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Premedication for Neonatal Intubation: Which Medications are Recommended and Why?

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Keywords

infant; intubation; medications

Three decades ago, few scientists and health care providers believed infants and young children were able to localize and/or perceive painful stimuli.[1] This assumption that infants and children did not feel pain led to infants undergoing surgical and other painful procedures (e.g., lumbar puncture, endotracheal intubation) without any medication for pain and anxiety.[2] This assumption has now been proven to be untrue. Today, infants routinely receive analgesia and sedation for surgical procedures in the operating room, but the extent to which infants routinely receive medication for other painful procedures varies. A common, painful procedure for critically ill neonates is endotracheal intubation;[3] however the administration of medications prior to intubation varies substantially.

In the most recent survey from 2006 in the United States,[4] only 44% of neonatology fellowship program directors reported routine use of analgesia and/or sedation before intubation. A survey of neonatal intensive care units (NICU) in the United Kingdom in 2009 reported that 90% of the units routinely administered premedication prior to elective intubations.[5] Intubation can cause traumatic injury to the airway,[6] as well as lead to physiologic instability during the procedure.[7, 8] Despite the possible negative impact of intubation, the procedure is often necessary and many times life saving. Critically ill neonates are often intubated nonemergently in the NICU due to prematurity, need for prolonged ventilation, endotracheal tube change, or an unstable airway.[9]

In 2010, the American Academy of Pediatrics (AAP)[10] recommended premedication be used for all intubations in neonates, except in the case of emergent intubation during resuscitation. The goal of premedication is to eliminate pain, discomfort, traumatic injury to the airway, and physiologic instability (e.g., bradycardia, hypotension/hypertension, decreased oxygen saturation) associated with endotracheal intubation procedure.[10] To implement this recommendation in the NICU, written policies are needed to guide health care providers. However, the previous surveys found that the number of NICUs with written policies on premedication ranged from ‘few’ to 75% of units.[4, 5]

It is ideal when clinical pharmacists, neonatologists, and neonatal nurse practitioners work together in the design of premedication policies.[11] However, since nurses often administer medications and act as advocates for their vulnerable patient; nurses also can also lead the way in collaborative policy development based on empirical evidence. Written policies when available and followed have the potential to reduce medication errors and improve the quality of care within the NICU. Therefore, the purpose of this integrated review is to

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explore current research evidence on medication(s) utilized for nonemergent intubation in preterm and term neonates.

PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and the Cochrane database were searched to obtain English language publications from 1990 to November 2011. The year 1990 was chosen because this is when the health care literature began conducting clinical trials on patients receiving procedural sedation and analgesia.[2] The inclusion criteria were clinical studies using medication(s) prior to neonatal (≤ 28 days of life) intubation. Studies were excluded if the average age of the participants was greater than 28 days of life, did not include humans, medications were no longer available in the United States, single case reports of infants with abnormal facies or rare diseases, and trials that focused on anesthetic gases due to lack of feasibility in the NICU. Sixteen studies met the inclusion criteria and included 436 neonates. The findings were organized by the classification of the medications administered (vagolytic agents, analgesia, sedation, and neuromuscular blocking agents) with advantages and disadvantages explained and current AAP recommendations and rationale provided. See Table 1 for a summary of medications utilized for premedication in nonemergent intubation.

Summary of Evidence

Vagolytic Agents

Vagolytic agents help prevent reflex bradycardia during intubation due to an exaggerated vagal response and decrease oral and bronchial secretions.[12] Atropine and glycopyrrolate were the most commonly administered vagolytic agents. Eleven[6, 13–22] of the 16 studies utilized atropine as the vagolytic agent with only 1 study administering glycopyrrolate.[13] The samples included both preterm and term infants. However, no study compared a placebo group to a group who received a vagolytic agent and no study compared the vagolytic agents to each other.

Limited evidence is available on the advantages and disadvantages of atropine or glycopyrrolate. The AAP suggests that when choosing premedication, medications with rapid onset and a short duration of action are preferred. Thus, the AAP preferred vagolytic agent is atropine because of the rapid onset and shorter duration of action compared to glycopyrrolate.[10]

Analgesia

Analgesia reduces pain and discomfort during intubation.[12] Empirical evidence supports that neonates feel pain at 26–28 weeks gestation;[23, 24] thus neonates should receive nonpharmacological and/or pharmacological interventions when undergoing painful procedures including intubation. Remifentanil, fentanyl, and morphine were used as analgesics. Eleven[6, 13–15, 18, 21, 22, 25–28] of the 16 studies identified utilized an analgesic; however, only 2 studies[25, 26] were comparison studies with analgesic. The first study[25] compared placebo to morphine and found no differences between groups on physiologic variables (heart rate and blood pressure) and no differences between number of attempts for successful intubation. However, 94% of the entire sample experienced bradycardia during intubation. The second study[26] compared morphine + midazolam to remifentanil + midazolam and found that more preterm infants who received remifentanil + midazolam exhibited better conditions for intubation (e.g., vocal cord position and movement, movement of the limbs, coughing, and laryngoscopy[29]). Successful intubation in this study[26] may be related to remifentanil having a shorter onset time (almost immediate) than morphine with a relatively long onset of action (3–10 minutes).[10] It also was hypothesized that if enough time was not provided for the drug to take action before proceeding with

intubation, the effective use of morphine may not have been captured. No severe complications (e.g., chest wall rigidity, bradycardia, significant hypotension) were reported after infusion of medications: morphine + midazolam or remifentanil + midazolam.[26] In another study, Norman et al.[13] conducted a randomized controlled trial administering atropine + morphine to the control group and the treatment group received vagolytic agent + analgesic + sedation + paralytic, the investigators found that the control group had neurophysiologic depression for six hours post-intubation compared to the treatment group. Based on these findings, morphine appears to be safe, but may not be as effective for premedication prior to intubation when other analgesics are available.

The AAP recommendations state that fentanyl is the preferred analgesic with remifentanil and morphine (only if no other option is feasible) listed as acceptable medications. Remifentanil and fentanyl both have similar onset of action times with remifentanil having the shorter onset. Yet, fentanyl has more extensive use in neonates, infants, and children in other situations than remifentanil.[10] The broader use of fentanyl makes it the preferred medication according to the AAP. Since the AAP recommendations, three randomized controlled trials[13, 15, 28] that include remifentanil in the treatment groups have been published. However, none of the new trials directly compare remifentanil to fentanyl or morphine, but evidence from these studies does support that when remifentanil is administered in combination with other medications, no adverse effects are directly associated with remifentanil.

Sedation/Hypnotic

Sedatives and hypnotics can be amnestic or render a person unconscious depending on the dose and individual responses to the medication.[10] The most common sedation/hypnotic medications administered for nonemergent intubation were midazolam, propofol, and thiopental. Ten[13, 16–20, 26–28, 30] of the 16 studies included sedation in the clinical trials with 3 studies comparing the use of sedation with placebo[16, 30] or another sedation medication.[28]

In one study when midazolam was used for sedation in preterm infants (n=8), investigators found the midazolam group needed more cardiopulmonary resuscitation (n=3) compared to the control group (n=0).[16] In addition, midazolam contains the preservative benzyl alcohol.[31] Benzyl alcohol toxicity is a concern in preterm infants as it increases mortality and increases intraventricular hemorrhages.[32] Therefore, use of midazolam is not recommended in preterm infants.[10, 33]

Propofol is a hypnotic agent in which spontaneous respiration is maintained in most cases.[12] Maintaining spontaneous respiratory effort may be an advantage if the neonate is not successfully intubated because a secure airway is maintained. In two observational clinical studies[19, 20] on preterm infants that examined atropine + propofol, the success on first intubation attempt was 85%; however, the physiologic outcomes (e.g., blood pressure) varied substantially. In one study, Welzing et al.[19] stopped the clinical trial early due to severe arterial hypotension when the propofol was administered within 8 hours of birth; while, Nauta et al.[20] reported no differences in systolic blood pressure when compared before and after administration of propofol when administering propofol at approximately 2 days of life. The differences in reported blood pressures between the two clinical trials may be related to the age of the neonate when the propofol was administered; however, more evidence is needed to better understand this difference. A recent double-blinded randomized controlled trial compared midazolam + remifentanil to propofol + remifentanil.[28] The investigators found no difference between the groups on the conditions for intubation or the number of attempts to a successful intubation. Additionally, the groups were not different on the physiologic variables of heart rate, blood pressure, and oxygenation saturation before, during, or 60 minutes after intubation.[28]

Thiopental is another hypnotic agent.[10] Only two of the clinical trials[13, 30] that included preterm and term infants administered thiopental. When thiopental was compared to placebo, the thiopental group had a shorter duration of the intubation procedure. However, the thiopental group had increased heart rate and decreased blood pressure compared to the placebo group. No differences in oxygen saturation were noted between groups.[30]

The AAP does not list any of the sedative/hypnotic medications as preferred.[10] The side effect profile of midazolam regarding benzyl alcohol toxicity in preterm infants, the controversial hypotensive side effect of propofol, and the limited use of thiopental and propofol fail to make any of these medications optimal for neonates. The AAP considers propofol and thiopental as acceptable hypnotic agents for preterm and term infants; however, midazolam is only an acceptable sedative for term infants when combined with analgesia.[10]

Neuromuscular Blocking Agents

Neuromuscular blocking agents, also known as paralytics, block the transmission of neurotransmitters between neurons with resultant paralysis.[34] When paralytic agents are utilized, analgesics and/or sedatives must also be administered.[12] The paralytic agents administered in the reviewed clinical trials were succinylcholine and rocuronium. No other paralytic medications were identified in the last 21 years for premedication. Two other paralytics have been used in other circumstances (e.g., surgery): pancuronium and vecuronium.[10] Seven[6, 13, 15, 17, 18, 21, 22] of the 16 studies administered paralytic agent in combination with analgesia and/or sedation. The only study[22] that directly compared administration of a paralytic to no paralytic compared atropine + fentanyl to atropine + fentanyl + rocuronium. The investigators found that the group who received rocuronium experienced greater success on first intubation attempt compared to no rocuronium. No physiologic variables were reported. The side effects attributed to rocuronium were bronchospasm, tachycardia, and bradycardia.[22] The other six studies administered succinylcholine, but comparisons about the effectiveness of succinylcholine to other paralytics cannot be made because the other studies did not compare succinylcholine administration with equivalent control groups. Succinylcholine is contraindicated in patients with hyperkalemia and those with a family history of malignant hyperthermia.[10]

Currently, the AAP acknowledges that no ideal paralytic exists. Ideally, the paralytic agent would have rapid onset, short duration of action, and limited or no negative effect on heart rate and blood pressure.[10] The side effect profile and contraindications of succinylcholine led to the preferred paralytic agent being vecuronium and rocuronium because of their short duration of onset and relatively short duration of action. Both succinylcholine and pancuronium were suggested as acceptable paralytic agents.[10]

Effective Combinations

The final issue in premedication for intubation is which combination of medications is best. Four[13, 15, 18, 22] of the 16 studies compared different combinations of medications (e.g., analgesia compared to analgesia + sedation) to provide evidence about which combination is more effective with minimal side effects. The first two studies[15, 22] in preterm infants compared vagolytic agent + analgesia to vagolytic agent + analgesia + paralytic agent. One trial[22] found that analgesic + paralytic agent improved the success on first intubation attempt; however, the other trial[15] found no differences between the group who received analgesia + paralytic agent to analgesia alone. Only one of the two trials[15] reported physiologic variables and found no differences on changes in oxygen saturation, heart rate, and blood pressure. Whether vagolytic agent + analgesia or vagolytic agent + analgesia + paralytic agent is better cannot be determined from the available evidence. The third study[13]

compared the control group (vagolytic agent + analgesia) to the treatment group (vagolytic agent + analgesia + sedation + paralytic agent) in preterm infants. The treatment group had better intubation conditions and a shorter duration of intubation when compared to the control group. No differences in pain scores over the 6-hour post-intubation period were observed. The final study,[18] a randomized controlled trial, compared the control group (vagolytic agent + analgesia + paralytic agent) to the treatment group (hypnotic only) in preterm infants. Investigators found that the treatment group had a shorter time to intubation compared to the control group. No differences were observed in heart rate, mean arterial pressure, or adverse events. The control group had lower oxygen saturation during intubation compared to the treatment group.

Recommendations & Conclusions

Based on the available evidence, no specific combination of premedications appears to be superior to another due to limited data. The AAP recommends administering either an analgesic or hypnotic medication and that sedatives alone (e.g., benzodiazepines) should be avoided. Vagolytic agents and rapid onset paralytics should be considered, but paralytics should not be used alone.[10] Further evidence is needed to better understand which combination of premedications and which specific medications are ideal for intubating neonates.

The use of premedication for nonemergent intubation reduces pain and discomfort.[10] Empirical evidence suggests premedication can also improve the success rate of intubation,[21] decrease the duration of the intubation procedures,[13] and prevent some complications associated with intubation.[17] Nurses can advocate through unit level clinical practice councils and professional organizations to ensure written policies/procedures exist to prevent pain in neonates, ensure safe administration practices, and provide evidence-based care for intubation. Nurses can also facilitate the utilization of premedication for intubation by assisting in the development of written protocols/policies and providing education to health care providers about the advantages and disadvantages of the medications. Despite our current knowledge, additional research is needed to determine the best combination of premedications for intubation to eliminate pain and anxiety, limit physiologic changes that lead to instability of the neonate, and have few side effects.

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Table 1

Medications for Premedication for Nonemergent Intubation

Medication[a]	Dosage Range[b,c]	Onset of Action[a,c]	Duration of Action[a,c]	Common Adverse Effects[a]
Atropine*	10–20 mcg/kg	1–2 minutes	30–120 minutes	Tachycardia, dry hot skin
Glycopyrrolate	5 mcg/kg	1–10 minutes	360 minutes	Tachycardia, arrhythmias, bronchospasm
Fentanyl*	1.5–4 mcg/kg	Almost immediate	30–60 minutes	Apnea, hypotension, CNS depression, chest wall rigidity
Remifentanil	1–3 mcg/kg	Almost immediate	3–10 minutes	Apnea, hypotension, CNS depression, chest wall rigidity
Morphine	100–300 mcg/kg	5–15 minutes	180–300 minutes	Apnea, hypotension, CNS depression
Midazolam	200 mcg/kg	1–5 minutes	20–30 minutes	Apnea, hypotension, CNS depression
Thiopental	2–6 mg/kg	30–60 seconds	5–30 minutes	Histamine release, apnea, hypotension, bronchospasm
Propofol	1–2.5 mg/kg	< 30 seconds	3–10 minutes	Histamine release, apnea, hypotension, bronchospasm, bradycardia; pain at injection site
Vecuronium*	100 mg/kg[a]	2–3 minutes	30–40 minutes	Mild histamine release, hypertension/hypotension, tachycardia, arrhythmias, bronchospasm
Rocuronium*	500 mcg/kg	1–2 minutes	20–30 minutes	Mild histamine release, hypertension/hypotension, tachycardia, arrhythmias, bronchospasm
Pancuronium	50–100 mcg/kg[a]	1–3 minutes	40–60 minutes	Mild histamine release, hypertension, tachycardia, bronchospasm, excessive salivation
Succinylcholine	1–2 mg/kg	30–60 seconds	4–6 minutes	Hypertension/hypotension, tachycardia, arrhythmias, bronchospasm, hyperkalemia, myoglobinemia, malignant hypertension

[a] Based on information provided by AAP recommendations for premedication for nonemergent intubation[10]

[b] Range of doses utilized in the clinical trials reviewed

[c] All dosages and pharmacokinetics based on intravenous (IV) administration

* Preferred medication by the AAP[10]