Intensive Care Med (2007) 33:190–194
DOI 10.1007/s00134-006-0387-z

PEDIATRIC BRIEF REPORT

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# Effects of low-dose naloxone on opioid therapy in pediatric patients: a retrospective case-control study

Received: 11 July 2005
Accepted: 25 August 2006
Published online: 7 November 2006


**Electronic supplementary material**
Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s00134-006-0387-z and is accessible for authorized users.

The authors gratefully acknowledge grant support from National Institute for Child Health and Human Development (NIH grants U10-HD50009 and R01-HD36484 to K.J.S.A.) and ZonMw 940-31-086, 940-39-004 (to D.T.) and the help of J.M. Tilford, Ph.D. for PRISM analyses.

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**Abstract** *Objective:* To develop novel therapies that prevent opioid tolerance in critically ill children we examined the effects of low-dose naloxone infusions on patients' needs for analgesia or sedation. *Design and setting:* Matched case-control study in a pediatric intensive care unit at a university children's hospital. *Patients:* We compared 14 pediatric ICU patients receiving low-dose naloxone and opioid infusions with 12 matched controls receiving opioid infusions. *Measurements and main results:* Opioid analgesia and sedative requirements were assessed as morphine- and midazolam-equivalent doses, respectively. No differences were observed between groups in opioid doses at baseline or during naloxone, but in the postnaloxone period opioid doses tended to be lower in the naloxone group. Compared to baseline the naloxone group required more opioids during naloxone but fewer opioids after naloxone. Total sedative doses were comparable at baseline in both groups, with no differences in the postnaloxone period. The naloxone group required less sedation after naloxone but sedation doses were unchanged in controls. The two groups did not differ in pain scores, sedation scores, or opioid side effects. *Conclusions:* Naloxone did not reduce the need for opioid during the infusion period but tended to reduce opioid requirements in the postnaloxone period without additional need for sedation. Randomized clinical trials may examine the effects of low-dose naloxone on opioid tolerance and side effects in pediatric ICU patients requiring prolonged opioid analgesia.

**Keywords** Opioid · Tolerance · Addiction · Neuroadaptation · Sedation

## Introduction

Critically ill children routinely require prolonged opioid analgesia for mechanical ventilation or other supportive therapies in the pediatric intensive care unit (PICU). Introducing opioid analgesia and preemptive analgesia improves pain management in these patients but also leads to increasing problems with opioid tolerance and withdrawal [1, 2]. Over 100,000 children are admitted to PICUs in the United States each year, and most are treated with opioids during mechanical ventilation [3]. Opioid tolerance and withdrawal occur in 35–57% of patients, often resulting in a prolonged PICU stay or other complications [1, 4, 5].

Crain and Shen [6, 7] discovered that selective antagonism of excitatory opioid receptor functions with low concentrations of opioid antagonists increases the efficacy of opioid analgesia and attenuates opioid tolerance. Randomized trials in adult patients report that low-dose naloxone reduces side effects [8, 9, 10] and opioid requirements without increasing postoperative pain scores [9]. The present case-control study was designed to examine the effect of low-dose naloxone infusions on the need for opioid analgesia and sedation in critically ill children at the Arkansas Children's Hospital.

## Materials and methods

PICU physicians started administering low-dose naloxone simultaneously with opioid infusions, based on encouraging data from three randomized controlled trials in adults [8, 9, 10]. All patients receiving naloxone infusions between January 2000 and February 2002 were identified ($n = 177$) from the hospital pharmacy database, and patients who had received low-dose naloxone infusions (a) during their PICU stay, (b) concomitantly with opioid infusions, and (c) at infusion rates less than 1.0 μg/kg per hour were included in the naloxone group. Their medical records were reviewed after approval from the institutional review board, and those who had received less than 72 h of naloxone infusion were excluded because any effects on opioid tolerance would be unlikely. We recorded demographic characteristics together with data on the length of admission in the PICU and hospital, diagnoses, surgical procedures, use of mechanical ventilation, pain and sedation scores. We assessed data on low-dose naloxone infusions, opioid analgesics, nonopioid sedatives, and occurrence of hypotension or constipation. The Pediatric Risk of Mortality (PRISM) score was calculated from admission data as a measure of the severity of illness.

Opioid tolerance usually occurs in pediatric patients receiving continuous opioid therapy for more than 72 h. Therefore we focused on the 3 days before (baseline) and 4 days after the start of the naloxone infusion (during naloxone). Pain was assessed by the Modified Objective Pain Score (MOPS) and Verbal Pain Scale (range 0–10 for both) and sedation by the Comfort scale (range 8–40). The use of adjuvant nonopioid therapies was recorded from 1 day before (baseline) to 4 days after the start of naloxone (during naloxone). We collected similar data for 48 h after the discontinuation of the naloxone infusions (postnaloxone). The period from baseline until postnaloxone was defined as the study period. Surgical procedures in the study period were noted. Constipation or hypotension were documented by the need for laxatives/stool softeners or vasopressor agents, respectively. Most patients required mechanical ventilation, urinary bladder catheterization and gastric drainage; therefore, we could not investigate the occurrence of respiratory depression, urinary retention, or nausea/vomiting as opioid side effects.

From the PICU admission log we identified 12 control group patients who did not receive low-dose naloxone but received opioid infusions for 4 days or longer, matched for age, gender, diagnosis and length of stay in the PICU. Patients in the naloxone or control groups were admitted to the PICU between May 2000 and October 2001. All the data obtained for the naloxone group were also collected for the control group from an equivalent 7-day period of their PICU stay. To compare the postnaloxone data in the naloxone group we used the control group data for 24 h before extubation (post). The two groups were comparable in demographic and clinical characteristics (Table 1). One patient in each group died during the study period, and another patient in the naloxone group died 2 weeks after discharge from the PICU; the causes of death for these patients were unrelated to the opioid or low-dose naloxone therapy.

Various opioid and nonopioid drugs were administered for analgesia and sedation in the PICU. Data were collected in the two groups during corresponding periods of their PICU stay, opioid therapy, and mechanical ventilation. To determine the effects of low-dose naloxone infusion on opioid therapy the doses of different opioid drugs administered were expressed as morphine-equivalent doses using widely accepted equipotency ratios [3]. The doses of the nonopioid sedatives were expressed as midazolam-equivalent doses. Chloral hydrate doses were analyzed separately because of infrequent use and lack of data on potency ratios compared with midazolam.

Nonparametric tests were used for statistical analysis, and median, interquartile range, and minimum and maximum values are reported due to small sample sizes and skewed data distribution. Within-group differences were tested by the Wilcoxon signed ranks and between-group differences by the Mann-Whitney $U$ test (continuous variables) and Fisher's exact test (nominal variables). Differences with a $p$ value of 0.05 or less were considered statistically significant.

**Table 1** Demographic and clinical characteristics

| | Naloxone group ($n = 14$) | Control group ($n = 12$) | $p$ [a] |
|---|---|---|---|
| Age at PICU admission (years) | 9 | 9 | 0.78 |
| Gender: M/F | 7/7 | 5/7 | 0.71 |
| Length of stay in PICU (days) | 24 | 22 | 0.49 |
| Length of stay in hospital (days) | 49 | 50 | 0.82 |
| Diagnoses | | | 0.68 |
| Infection/sepsis | 5 (36%) | 5 (42%) | |
| Malignancy | 5 (36%) | 1 (8%) | |
| Trauma | 1 (7%) | 4 (33%) | |
| Congenital anomaly | 2 (14%) | – | |
| Others | 1 (7%) | 2 (17%) | |
| Mechanical ventilation | 13 (93%) | 12 (100%) | 1.00 |
| Surgical procedures | 3 (21%) | 2 (17%) | 1.00 |
| Total PRISM scores (median, range) | 8 (1–16) | 10 (1–24) | 0.33 |
| Predicted mortality risk (mean, range) | 4.3% (0–18%) | 7.3% (0–36%) | 0.33 |
| Total cumulative naloxone dose (μg/kg) | 28.6 | – | – |
| Duration of naloxone infusion (h) | 218 | – | – |
| Naloxone infusion rate ($\mu g\,kg^{-1}\,h^{-1}$) | 0.10 | – | – |

[a] Mann-Whitney $U$ test or Fisher's exact test

## Results

Infection/sepsis (36%), malignancy (36%) and surgical procedures (21%) occurred commonly in the naloxone group, whereas the control group experienced infection/sepsis (42%), trauma (33%), and fewer surgical operations (17%). The severity of illness was comparable, with median PRISM scores of 8 and 10 in the naloxone and control groups, respectively ($p = 0.33$). The median naloxone infusion rate was 0.1 μg/kg per hour (Table 1); both groups received opioid infusions and most received sedative infusions during the study period. Various opioid (morphine, hydromorphone, fentanyl, and methadone) and nonopioid drugs (midazolam, propofol, lorazepam, ketamine, chloral hydrate, and haloperidol) were used for analgesia and sedation, with key interindividual differences in the median amounts and bolus doses in the two groups. Morphine and fentanyl infusions were used equally in the naloxone group (7/14 each) whereas the control group received more morphine (8/12) than fentanyl (4/12) infusions. The use of midazolam infusions did not differ significantly ($p = 0.58$, Fisher's test).

Opioid (morphine-equivalent) doses were comparable at baseline ($p = 0.28$, $U$ test) and during naloxone ($p = 0.87$, $U$ test) in the two groups (Fig. 1). After the naloxone period more opioid doses were required in controls than in the naloxone group ($p = 0.06$, $U$ test). In the naloxone group opioid doses increased significantly from baseline to the naloxone period ($p = 0.005$, Wilcoxon) and reduced significantly after the naloxone period ($p = 0.005$, Wilcoxon). Sedative (midazolam-equivalent) doses were comparable at baseline ($p = 0.08$, $U$ test) and after naloxone ($p = 0.85$, $U$ test) (Fig. 2). In the naloxone group sedative doses were significantly lower after the naloxone

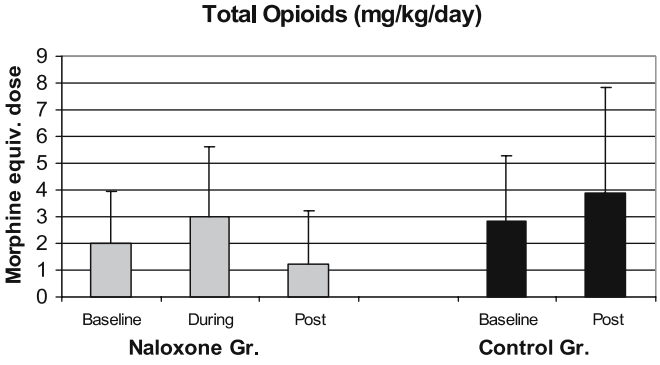


**Fig. 1** Total opioid therapy per study period. Opioid therapy was calculated in terms of morphine-equivalent doses at baseline and during naloxone and postnaloxone periods, compared within and between the two groups (*bars* mean SD). Analgesic doses were comparable at baseline for the two groups ($p = 0.28$), but the control group required higher opioid doses ($p = 0.06$) in the postnaloxone period. Within the naloxone group opioid doses increased from baseline to during naloxone ($p = 0.005$) periods and then decreased in the postnaloxone period ($p = 0.005$)

period than at baseline ($p = 0.025$, Wilcoxon) and during naloxone ($p = 0.003$, Wilcoxon), but sedatives remained unchanged within the control group ($p = 0.62$, Wilcoxon). Very few patients received chloral hydrate, and its use was comparable in the two groups.

Comfort scores increased significantly in the control group, with greater sedation at baseline than in the postnaloxone period (median 13.6 vs. 19.0; $p = 0.02$, Wilcoxon). In the naloxone group the Comfort and pain scores remained unaltered from baseline to the naloxone and postnaloxone periods. The control group developed constipation ($n = 11/12$, 92%) and hypotension ($n = 11/12$, 92%), comparable to the incidence of constipation

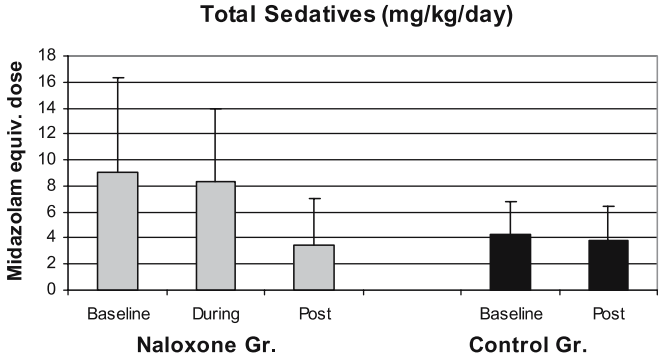


**Fig. 2** Total nonopioid therapy per study period. Sedative therapy was calculated in terms of midazolam-equivalent doses at baseline and during naloxone and postnaloxone periods, compared within and between the two groups (*bars* mean SD). Doses were comparable at baseline ($p = 0.08$) and after naloxone ($p = 0.85$) between the two groups. In the naloxone group sedative doses were significantly lower during naloxone ($p = 0.003$) and after naloxone ($p = 0.025$) compared to baseline, but sedation doses were unchanged in the control group ($p = 0.62$)

($n = 10/14$, 71%, $p = 0.33$) and hypotension ($n = 11/14$, 79%; $p = 0.60$. Fisher's test) in the naloxone group.

## Discussion

This case-control study found that: (a) baseline opioid doses were comparable in naloxone and control groups but tended to be higher among controls in the postnaloxone period, (b) within the naloxone group, opioid doses were higher during naloxone infusions than at baseline or after naloxone, and (c) the need for sedation decreased during the postnaloxone period in the naloxone group but remained unchanged in the control group. Opioid-related side effects (hypotension and constipation), pain assessments, and sedation scores were similar in the two groups. These pilot data suggest that low-dose naloxone infusions may reduce opioid tolerance following opioid therapy for longer than 4 days. Owing to the study design and sample size we can only generate hypotheses for effects of low-dose naloxone on patients receiving opioids.

Increased opioid requirements during naloxone could be explained by a short duration of naloxone effects [8] and opioid inhibition from infusions up to 0.5 μg/kg per hour [8, 10]. Patients receiving combined naloxone and buprenorphine infusions postoperatively experienced less analgesic effects, required higher opioid doses, with higher pain scores [10]. In contrast, low-dose naloxone infusions may reduce opioid requirements [9] and side effects [8, 9, 10]. Naloxone doses used for adults may not be appropriate or effective for children. Naloxone infusions ranged 0.03–0.50 μg/kg per hour in our study, but opioid requirements were increased during naloxone with reduced needs for opioids and sedatives after stopping the naloxone infusion.

The limitations of this study result from its retrospective, case-control design. Patients were not randomized, variable naloxone infusion rates were used, and sample size was limited. Although patients characteristics were comparable, the types of analgesia/sedation varied within each group. Different opioids have differential receptor effects which influence the development of tolerance [11]. The two groups had similar pain and sedation scores, and a similar incidence of opioid side effects. These data can only serve to generate hypotheses for future trials of low-dose naloxone infusions in pediatric patients enrolling larger sample sizes. Randomized controlled trials using hourly naloxone infusion rates of 0.25 μg/kg would require a sample size of 350 in each group for statistical power over 80% to show a clinically meaningful reduction in opioid tolerance between groups.

**Acknowledgements.** The authors thank J.M. Tilford, Ph.D. for help with PRISM analyses. The work was performed at Arkansas Children's Hospital Research Institute.

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