Efficacy and Safety of Continuous Infusion of Fentanyl for Pain Control in Preterm Newborns on Mechanical Ventilation

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Objective To evaluate the analgesic superiority and the safety equivalence of continuous fentanyl infusions versus fentanyl boluses in preterm infants on mechanical ventilation.

Study design In this multicenter, double-blind, randomized controlled trial, mechanically ventilated newborns ($\leq 32^{+6}$ weeks gestational age) were randomized to fentanyl (continuous infusion of fentanyl plus open-label boluses of fentanyl) or placebo (continuous infusion of placebo plus open-label boluses of fentanyl). The primary endpoint was analgesic efficacy, as evaluated by the Echelle Douleur Inconfort Nouveau-Né (EDIN) and Premature Infant Pain Profile scales. Safety variables were evaluated as well.

Results Sixty-four infants were allocated to the fentanyl group, and 67 were allocated to the placebo group. The need for open-label boluses of fentanyl was similar in the 2 groups ($P = .949$). EDIN scores were comparable in the 2 groups; 65 of 961 (6.8%) EDIN scores were >6 in the fentanyl group and 91 of 857 (10.6%) in the placebo group ($P = .003$). The median Premature Infant Pain Profile score was clinically and statistically higher in the placebo group compared with the fentanyl group on days 1, 2, and 3 of treatment ($P < .05$). Mechanical ventilation at age 1 week was required in 27 of 64 infants in the fentanyl group (42.2%), compared with 17 of 67 infants in the placebo group (25.4%) ($P = .042$). The first cycle of mechanical ventilation was longer and the first meconium passage occurred later in the fentanyl group ($P = .019$ and .027, respectively).

Conclusion In very preterm infants on mechanical ventilation, continuous fentanyl infusion plus open-label boluses of fentanyl does not reduce prolonged pain, but does reduce acute pain and increase side effects compared with open-label boluses of fentanyl alone. *(J Pediatr 2013;163:645-51)*.

See editorial, p 618

Mechanical ventilation by endotracheal tube and related invasive procedures are sources of pain and stress. Adult patients report that mechanical ventilation causes discomfort, episodic pain (during tracheal suctioning and other procedures), and feelings of breathlessness.[1,2] Neonates also can perceive pain during mechanical ventilation, as demonstrated by improved physiological, biochemical, and behavioral indicators of pain and stress seen on treatment with opioids rather than placebo.[3-5] These changes may lead to clinical instability and possibly increased morbidity and mortality in critically ill neonates.[6,7] Along with nonpharmacologic approaches,[8-12] the use of opioids to improve morbidity and mortality in infants receiving mechanical ventilation has been studied.[3,5,7,13] National and international consensus statements, guidelines, and policy directives have recommended low-dose continuous infusion of morphine or fentanyl to control stress and pain during mechanical ventilation.[14-16]

Despite this progress, however, there remains much uncertainty regarding the optimum analgesic drug, dosage, and therapeutic regimen (ie, continuous infusion or bolus) for this application. Fentanyl has been shown to be safer than morphine, but previous studies of fentanyl involved limited populations and very different designs.[3-5,17] Moreover, the long-term safety of opioids has not yet been established, with brain damage seen in animal models.[18] Rational evidence-based guidelines are needed to determine the safety and efficacy of analgesic and sedative drugs in mechanically ventilated neonates.[19,20] Assessing pain in preverbal patients is difficult, and the gold standard for pain assessment in newborns still remains to be defined. Evoked potentials, generated by noxious stimulation in the human infant brain, cannot be applied in clinical practice.[21] Algometric scales to measure acute and prolonged pain that have been developed and validated in preterm ventilated newborns are the best available tools for detecting pain and guiding treatment in

EDIN	Echelle Douleur Inconfort Nouveau-Né
GA	Gestational age
NICU	Neonatal intensive care unit
PIPP	Premature Infant Pain Profile

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these patients.[22,23] The present study was designed to investigate the analgesic efficacy and safety of 2 therapeutic regimens of fentanyl administration in a population of mechanically ventilated preterm newborns of <32 weeks gestational age (GA).

Methods

This multicenter, randomized, controlled double-blind study was approved by the Ethics Committee of each participating center. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Data were collected by investigators on a paper case report form and then entered into an online case report form. A logical system to check data accuracy during data entry was used.

The study cohort comprised all inborn newborns admitted to the neonatal intensive care unit (NICU) at $\leq 32^{+6}$ weeks GA who received mechanical ventilation administered through an endotracheal tube during the first 72 hours of life. Once the parents had agreed to the study and provided signed informed consent, all eligible neonates were randomized to start treatment within 24 hours from the initiation of mechanical ventilation. Exclusion criteria were known genetic or chromosomal disorders, severe intraventricular hemorrhage (grade III and intraparenchymal hemorrhage according to the Volpe classification[24]), cystic periventricular leukomalacia, the need for postoperative analgesic therapy during the first week of life, participation in another clinical trial, and probable rapid extubation.

The randomization code was developed using a computerized random number generator. The center-specific randomization lists, stratified by GA (3 strata: 23-26 weeks, 27-29 weeks, and 30-32 weeks) and balanced in blocks of 6 with a 1:1, were developed by the pharmacy of the coordinating center and sent to the pharmacies of each participating center. Eligible infants were randomized into the study through a request sent to the local pharmacy. The pharmacist assigned the randomization code, prepared the experimental drug, and sent it to the NICU to maintain the double-blind design. The study medication (fentanyl or placebo) was packed in a similar way, with a label providing data for controlled drug handling.

Randomized infants were allocated to the fentanyl group to receive a continuous infusion of fentanyl or to the placebo group to receive a continuous infusion of placebo. In both groups, infants could receive open-label boluses of fentanyl as required. Fentanyl was administered as an intravenous loading dose of 1 μg/kg in 30 minutes, followed by a continuous intravenous infusion of 1 μg/kg/hour. The infusion was administered through a central or peripheral line, through which no boluses were allowed (to avoid inadvertent boluses of fentanyl). Infants treated with a bolus of fentanyl for endotracheal intubation did not receive the loading dose if fentanyl had to be initiated within 1 hour after intubation. Fentanyl infusion initiated within 24 hours after the start of mechanical ventilation had to be continued until the end of mechanical ventilation, and not longer than 7 days of life. A newborn still receiving mechanical ventilation after the seventh day of life was treated for pain according to local protocols.

Once the decision to extubate was made, dose was tapered by 25% every 12 hours. Treatment was interrupted when it reached 50% of the initial dose, in the absence of withdrawal symptoms, as evaluated by the Finnegan score.[25] If withdrawal symptoms appeared, then the previous dosage was resumed.

Before peripheral vein insertion of a central catheter, reintubation, lumbar puncture, or thorax drainage, and in the presence of an Echelle Douleur Inconfort Nouveau-Né (EDIN) score >6,[23] infants received an open-label intravenous bolus of fentanyl administered slowly (over at least 5 minutes) at a dosage of 1 μg/kg. If the criteria for an open-label bolus of fentanyl were met, bolus doses could be repeated, based on clinical judgment, at a minimum interval of 2-4 hours in accordance with published guidelines on drug use in newborns.[26,27]

Prerandomization Phase

Before randomization into the fentanyl group or the placebo group, the following data were obtained: maternal history, including medical and pregnancy history; prenatal care; antenatal steroid administration; estimated GA; and birth weight. Brain ultrasonography was performed.

Study Phase

The study phase lasted up to day 7 of life or until the end of mechanical ventilation (if interrupted before 7 days of life). Acute pain was measured once daily during a heel prick (performed by an automatic device) using a validated algometric scale for acute pain (Premature Infant Pain Profile [PIPP]).[22] Prolonged pain was measured 3 times daily using the EDIN validated algometric scale.[23] Before the start of the study, the coordinating center offered a theoretical and practical course on the correct application of the PIPP and EDIN scales for all of the participating centers, to reduce intercenter variability in pain measurement. Care practices to reduce stress before pain assessment (ie, correct positioning or swaddling, control of external stimuli [eg, vestibular, auditory, visual, tactile], and clustering of nursery care activities) were also addressed in this course. Heart ultrasonography was obtained in all newborns in the first week of life to detect patent ductus arteriosus. Brain ultrasonography was repeated at 4 days and 7 days of age and twice a month or as clinically indicated thereafter. The following drugs were not allowed during the study phase: midazolam, paracetamol, morphine, muscle relaxants, phenobarbital, phenytoin, and chloral hydrate. If an infant needed any of these drugs after randomization (eg, in the event of seizures), then the experimental treatment was interrupted, and the infant was analyzed according to the intention-to-treat principle.

Follow-Up Phase

The follow-up phase began at the end of day 7 of life. Assessments continued until hospital discharge. In addition, the following information was collected at hospital discharge: