Remifentanil versus Morphine-Midazolam Premedication on the Quality of Endotracheal Intubation in Neonates: A Noninferiority Randomized Trial

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Objective To compare remifentanil and morphine-midazolam for use in nonurgent endotracheal intubation in neonates.

Study design In this prospective noninferiority randomized trial, newborns of gestational age ≥28 weeks admitted in the neonatal intensive care unit requiring an elective or semielective endotracheal intubation were divided into 2 groups. One group (n = 36) received remifentanil (1 μg/kg), and the other group (n = 35) received morphine (100 μg/kg) and midazolam (50 μg/kg) at a predefined time before intubation (different in each group), to optimize the peak effect of each drug. Both groups also received atropine (20 μg/kg). The primary outcome was to compare the conditions of intubation, and the secondary outcome was to compare the duration of successful intubation, physiological variables, and pain scores between groups for first and second intubation attempts. Adverse events and neurologic test data were reported.

Results Intubation with remifentanil was not inferior to that with morphine-midazolam. At the first attempted intubation, intubation conditions were poor in 25% of the remifentanil group and in 28.6% of the morphine-midazolam group (P = .471). For the second attempt, conditions were poor in 28.6% of the remifentanil group, compared with 10% of the morphine-midazolam group (P = .360). The median time to successful intubation was 33 seconds (IQR, 24-45 seconds) for the remifentanil group versus 36 seconds (IQR, 25-59 seconds) for the morphine-medazolam group (P = .359) at the first attempt and 45 seconds (IQR, 35-64 seconds) versus 56 seconds (IQR, 44-68 seconds), respectively, for the second attempt (P = .302). No significant between-group difference was reported for hypotension, bradycardia, or adverse events.

Conclusion In our cohort, remifentanil was at least as effective as the morphine-midazolam regimen for endotracheal intubation. Thus, premedication using this very-short-acting opioid can be considered in urgent intubations and is advantageous in rapid extubation. *(J Pediatr 2014;164:1032-7)*.

Today, premedication before endotracheal intubation is becoming a standard of care for newborns,[1] because management of pain and stress is a goal of neonatal practice for both ethical and humane reasons. In addition, early pain experiences may modify the pain response and affect neurodevelopmental outcomes.[2,3]

The management of neonatal respiratory distress syndrome, especially in very low birth weight infants, is changing toward minimal mechanical ventilation to avoid lung injury[4] and use of the intubation-surfactant-extubation strategy.[5] In several trials, the use of premedication for neonates undergoing intubation significantly improved the quality condition of intubation and decreased both the procedure time and the number of attempts.[6-8] This is important in the neonatal intensive care unit (NICU), where intubations are performed by pediatricians with widely varying skills and experience.[9] An ultra-short-acting premedication meets the objective of using a common effective premedication that provides rapid, safe, and adequate analgesia to neonates while improving intubation conditions. A short-acting drug is also advantageous for rapid return of spontaneous breathing with minimal adverse effects.

Morphine is currently the most commonly used analgesic,[10] but it has some limitations, mainly a delayed onset of action after injection,[11] which makes it unsuitable for semiurgent intubation.[12] Midazolam, a nonanalgesic sedative frequently used with morphine, has a long half-life, which can delay the recovery of spontaneous breathing, and is associated with a higher incidence of adverse events.[13] Remifentanil is a highly potent synthetic opioid with a rapid onset of action and a very short half-life owing to its unique pharmacokinetics, being metabolized by nonspecific esterases in blood and tissues. These properties result in quick recovery of spontaneous respiration,[14,15] without the need for renal and hepatic metabolism.[16] In the present study, a noninferiority randomized trial, we compared remifentanil with the classical morphine-midazolam regimen used before intubation in our NICU.

HR	Heart rate
MABP	Mean arterial blood pressure
NICU	Neonatal intensive care unit
SpO_2	Peripheral oxygen saturation

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Methods

This prospective randomized study was conducted from October 2009 to February 2012 in the NICU at Hôpital Universitaire des Enfants Reine Fabiola in Brussels, Belgium. The trial was approved by the hospital's Ethics Committee. Written informed consent was obtained from both parents before enrollment.

Newborns needing elective or semielective intubation as determined by the clinical team were randomized sequentially using a random numbers table to either remifentanil or morphine-midazolam. Inclusion criteria were gestational age ≥28 weeks and no administration of analgesics on the previous day. Exclusion criteria were urgent intubation or transport, congenital anomalies of the airway, and grade 4 intraventricular hemorrhage.

Owing to the differing delay of action of the administered drugs, the procedure could not be treated as a blind test. In accordance with our standard policy, and to prevent bradycardia and hypotension induced by opioids, both groups received atropine 20 μg/kg at 2 minutes before intubation. Atropine also blocks vagal reactions to pain, stress, and hypoxemia.

For premedication, remifentanil was infused over 60 seconds to prevent chest wall rigidity, and intubation proceeded after complete infusion. Morphine (100 μg/kg) and midazolam (50 μg/kg) were given at 10 and 3 minutes before intubation, respectively.

Three persons performed the procedure: an experienced neonatologist, a nurse, and an assessor not involved in the intubation procedure who recorded the intervention times and other data. The timing of administration of each drug was based on the time to peak effect. The following physiological variables were measured at baseline, at the time of drug injection, and at several points throughout the procedure and up to 60 minutes after intubation: continuous heart rate (HR); noninvasive mean arterial blood pressure (MABP), with a Viridia CMS monitor (Hewlett Packard, Böblingen, Germany); and continuous pulse oximetry, with a Nellcor NPB-295 pulse oximeter (Covidien, Dublin, Ireland; averaging time, 3 seconds). During premedication administration, each newborn was ventilated and oxygenated with a mask and T-piece device (Neopuff infant resuscitator; Fisher & Paykel Healthcare, Auckland, New Zealand) to achieve a peripheral oxygen saturation (SpO_2) level of 90%-95%. Certified neonatologists performed all intubations orally, considered the easier and quicker route. The intubation time was calculated from the introduction of the laryngoscope (fiber optic straight blade; Heine, Hersching, Germany) in the mouth to the successful insertion of the endotracheal tube (Mallinckrodt; Covidien) with confirmation of appropriate position. The attempt was interrupted when SpO_2 dropped below 80% and when the HR was consistently decreased. If the intubation was unsuccessful, the procedure was repeated, after administration of a second dose of the same premedication in the exact same sequence as for the first attempt. Between the 2 attempts, the neonate was ventilated for reoxygenation (SpO_2 >90%). After 2 failed intubation attempts, a neonate was removed from the trial.

The intubation conditions were assessed by a neonatologist using the validated Viby-Mogensen scoring system,[17] including 5 assessments (jaw relaxation, position and movement of vocal cords, limb movements, and coughing), evaluated on a clinical scale of acceptable or unacceptable. The number and duration of attempts were recorded, and the newborn's pain was assessed before intubation and at 10 and 60 minutes after intubation using the validated Douleur Aigüe du Nouveau-né scale.[18] The Viby-Mogensen score was used to assess the conditions for intubation, with some variables (eg, limbs movements, relaxed jaw) also providing information about the neonate's comfort level. Blood gas values (pH, partial pressure of carbon dioxide, and lactate) were measured at baseline and at 30 minutes after intubation using capillary blood samples. Adverse events, such as chest wall rigidity, were recorded, and cranial ultrasound, electroencephalography, and auditory evoked potentials were performed before discharge.

The primary study outcome was to demonstrate that the quality of intubation (evaluated by the validated Viby-Mogensen scoring system) in the group receiving remifentanil was not worse than or was at least equal to that in the group receiving morphine-midazolam. Secondary outcomes compared physiological measurements, including HR, MABP, SpO_2, pain assessment, blood gas analysis, and duration of and number of attempts during the intubation procedure, between the 2 groups.

We used the noninferiority criterion[19] to calculate the appropriate sample size. We assumed that the proportion of poor intubations was 10% in the morphine-midazolam group and 15% in the remifentanil group. Considering that a difference of <15% was of no clinical importance, we chose a noninferiority margin of $\delta = 0.15$. With equal allocation ($r = 1$), obtaining 80% power ($\beta = 0.2$) with a 1-sided α of 0.05 required approximately 34 neonates in each group.

We analyzed primary and secondary outcomes according to the intention-to-treat principle. For the primary outcome, the difference in proportion of poor intubation between the 2 groups was analyzed using the χ^2 test with a 1-sided exact test, with $\alpha = 0.05$. For the secondary outcome variables, differences between groups were evaluated using the Student t test for means and the Mann-Whitney U test for group medians, with the χ^2 and Fisher exact tests applied for binary outcomes as appropriate. P values with a 2-sided α of 0.05 for secondary outcomes are reported. Data were analyzed with IBM SPSS version 20 for Windows (IBM, Armonk, New York).

Results

Between October 2009 and February 2012, 232 neonates were assessed for eligibility to participate in the trial. Of these, 79 neonates were eligible and randomized, but 4 neonates in