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Guidance for the Clinician in Rendering Pediatric Care

Clinical Report—Premedication for Nonemergency Endotracheal Intubation in the Neonate

abstract

Endotracheal intubation is a common procedure in newborn care. The purpose of this clinical report is to review currently available evidence on use of premedication for intubation, identify gaps in knowledge, and provide guidance for making decisions about the use of premedication. *Pediatrics* 2010;125:608–615

INTRODUCTION

Endotracheal intubation is a common procedure in NICUs and should be performed expeditiously in as controlled an environment as possible to reduce complications. Several studies that evaluated the success rate of neonatal endotracheal intubations have reported that successful intubations frequently require more than 1 attempt and are rarely accomplished within the currently recommended time frame.[1–3] Many failed attempts can be attributed to suboptimal intubating conditions. Excellent intubating conditions are characterized by good jaw relaxation, open and immobile vocal cords, and suppression of pharyngeal and laryngeal reflexes assessed by the absence of coughing or diaphragmatic movements in response to intubation.[4] Several trials have demonstrated that the use of premedication for intubation of the newborn significantly improves intubating conditions, decreases the time and number of attempts needed to complete the intubation procedure, and minimizes the potential for intubation-related airway trauma.[5–10]

The alleviation of pain in neonates should be the goal of all caregivers, because repeated painful experiences have the potential for deleterious consequences.[11] The experience of being intubated is unpleasant and painful and seriously disturbs physiologic homeostasis.[12,13] A consensus statement from the International Evidence-Based Group for Neonatal Pain concluded that "tracheal intubation without the use of analgesia or sedation should be performed only for resuscitation in the delivery room or for life-threatening situations associated with the unavailability of intravenous access."[14] Subsequently, in a recent policy statement the American Academy of Pediatrics also recommended that every health care facility caring for neonates implement an effective pain-prevention program and use pharmacologic and nonpharmacologic therapies for the prevention of pain associated with procedures.[11] Despite these recommendations, there remains wide variation in the frequency of use of premedication before intubation, and in the medications used for premedication.[15,16] Some of the reasons offered for not using premedications before intubation are concern for ad-

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KEY WORDS
neonate, endotracheal intubation, premedication

ABBREVIATION
LMA—laryngeal mask airway

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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verse reactions and/or toxic effects of the medications, inadequate time for administration of medications in emergency situations, and the perception that risk/benefit ratios are worsened by using premedications.[13] This report will address some of these issues, including the choices of available medications, the circumstances for the use of medications, the risks of these medications, and the appropriate precautions to take while adopting these procedures.

PHYSIOLOGIC RESPONSES TO INTUBATION

The process of intubation may cause hypoxemia,[17] bradycardia,[18] intracranial hypertension,[19] systemic hypertension,[17] and pulmonary hypertension.[20] Hypoxemia seems to be related either to apnea at the time of intubation or possible airway obstruction associated with positioning.[17] Bradycardia is presumed to be vagal in origin, because the very rapid onset is suggestive of a reflexive etiology[17] and is not prevented by preoxygenation and the avoidance of hypoxemia.[18] The increase in intracranial pressure may be a result of coughing and struggling of the infant that can result in venous stasis with an increase in cerebral blood volume.[19,21] Systemic arterial hypertension has been investigated in adults and seems to be caused by an increase in systemic vascular resistance, which is probably caused by catecholamine release.[22] Pulmonary hypertension leading to right ventricular failure has been described in adults,[23] and although pulmonary artery pressures have not been measured in newborn infants undergoing intubation, endotracheal suctioning is known to cause an increase in pulmonary artery pressure postoperatively in infants with congenital heart disease[20] and is presumed to occur with intubation. In addition, improperly performed direct laryngoscopy can cause traumatic injuries to the face, eyes, tongue, and gums, and placement of the endotracheal tube can dislodge the arytenoids or damage other glottic structures. These injuries can be avoided by improved technique that can be enhanced by the use of premedication.[24]

CHARACTERISTICS OF AN IDEAL STRATEGY

An ideal strategy for premedication for intubation eliminates the pain, discomfort, and physiologic abnormalities of the procedure, helps to carry out intubation expeditiously, minimizes the chances for traumatic injury to the newborn, and has no adverse effects. An individual skilled in the use of bag-mask ventilation should be present to ensure adequate ventilation after the use of premedication and before the intubation. An ideal approach would be to administer supplemental oxygen, as needed, via a properly sized face mask, then a vagolytic agent, followed by analgesic and/or hypnotic medications before infusion of a muscle relaxant. The vagolytic drug prevents bradycardia, the analgesic and/or hypnotic drug can control pain and may render the infant unconscious and minimize adverse hemodynamic responses to laryngoscopy, and the muscle relaxant provides the best possible intubating conditions. Nonpharmacologic interventions, including swaddling and comfortable positioning, would contribute to the infant's comfort as well.

Analgesia

Premedication with an analgesic reduces the pain and discomfort of intubation. An ideal analgesic agent would have a rapid onset, be of short duration, have no adverse effects on respiratory mechanics, and possess predictable pharmacokinetic properties. None of the currently available agents fit this profile.

Opioids are the most commonly used medications for analgesia in the neonate. The mechanism of action of the individual opioids involves interaction at various receptor sites in both the central and peripheral nervous system to modify transmission of painful signals and diminish pain perception.[25] Morphine is the most frequently used opiate for pain control in the neonate. It has been used for acute postoperative pain control and as a continuous infusion for ventilated infants. The use of morphine for premedication for intubation was studied in a randomized, controlled trial of 34 premature infants in which infants were given either morphine alone or placebo 5 minutes before the intubation. There was no effect on the severity of physiologic disturbances during intubation including the duration of severe hypoxemia, incidence of bradycardia, and change in mean blood pressure.[26] This lack of effect is thought to be because of the delayed onset of action of morphine[27] related to the relative hydrophilic nature of the drug. Intravenous morphine has a mean onset of action at 5 minutes and peak effect at 15 minutes.[25] Another randomized, controlled trial of 20 preterm infants compared the use of morphine and midazolam versus remifentanil and midazolam for intubation.[8] No differences were noted between the groups with regard to pain control or hemodynamic variables, but the probability of having excellent intubation conditions was significantly higher with remifentanil than with morphine. All infants pretreated with remifentanil and midazolam were intubated at first attempt compared with only 60% of the infants in the morphine and midazolam group.[8] In another study, when morphine was used in combination with a vagolytic and a paralytic agent, the time needed to intubate was reduced and bradycardia was decreased.[24] However, these effects may be related to the vagolytic and paralytic agents used in the study, not to

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morphine effects. Furthermore, the status of pain control was not assessed in that study. For these reasons, morphine alone would not be the most appropriate choice for premedication for intubations. Meperidine is rarely used in neonates because of its slow onset of action, variability in metabolism, and risk of toxic effects of its metabolites; as a result, it is not recommended.[27]

Fentanyl is the most frequently used synthetic opioid in the neonate. This drug may be preferable to morphine for pain control for intubation because of a more rapid onset of action related to its more lipophilic nature.[25] Fentanyl's impact on some of the physiologic disturbances during intubation has been studied. In older infants and children this drug blunts physiologic disturbances during endotracheal suctioning and, in patients after surgery, decreases pulmonary arterial pressure and systemic hypertension.[20,23] It is likely that such responses may occur during intubation too. Its impact on cerebral and systemic hemodynamics was studied with a short-term infusion in 15 preterm infants, and there were no significant changes in the systemic or cerebral perfusion or pressure.[28] Although fentanyl as a single agent in intubation has not been studied, a cohort study of 33 preterm and term infants intubated after a combination of atropine, fentanyl, and a paralytic agent showed that fentanyl had no significant adverse effects.[7] Remifentanil, another synthetic opiate, has a rapid onset of action and an ultrashort duration of action and has been shown to be a useful drug for neonatal intubation.[8,29] A primary concern with synthetic opioid use is the risk of chest wall rigidity, but this risk can be reduced by slow administration and can be treated with either naloxone or muscle relaxants.[30] However, it is important to remember that the use of naloxone, a competitive antagonist at all opioid receptors, will also reverse the analgesic effects of these drugs.

Sedation

Sedatives do not always reduce pain but can sedate or render individuals unconscious or amnestic depending on the dose and individual response. Benzodiazepines have been frequently used for sedation before elective intubations but may not be appropriate in many cases. Midazolam is the most commonly used medication in this category[31] in the United States, but it has not been shown to reduce any physiologic changes during intubation. In a randomized, double-blind trial (stopped after only 16 intubations because of adverse events and reported in a letter to the editor), preterm infants who received midazolam and atropine for intubation had more desaturations, and 29% required cardiopulmonary resuscitation compared with those in the groups that received either atropine alone or no premedication.[32] Midazolam can cause hypotension in both preterm and term infants,[33–36] decreased cardiac output in older children,[37] and decreased cerebral blood flow velocity in premature infants.[33,38] The studies that demonstrated these effects were not performed as part of premedication for intubation, and the results may not be applicable to the circumstances necessitating endotracheal intubation. However, kinetic studies in preterm and term infants have shown that the serum half-life of midazolam given as continuous infusion or by repetitive dosing can exceed 22 hours.[38,39] Further concern in the use of midazolam for preterm infants is the exposure to the preservative benzyl alcohol.[40,41] For these reasons, midazolam should not be used in preterm infants, but it can be considered for use in the term or older infant as part of the premedication sequence for elective intubation in the NICU.

Elective intubation of patients before surgery is often accomplished with a sedative-hypnotic agent such as a barbiturate and a muscle relaxant. Barbiturates have been used for induction of anesthesia for decades; however, barbiturates are poor analgesics.[42] Barbiturates such as thiopental and methohexital have a rapid onset and short duration of action. In a randomized, placebo-controlled trial in term infants, thiopental was shown to reduce changes in heart rate and blood pressure during intubation and to shorten the time to intubation.[43] In a small cohort study of term and preterm infants, methohexital facilitated intubation with rapid onset within 1 minute of sedation and recovery within 10 minutes.[44] However, more studies are necessary before methohexital can be recommended for use.

Propofol is a nonbarbiturate anesthetic that is frequently used for induction of anesthesia in older children and adults but has not been well evaluated in newborns. Propofol is lipophilic and rapidly equilibrates between plasma and brain with quick loss of consciousness and also has a short duration of action after a single-bolus dose.[25] In a randomized, controlled trial in 63 premature infants, propofol was shown to be a more effective induction agent than the morphine, atropine, and suxamethonium regimen to facilitate neonatal intubation.[9] Oxygenation during intubation was maintained better in the propofol group and was attributed to the maintenance of spontaneous respiration in infants who received propofol. Twenty-three percent of the infants in the morphine, atropine, and suxamethonium group and 6% of the infants in the propofol group sustained intubation-related trauma. No other adverse events were noted in the propofol group. Although the results of this study are encouraging, more research

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confirming these initial findings is necessary before propofol can be recommended as a single premedication agent for neonatal intubation. Propofol can only be administered intravenously, and pain at the site of injection that may sometimes be moderately severe has been reported with intravenous injection of propofol in 10% to 20% of patients.[45]

Vagolytic Agents

Vagolytic agents prevent bradycardia during intubation and decrease bronchial and salivary secretions but are infrequently used for neonatal intubation.[46] One reason for their sparse use has been the concern that vagolytic agents mask hypoxia-induced bradycardia during intubation; however, most episodes of bradycardia during intubation are secondary to vagal stimulation, not hypoxia. Glycopyrrolate and atropine are both effective vagolytic agents, and although they have not been directly compared in neonates, they have been studied in infants and children. In a randomized, controlled trial in 90 older infants and children that compared the use of glycopyrrolate and atropine at anesthetic induction, none had bradycardia, but more subjects who received atropine developed sinus tachycardia than those who received glycopyrrolate.[47] Glycopyrrolate is widely used in pediatric intensive care and anesthesia; however, its pharmacokinetics in small preterm infants is not known.

Muscle Relaxants

The ideal muscle relaxant for intubation would have a rapid onset, short duration of action, and minimal or no deleterious effect on heart rate and blood pressure. None of the currently available agents meet all these criteria for neonates, but use of a muscle relaxant to facilitate intubation can eliminate or minimize the increase in intracranial pressure that occurs during awake intubation. This has been demonstrated with both succinylcholine in preterm infants[48] and pancuronium in preterm and term infants.[18]

Succinylcholine, the only depolarizing agent in clinical use, blocks neuromuscular transmission by binding to the acetylcholine receptors of the muscle membrane and depolarizing the membrane. It has both a rapid onset and a short duration of action. In a randomized, controlled trial in preterm infants, succinylcholine given with morphine and atropine was compared with awake intubation. This combination resulted in faster intubation with less bradycardia and less trauma as defined by less blood in the oral and nasal passages.[48]

The nondepolarizing muscle relaxants compete with acetylcholine for receptors on the motor endplate but do not result in depolarization of the membrane. Of these agents, pancuronium is widely used in newborns and has few adverse effects but is slower in onset of action and longer acting compared with the other available muscle relaxants. Pancuronium has a vagolytic effect that helps minimize the reflex bradycardia that often accompanies laryngoscopy. In a randomized, controlled trial, infants who received pancuronium and atropine showed less hypoxia during intubation and less increase in intracranial pressure compared with infants who received no premedication or atropine alone.[18]

Mivacurium, another nondepolarizing agent, is no longer commercially available because of its adverse effect of histamine release and associated bronchospasm. Cisatracurium has been introduced to replace mivacurium and seems to have similar physiologic effects but has not yet been tested in a neonatal population. Vecuronium and rocuronium, 2 other nondepolarizing muscle relaxants in wide use in pediatric anesthesia and PICUs, are characterized by their minimal effects on blood pressure or heart rate. Rocuronium is a metabolic derivative of vecuronium and has quicker onset to paralysis and shorter duration of action compared with vecuronium.

ADVERSE EFFECTS

Concern for adverse effects has been a barrier to implementing premedication for intubation,[49] but most reports and randomized, controlled trials have not demonstrated serious adverse effects. A large multicenter observational study showed no increase in the frequency of adverse effects when infants were premedicated.[31] When used alone, fentanyl and other synthetic opioids have been associated with acute chest wall rigidity in both preterm and term infants, which can significantly impair ventilation.[30] However, this adverse effect may be related to dose and rapid delivery and can be prevented by slow infusion of an appropriate dose and overcome with muscle relaxant[50] or reversed with naloxone.[30]

Succinylcholine has been reported to have rare serious adverse effects in children, including hyperkalemia, myoglobinemia, and cardiac arrhythmias. Atropine seems to protect against bradyarrhythmias induced by succinylcholine.[51] Hyperkalemia is also unlikely, because marked elevations have been reported only in clinical circumstances associated with significant tissue destruction.[51] Succinylcholine is a known trigger of malignant hyperthermia, a skeletal muscle disorder inherited as an autosomal dominant trait. The incidence of malignant hyperthermia is estimated to be 0.4 to 0.5 in 10 000 in the general population.[52] Diagnosis and management of malignant hyperthermia is beyond the scope of this report. Succinylcholine should not be used in the presence of hyperkalemia and/or a family history of malignant hyperthermia.[53]

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CLINICAL CIRCUMSTANCES FOR INTUBATION WITHOUT PREMEDICATION

Intubation without premedication may be acceptable during resuscitation or after acute deterioration or critical illness at a later age. The risk/benefit ratio may also support intubation without premedication in infants with upper airway anomalies such as Pierre Robin sequence. Intubation of infants with severely abnormal airways can be difficult, and the infant's own respiratory effort may be essential for maintaining an open airway. If intubation attempts are unsuccessful in these infants, the use of laryngeal mask airway (LMA) or anticipatory transfer to a center with a team of personnel, including a neonatologist, pediatric otolaryngologist, and pediatric anesthesiologist, experienced in managing infants with structurally abnormal airways should be considered. It is important to note that LMA is a temporary airway device and should be used only as a last resort while preparations for a secure airway are in progress. One might also consider the use of a fiber-optic bronchoscope for intubation if personnel experienced in its use are available.[54]

GAPS IN KNOWLEDGE

Many unanswered questions remain regarding the practice of premedication for nonemergent intubation in the newborn.

- The optimal pharmaceutical agents have not been developed for use in newborns, and appropriate drug doses of currently available agents based on gestational age are currently unknown.
- The pharmacokinetic and pharmacodynamic characteristics of many drugs used in premedication have not been well studied in newborns.
- An ideal combination and/or sequence of premedications have not been established.
- Alternative routes of administration of premedications have not been systematically studied.
- Long-term benefits and adverse effects of premedications are unknown.

Further research must continue to answer these and other questions.

CLINICAL IMPLICATIONS

- Preparation should include having appropriate equipment such as an oxygen source, appropriately sized bags, face masks, endotracheal tubes, stylet, laryngoscope, and suction.
- All support staff assisting with the procedure should have clearly preassigned responsibilities during the procedure.
- Infants should have cardiorespiratory, oxygen saturation, and noninvasive blood pressure monitoring during nonemergent intubation, and an end-tidal carbon dioxide detector should be available. Intravenous access should preferably be established, and the stomach should be decompressed.
- All personnel who intubate neonates should acquire training with LMAs, because this device may prove to be an effective bridge to intubation in some cases in which bag-mask ventilation is suboptimal.[55,56] Appropriately sized LMAs should be available for all intubations, particularly when any difficulty is anticipated. LMAs have been used successfully in late-preterm and term newborns weighing more than 2500 g.
- Individuals who perform intubations should be experienced in the use of bag-mask ventilation and be knowledgeable about the effects of the procedure of laryngoscopy and intubation, as well as risks and benefits of premedications. Ascertainment of appropriate endotracheal tube position immediately after intubation should be done by auscultation and end-tidal carbon dioxide monitoring.
- Except for emergent intubation during resuscitation either in the delivery room or after acute deterioration or critical illness at a later age, premedication should be used for all endotracheal intubations in newborns. Medications with rapid onset and short duration of action are preferable (Table 1).
  - Analgesic agents or anesthetic dose of a hypnotic drug should be given.
  - Vagolytic agents and rapid-onset muscle relaxants should be considered.
  - Use of sedatives alone such as benzodiazepines without analgesic agents should be avoided.
  - A muscle relaxant without an analgesic agent should not be used.
- Each unit should develop protocols and lists of preferred medications to improve compliance and minimize medication errors and adverse effects.
- For circumstances in which intravenous access is not available, alternative routes such as intramuscular administration can be considered.

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TABLE 1 Medications for Premedication for Nonemergency Intubation

Drug	Route/Dose	Onset of Action	Duration of Action	Common Adverse Effects	Comments[a]
Analgesic					
Fentanyl	IV or IM[b]/1–4 μg/kg	IV, almost immediate; IM, 7–15 min	IV, 30–60 min; IM, 1–2 h	Apnea, hypotension, CNS depression, chest wall rigidity	Preferred analgesic Effects reversible with naloxone Give slowly (preferably over 3–5 min, at least over 1–2 min) to avoid chest wall rigidity Chest wall rigidity can be treated with naloxone and muscle relaxants
Remifentanil	IV/1–3 μg/kg May repeat in 2–3 min if needed	IV, almost immediate	IV, 3–10 min	Apnea, hypotension, CNS depression, chest wall rigidity	Acceptable analgesic Short duration of action and limited experience in neonates Effects reversible with naloxone Give slowly over 1–2 min to avoid chest wall rigidity Chest wall rigidity can be treated with naloxone and muscle relaxants
Morphine	IV or IM/0.05–0.1 mg/kg	IV, 5–15 min; IM, 10–30 min	IV, 3–5 h; IM, 3–5 h	Apnea, hypotension, CNS depression	Acceptable analgesic agent Use only if other opioids are not available; if selected, must wait at least 5 min for onset of action Effects reversible with naloxone
Hypnotic/sedative					
Midazolam	IV or IM/0.05–0.1 mg/kg	IV, 1–5 min; IM, within 5–15 min	IV, 20–30 min; IM, 1–6 h	Apnea, hypotension, CNS depression	Acceptable sedative for use in term infants in combination with analgesic agents Hypotension more likely when used in combination with fentanyl Not recommended in premature infants Effects reversible with flumazenil
Thiopental	IV/3–4 mg/kg	IV, 30–60 s	IV, 5–30 min	Histamine release, apnea, hypotension, bronchospasm	Acceptable hypnotic agent Hypotension more likely when used in combination with fentanyl and/or midazolam
Propofol	IV/2.5 mg/kg	Within 30 s	3–10 min	Histamine release, apnea, hypotension, bronchospasm, bradycardia; often causes pain at injection site	Acceptable hypnotic agent Limited experience in newborns Neonatal dosing has not been well established
Muscle relaxant					
Pancuronium	IV/0.05–0.10 mg/kg	1–3 min	40–60 min	Mild histamine release, hypertension, tachycardia, bronchospasm, excessive salivation	Acceptable muscle relaxant Relatively longer duration of action Effects reversible with atropine and neostigmine
Vecuronium	IV/0.1 mg/kg	2–3 min	30–40 min	Mild histamine release, hypertension/hypotension, tachycardia, arrhythmias, bronchospasm	Preferred muscle relaxant Effects reversible with atropine and neostigmine
Rocuronium	IV/0.6–1.2 mg/kg	1–2 min	20–30 min	Mild histamine release, hypertension/hypotension, tachycardia, arrhythmias, bronchospasm	Preferred muscle relaxant Effects reversible with atropine and neostigmine
Succinylcholine	IV/1–2 mg/kg; IM[b]/2 mg/kg	IV, 30–60 s; IM, 2–3 min	IV, 4–6 min; IM, 10–30 min	Hypertension/hypotension, tachycardia, arrhythmias, bronchospasm, hyperkalemia, myoglobinemia, malignant hyperthermia	Acceptable muscle relaxant Contraindicated in presence of hyperkalemia and family history of malignant hyperthermia
Vagolytic					
Atropine	IV or IM/0.02 mg/kg	1–2 min	0.5–2 h	Tachycardia, dry hot skin	Preferred vagolytic agent
Glycopyrrolate	IV/4–10 μg/kg	1–10 min	~6 h	Tachycardia, arrhythmias, bronchospasm	Acceptable vagolytic agent Limited experience in newborns Contains benzyl alcohol as preservative

Most of these drugs have limited pharmacokinetics data from newborns and are not approved for use in the newborn, but they have been used in newborns. IV indicates intravenously; IM, intramuscularly; CNS, central nervous system.

[a] Preferred and acceptable designation of medications is based on consensus opinion after review of available evidence.

[b] Consider only if no intravenous access.

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