatment per protocol, then the opioid delivered by PCA was changed to morphine with a 20-μg/kg demand dose, 40-μg/kg bolus dose up to twice in 4 hours, and, if needed, 20-μg/kg/h continuous infusion. Patients were asked daily to rate pruritus and nausea on a visual analog scale (VAS) from 0 "none" to 10 "worst possible" for the preceding 24-hour time period. Additionally, a respiratory depression dose of naloxone was