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Is Premedication for Intubation of Preterm Infants the Right Choice?

Paul S. Kingma, MD, PhD

Perinatal Institute, Section of Neonatology, Perinatal and Pulmonary Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

The question of premedicating neonates before intubation has been actively debated in neonatology over the past 20 years, and neonatologists' views on this matter are gradually changing. A 1992 survey of neonatal intensive care units (NICU) in the US found that only 3% routinely used sedatives before intubation and 97% never or rarely used a muscle relaxant.¹ In contrast, a similar survey conducted in 2006 found that 44% of NICUs routinely used premedication and 25% routinely used muscle relaxants.² Although the use of premedication is on the rise, and the American Academy of Pediatrics recently recommended premedication for nonemergent neonatal intubation, it still is not the standard of care in many NICUs.^{3,4} In addition, many neonatologists hesitate to use premedication during the intubation of preterm infants. Reasons for this hesitation may include fear of adverse effects on the infant's hemodynamic status or neurodevelopment, perceived lack of benefit in improving the intubation, and lack of consensus regarding the optimal drug regimen.

Several previous studies examining the use of premedication in term infants have demonstrated that anticholinergics attenuate bradycardia, analgesics prevent hypertension, and muscle relaxants attenuate increased intracranial pressure and decrease the number of attempts and time required for successful intubation.⁵⁻¹⁸ Few of these studies included preterm infants, however, and most of the studies that did include preterm infants did not specifically examine the effects of premedication on these infants. Thus, the benefits and risks of premedication in the preterm population, as well as the optimal drug regimen to use for premedication, remain uncertain.

In this issue of the *The Journal*, Norman et al¹⁹ compare premedication with atropine and morphine versus a rapid sequence intubation (RSI) regimen of glycopyrrolate, thiopental, suxamethonium, and remifentanyl in 34 preterm infants. Similar to previous studies with term infants, the authors find that RSI improves intubation conditions and decreases the time to successful intubation in preterm infants. Traditional thinking in neonatology holds that premedication is beneficial in more active term infants, but not in passive preterm infants. The findings of Norman et al suggest that these assumptions are incorrect. However, it is important to note that the authors used the more difficult nasal approach for intubation, which, unfortunately, still leaves open the possibility that premedication with RSI will not improve conditions during intubation using the oral route, which most neonatologists consider the easier and faster method.

The authors also examined several physiological and biochemical variables and found that compared with the RSI group, the group treated with morphine had a significantly prolonged

decrease in heart rate and increase in mean arterial blood pressure during intubation and a subsequent lower blood pressure at 3 hours after intubation. Most of the patients received a fluid bolus within 2 hours before intubation, which is not the standard of care in most units and complicates the interpretation of these patients' hemodynamic data. This limitation notwithstanding, the authors' findings support the conclusion that RSI premedication improves the hemodynamic stability of preterm infants during and several hours after intubation.

In addition to examining hemodynamic variables, Norman et al also took the unique approach of evaluating amplitude integrated electroencephalography during the procedure and at 24 hours after intubation. Although the RSI group received more sedation during the procedure, they recovered faster than the morphine group, in which central nervous system depression persisted for up to 6 hours after the procedure. These results are rather interesting considering the recent emphasis on the impact of pain and sedation on the neurodevelopmental outcome of neonates, and suggest that similar measures of neurophysiological recovery should be included in future studies evaluating premedication in neonates.²⁰

There is a growing body of evidence indicating that, much like the adult and pediatric population, both preterm and term neonates do better if premedicated before intubation. However, the optimal drug regimen for this premedication remains to be determined. Norman et al compared morphine and atropine versus their RSI regimen, but their protocol administered the morphine 5 minutes before the intubation attempt, much earlier than the 20 minutes required for morphine to achieve its peak analgesia effect. Therefore, although their results would seem to suggest that RSI is better than morphine and atropine, the authors really compared RSI with atropine alone. Although this is a weakness of the authors' study, it also underscores one of the most compelling reasons for not using morphine for premedication before neonatal intubation.

Norman et al state that optimal premedication should eliminate pain and physiological instability and provide conditions to support rapid and safe intubation without adverse effects. It is likely that these goals will be achieved with an RSI combination of an anticholinergic agent (eg, atropine, glycopyrrolate), a short-acting sedative and analgesic agent (eg, thiopental, fentanyl, remifentanyl), and a neuromuscular blocking agent (eg, suxamethonium, rocuronium, vecuronium). Unfortunately, randomized trials in neonates have compared different single drug regimens or RSI regimens with placebo or single drugs, and thus determining the best RSI combinations is not yet possible.

In summary, Norman et al provide the strongest evidence to date indicating that premedication with an RSI regimen that includes a neuromuscular blocking agent improves both intubation conditions and hemodynamic outcome in preterm infants. In addition, they provide the first evidence that depending on the type of premedication used, the preterm infant's neurologic activity may be affected for several hours after the procedure. Although their findings support the use of premedication during neonatal intubation, the optimal premedication regimen remains unclear.

Glossary

NICU	Neonatal intensive care unit
RSI	Rapid sequence intubation

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