Title: Parent/Nurse Controlled Analgesia in the Neonatal Intensive Care Unit

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Methods

This single-center, prospective, RCT was approved by the hospital Institutional Review Board, and was registered at www.clinicaltrials.gov (ID: NCT01823497) by the principal investigator prior to study enrollment.

Setting

This study took place in the NICU at Children's Hospital of Wisconsin (CHW), with data collected between April 2013 and April 2015. At the time of the study, the unit consisted of a 43 bed intensive care unit and a 16 bed step-down unit with approximately 600 admissions per year.

Procedure

Potential participants were identified from the surgery schedule and the surgical team's work list that included any infant with a planned surgery. Initially, the study team also made contact with the mothers of potential participants in the hospital's Fetal Concerns Clinic. However, this recruitment method was unsuccessful, and was therefore discontinued.

Inclusion criteria: Infants 1) born no earlier than 34 weeks post menstrual age and having a corrected age no greater than 44 weeks at the time of enrollment, 2) having a birth or current weight of at least 2 kg, 3) undergoing an abdominal or thoracic surgical procedure conducted by the pediatric general and thoracic surgery team, and 4) expected to require opioids for at least 24 hours after the surgical procedure based on the opinion of the surgeon. Additionally, at least one parent was able to read and speak English. As recruitment proved more difficult than anticipated, the protocol was amended to remove the upper age limit, but the requirement of being cared for in the NICU remained.

Exclusion criteria: Infants 1) requiring vasopressors, 2) with significant prior opioid exposure (defined as > 2 days of continual exposure before surgery, or > 3 doses over the 5 days prior to the surgery), and 3) who were expected to be chemically paralyzed after surgery.

Design

This study utilized an unblinded design. Parents were approached prior to surgery. After informed consent was obtained, infants were randomized to 1 of 2 arms: either the morphine PNCA with a basal infusion (PNCA) group, or the morphine COI group. Randomization was stratified by gender and surgical location (thoracic, upper or lower abdomen) in blocks of 4. The randomization scheme was created by a statistician on the research team using Windows version 6.0 of "rand.exe" (http://block-stratified-randomization.software.informer.com/). The clinical research coordinator used the scheme to assign participants to groups.

Protocol Details

Morphine was administered using PNCA for Group 1 and COI for Group 2. Conditions were designed to replicate current pain management procedures in our NICU. For the PNCA group, orders were entered by a member of the Acute Pain Service (APS) or the patient's anesthesiologist. Using a 250 mcg/mL solution, PNCAs were ordered as morphine 0.010-0.0125 mg/kg button dose, 8 min lockout, 0.010-0.0125 mg/kg/hr basal rate, and 0.060 mg/kg/hour total maximum. Doses were rounded to the nearest microgram. Parents were instructed on signs of pain, to only push the PNCA button when the child was awake and in pain, never to push the PNCA button when the child was asleep, and to notify their nurse if they felt their child's pain was not well controlled. For the COI group, morphine was ordered at 0.030 mg/kg/hr with a 0.030 mg/kg/hr nurse bolus available each hour to a maximum of 0.060 mg/kg/hr total. Parents were instructed on signs of pain and to notify their nurse if their child's pain was not well

controlled. The post-surgical opioid delivery system was initiated upon return to the NICU. Based on our current practice, PNCA patients were managed by the APS and COI patients were managed by the neonatology team. COI patients were checked on daily by the APS, but opioid adjustments were made only by the neonatology team. Monitoring of all patients was consistent with current practice. Patients had continuous pulse oximetry and cardiopulmonary monitoring. Pain and sedation scores (Hoffman, Nowakowski, Troshynski, Berens, & Weisman, 2002) were recorded at least every 2 hours for the first 24 hours, with a minimum of every 4 hours thereafter. To calculate total opioid consumption, PNCA doses (PNCA group) and morphine boluses (COI group) were documented hourly.

Enrolled patients who at any point prior to PNCA or COI discontinuation, subsequently required vasopressors, a high frequency oscillating ventilator, or benzodiazepines, acetaminophen or anti-inflammatory agents as adjuncts for pain were discontinued early from the study. At the time of the study, acetaminophen was not used as routinely as it is now. In order to not confound pain assessment and opioid consumption by having some patients receive it and others not, the study team chose to stop data collection if acetaminophen (or benzodiazepine) was administered. Data collection terminated for all other patients when the PNCA or COI was discontinued. However, patient orders were monitored for 5 additional days to assess whether methadone was started.

Independent variables were collected to describe the sample and to determine whether groups were equivalent on all potentially confounding variables. Demographic and anthropometric data were extracted from the electronic health record, and included gender, race, ethnicity, gestational age, weight at time of surgery, total time PNCA or COI was used, and whether the current surgery was the infant's first. We also recorded mechanical ventilation and

any unplanned re-intubation occurrences. PNCA injections and attempts, as well as COI boluses were recorded for day (0700-1859) and nighttime (1900 – 0659) shifts. Mothers were asked about perinatal use of antidepressant or illicit drugs.

Primary Outcome

Our primary outcome was opioid consumption, defined as the average amount of opioid consumed over the time on study, and reported in mg/kg/hr. For the PNCA group, it was calculated based on the number of hourly injections plus the basal rate. For the COI group, it was based on the infusion rate across the time on study and any boluses administered.

Secondary Outcomes

1) Average pain intensity over the time on study. Participant pain intensity was assessed using the Revised-Face, Legs, Activity, Cry, Consolability (Revised-FLACC) scale (Malviya, Voepel-Lewis, Burke, Merkel, & Tait, 2006), the scale currently used in our NICU for this patient population. The FLACC has been used previously for NICU infants (Ahn, Kang, & Shin, 2005), has been validated in numerous pediatric populations (McGrath et al., 2008), and was originally validated in children from 2 months – 7 years (Merkel, Voepel-Lewis, Shayevitz, & Malviya, 1997).

2) Adverse events, defined a priori as naloxone rescue doses and any reintubation while on the opioid delivery system. Requiring methadone after the opioid delivery system was discontinued, was used as a measure of opioid tolerance. A modified Ramsey scale was used (Hoffman et al., 2002). Nurses reported sedation scores from 1 to 6, with 1 to 3 indicating significant sedation, 4 indicating asleep and easily arouseable or awake but drowsy, 5 indicating normal awake/alert, and 6 indicating anxiety and/or pain higher than baseline. Sedation scores below 4 were considered an indication of somnolence.

3) Parent and nurse satisfaction**.** No satisfaction tools in the extant literature would meet study requirements, therefore the investigators developed parent (Appendix A) and nurse (Appendix B) satisfaction surveys based on our previous studies (Czarnecki et al., 2017). Parents were asked about their satisfaction with 1) the pain management for their infant and 2) their involvement in the pain management for their infant. Parents in the PNCA group were also asked how often they pushed the PNCA button. Nurses were asked about 1) their satisfaction with the method of pain management for their patient, 2) whether parents were present during their shift, 3) whether they provided education to parents, and if so, 4) how long it took to provide the education. Directions for both surveys were explained at the time of consent to parents, and to nurses during daily rounds. Additionally, the study team contacted nurses on "off shifts" by phone to remind them of the need to complete the surveys. Printed blank copies of the parent surveys were left in their infant's NICU suite. Printed blank copies of the nurses survey were available in a 2-sided envelope in the participant's suite, with one side used to hold blank copies, and the other side clearly labeled for completed surveys (to protect anonymity). Parents were asked to complete the survey once a day, and nurses, once each shift. The research coordinator collected completed surveys daily.

Statistical Analysis and Data Management

Data were entered into a REDCap (http://www.project-redcap.org) database. Bimonthly reports were generated to look for missing data, outliers, and inconsistencies. Inconsistencies were checked against original data forms and corrections made as needed. CONSORT principles (Schulz, Altman, Moher, & Group, 2011) were used to assess recruitment success.

Statistical analyses were calculated using SPSS 24 (IBM SPSS Inc., Chicago, IL) and SAS 9.4 software (SAS Institute Inc.). An unadjusted two-sided $P < .05$ was used for statistical

significance in all analyses. Unless otherwise noted, all analyses include data from post-operative days (POD) 0-3. All participants who received the allocated intervention, and had at least one post-randomized outcome were included in the modified intent-to-treat analyses. In addition, descriptive and frequency analyses were used to provide summary information about patient characteristics. We report the median (Mdn) with Interquartile range (IQR) throughout. A Wilcoxon signed rank test was used to compare paired data of day and nighttime injections and attempts for the PNCA group, and paired day and nighttime boluses for the COI group. A Mann Whitney test was used to compare PCNA and COI groups; comparisons based on categorical data were analyzed using Chi-square or Fischer's exact tests. We used a mixed model with random post-operative day (POD) to examine the associations between opioid consumption and considered covariates, which included race, gender, surgery location, gestational age, study group and POD. Covariance structure used was AR(1), model was estimated by using maximum likelihood, POD and intercept were modelled as random effects. To meet the normality assumption of the linear mixed model, the outcome opioid consumption was transformed by using logarithm at base 10. For model selection procedure, we first included one of the considered covariates in the model to examine any time-varying effects on the outcome (univariable model analysis), then repeated the same procedure for other covariates. Based on the univariable model analyses, any covariates and interaction terms with $P < 0.20$ were included in the final multivariable analysis. The final model only includes those covariates with $P < 0.05$. Adverse events are reported based on incidence collapsed across POD.

Sample Size/Power Analysis

Based on our retrospective study (Czarnecki et al., 2014), and using an estimate of a large effect size, we planned to include 30 patients in each group (60 patients total). This sample size

would have allowed for an 80% power at 5% significance level to use a t-test to detect opioid consumption differences between groups of at least 0.74 SD. The study was terminated early however, due to difficulty recruiting, time and cost constraints.