Intravenous Paracetamol Decreases Requirements of Morphine in Very Preterm Infants

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Objective To determine whether intravenous paracetamol therapy is effective in pain therapy in premature infants.
Study design From June 2009 to December 2011, 108 infants born very low gestational age (<32 weeks) (VLGA) were given intravenous paracetamol before the age of 72 hours. The loading dose was 20 mg/kg followed by 7.5 mg/kg every 6 hours. One hundred ten VLGA infants admitted from October 2007 to May 2009 formed the comparison group who received no paracetamol. Intravenous morphine was exclusively used as the opiate. Morphine dosage was calculated as the cumulative dose administered during the neonatal intensive care unit period. Pain symptoms were screened using pain scale scoring Neonatal Infant Acute Pain Assessment Scale. The number of apneas during the neonatal intensive care unit stay, and ventilation days per patient, were calculated.
Results The mean (SD) total number of paracetamol doses per patient was 16.9 (11.7), and the postnatal age for the first dose was 13.3 (13.8) hours. Infants in the paracetamol group needed significantly fewer morphine doses per patient than the comparisons, 1.78 (4.56) doses vs 4.35 (11.53), P = .044. The exposed had lower cumulative morphine dosage 0.17 (0.45) mg/kg vs 0.37 (0.96) mg/kg, P = .047. There were no differences in the Neonatal Infant Acute Pain Assessment Scale scores, or the numbers of apneas, or ventilation days. There was no evidence of adverse events including hepatic toxicity.
Conclusion The need for morphine decreased significantly after the introduction of paracetamol for the VLGA infants. *(J Pediatr 2016;168:36-40)*.

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Small preterm infants are likely to experience numerous painful and stressful procedures in neonatal intensive care units (NICUs).[1-3] Nonpharmacologic pain treatment interventions are commonly used and they are mostly effective. A common medication for pain therapy of newborn infants is intravenous opiate, often morphine.[4] However, it may induce side effects, including apneas and hypotension. In ventilated preterm infants, morphine has been reported to have several adverse effects.[5-7]

Nonsedative pain medication is preferred during noninvasive respiratory therapies for newborn infants. Paracetamol (acetaminophen), the suggested cyclooxygenase-2 enzyme inhibitor,[8] was effective in postoperative pain management in neonates and infants.[9] Paracetamol has been used in the treatment of mild to moderate pain in newborn infants.[10] The pharmacokinetics of intravenous paracetamol has been studied with different dosage regimens in neonates.[11-14] Repeated doses have predictable pharmacokinetic profiles.[15] No signs of hepatic toxicity have been observed at the doses used.[16]

We introduced intravenous paracetamol in the NICU in June 2009 for the management of pain and discomfort in very low gestational age (<32 weeks) (VLGA) infants. The aim of the present cohort study was to evaluate whether paracetamol therapy initiated shortly after birth was effective in decreasing pain as judged on the basis of the need of morphine. A standardized pain scale was used to assess the need of pain medication.

Methods

All premature infants born before 32 weeks of gestation and admitted to NICU of Oulu University Hospital from October 1, 2007 to December 31, 2011, were screened for the study. Intravenous paracetamol was introduced as common practice in June 2009 in order to use nonsedative pain medication during the mostly brief periods

CYP	Cytochrome P450
NAPQI	*N*-acetyl-p-benzoquinone imine
NEC	Necrotizing enterocolitis
NIAPAS	Neonatal Infant Acute Pain Assessment Scale
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
VLGA	Very low gestational age

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of mechanical ventilation and generalized noninvasive respiratory support in VLGA infants. Permission for the use of the hospital databases was from the Administrative Chief of Oulu University Hospital.

The sample size calculation for this cohort study was based on a previous study where paracetamol medication decreased the cumulative morphine dosage for term-born neonates requiring postoperative intensive care.[9] We considered that the use of intravenous paracetamol would decrease morphine consumption in the NICU substantially, by 75% (from 0.40 to 0.10 mg/kg). As the alpha level of significance was set at 0.05 and beta at 0.20, we calculated that approximately 104 infants would be needed in both study groups.

All VLGA infants who were given intravenous paracetamol (Perfalgan 10 mg/mL solution for infusion; Bristol-Myers Squibb Finland, Espoo, Finland) before the age of 72 hours from June 2009 to December 2011 were designated as the exposed group. The loading dose was 20 mg/kg followed by 7.5 mg/kg every 6 hours. For preterm infants, intravenous paracetamol is recommended for use in a regular dosing manner: to start with higher loading dosage to reach acutely sufficient level in the circulation, and then to continue with the lower doses with short intervals to maintain the effective concentration.

VLGA infants admitted to the NICU from October 2007 to May 2009 did not receive paracetamol and were the comparison group. Infants who did not receive paracetamol during the paracetamol era were excluded from comparisons because these infants, who were doing well, did not usually need mechanical ventilation or any other invasive therapies. They were not likely to be prescribed paracetamol, let alone morphine.

Intravenous morphine was exclusively used as the opiate. Morphine dosage was calculated as the cumulative dose administered during the NICU period per patient (mg, mg/kg). No other changes in the NICU protocol took place during the study period.

Throughout the study period, nonpharmacologic pain management and evaluation of pain were the priority in our NICU. The nonpharmacologic interventions included facilitated tucking, skin-to-skin (Kangaroo) care, and swaddling. Pacifiers, oral glucose (20%), and body positioning were used routinely. Other aspects of care included dimming of lights, and avoiding noise, and excessive handling of the newborn.

The signs of pain were screened using the Neonatal Infant Acute Pain Assessment Scale (NIAPAS).[17] NIAPAS is a multidimensional pain scale designed for use in the NICU. It was originally validated using heel sticks and tracheal suctioning as examples of painful procedures. However, as it developed to be in routine use in our NICU, it was useful and further validated for assessing pain and discomfort in the intensive care of the premature infants. NIAPAS includes 5 behavioral and 3 physiological indicators rated on a 2-, 3-, or 4-point scale for a possible total score of 18. When assessing a patient, gestational age is taken into account. Alertness, facial expressions, crying, muscle tension, reaction to handling, and breathing are examined. In addition, neonates connected to monitors are assessed for changes in heart rate and oxygen saturation. According to protocol, NIAPAS scores were given when pain or discomfort was detected or anticipated. The scores were recorded before and after handling (eg, cleaning, changing diapers, etc.) or procedures, and when pain medication was given.

With NIAPAS, pain or discomfort is classified from no pain/mild pain (scores 0-5), to moderate (scores 6-9), and severe pain (scores $\geq$10). A score of more than 5 indicated the need for pharmacologic pain management. However, not every score over 5 resulted in pain medication. According to the protocol, when score reached the range between 5 and 10, nurses first made an effort to relieve the pain and discomfort using the nonpharmacologic methods. The decision of medication was made individually, sometimes after consulting the doctor.

Moderate-to-severe bronchopulmonary dysplasia was diagnosed at 36 weeks using physiological definition.[18] Intraventricular hemorrhage was defined on the basis of weekly ultrasound examinations.[19] Necrotizing enterocolitis (NEC) grade 2 to 3 was defined as described.[20] Patent ductus arteriosus (PDA) was defined as the requirement of ibuprofen medication for pharmacologic closure or ligation.[21] Signs of PDA were examined by ultrasound after birth of the VLGA infants. PDA was diagnosed as significant left-to-right shunt with signs of hemodynamic distress (left-atrium-to-aorta ratio >1.30, tachycardia, or high systolic–diastolic blood pressure difference) and persistent respiratory distress. The size of PDA was measured as internal ductal caliber vs. pulmonary artery main branch root caliber. PDA was treated with a course of intravenous ibuprofen that was repeated once if necessary. Surgical closure of PDA was performed when ibuprofen was not effective or contraindicated. The closure of PDA was determined by cardiac ultrasound. The highest bilirubin levels were screened for the possible effect of paracetamol on hepatic function.

Accurately recorded data on paracetamol and morphine dosages, NIAPAS scores, the number of days until discharge from NICU, the number of apneas during the NICU stay, and ventilation days per patient were calculated. These data and clinical outcomes were from the NICU patient database, Centricity Critical Care Clinisoft (GE Healthcare Finland, Helsinki, Finland), and reviewed with Crystal Reports XI software (SAP Finland Oy, Espoo, Finland).

Statistical analyses were performed using the PASW Statistics 18 (SPSS Inc, Chicago, Illinois). Continuous variables were analyzed using independent samples *t*-test and nonparametric Mann–Whitney U-test. Dichotomous variables were analyzed using the 2-tailed χ^2 test. Correlations were calculated using Pearson correlation coefficient test. Significance was set at $P < .05$.

Results

Between June 2009 and December 2011, 108 VLGA infants received early paracetamol during their NICU stay. During the preceding 20 months, from October 2007 to June 2009,