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Premedication for Nonemergent Neonatal Intubation

A Systematic Review

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ABSTRACT

This systematic review evaluates research regarding the use of premedication for nonemergent neonatal intubation. Unmedicated intubation is associated with adverse outcomes such as physiologic instability and decompensation, repeat and prolonged intubation attempts, and trauma. Included studies compared medicated intervention groups against an unmedicated control. Medications vary greatly across studies and include anesthetics, opioids, benzodiazepines, barbiturates, vagolytics, and neuromuscular blockades (muscle relaxants). A comprehensive search of randomized control trials, retrospective cohort studies, and prospective observational studies was completed from the electronic databases of CINAHL EBSCOhost, Ovid MEDLINE, PubMed, EMBASE, Google Scholar, Cochrane Collaboration, and ClinicalTrials.gov and footnotes were used to complete the search. Twelve studies are included in this review dating back to 1984 and are from 5 countries. Outcome measures include changes in heart rate, oxygen saturation, and blood pressure; number and duration of attempts to intubate; and trauma to the oral cavity and upper airway. Twelve studies are included in this review and include 5410 patients. No studies were excluded based on level of evidence or quality appraisal. Findings in this review support the recommendation that opioids and vagolytic agents should be used for premedication for nonemergent neonatal intubation and adjuvant sedation and muscle relaxants should be considered.

Key Words: infant, intubation, neonatal, neonate, NICU, premedication, sedation, systematic review

Intubation is a common procedure in the neonatal intensive care unit (NICU). It is performed for many reasons including resuscitation, apnea, surgery, and mechanical ventilation. Unmedicated neonatal intubation is often poorly tolerated and leads to physiologic instability and vital sign changes including bradycardia, oxygen desaturation, hypertension in any system, and hypotension.[1–3] This physiologic instability increases the number and duration of attempts to intubate and the risk for trauma to the mouth and upper airway during intubation.[3] These adverse outcomes increase the need for resuscitation, and severe physiologic decompensation such as cardiac arrest or increased intracranial pressure can cause intraventricular hemorrhage (IVH) and increases the risk for long-term neurodevelopmental sequelae.[3,4]

Historically, it was believed infants could not feel or localize pain like adults.[5] Since the early 1980s evidence has proven infants do feel pain and many providers now agree.[5] However, there is still great variability in the practice of providing premedication.[6,7] Common reasons for not providing premedication include medication safety and side effects such as

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prolonged respiratory depression during surfactant administration[8]; the ability to intubate without premedication despite adverse effects for the baby[9]; and a reluctance to change practice despite the 2010 American Academy of Pediatrics (AAP) recommendations for premedication, which included specific medications and doses.[9,10]

Currently, 4 categories of drugs are commonly used for premedication in the NICU. Opioids are prescribed for analgesia for pain. Benzodiazepines are commonly prescribed for adjuvant sedation and anxiolysis. Vagolytics are prescribed to decrease vagal-induced bradycardia during the procedure. Neuromuscular blockades, or muscle relaxants, are sometimes prescribed for paralysis. One of the most common indications for neonatal intubation is surfactant administration. For many neonates receiving surfactant, the preferred method is InSurE (Intubate, give Surfactant directly into the lungs through the endotracheal tube, and immediately Extubate back to noninvasive ventilation); therefore, paralysis is not indicated. For the majority of neonates undergoing mechanical ventilation, the goal is to support their spontaneous respiratory effort, thus paralysis would not be desired.[11] Fentanyl and midazolam are the 2 medications most likely to be prescribed, oftentimes as monotherapy, but it is important to note that midazolam does not provide analgesia.[2] Additionally, there are concerns regarding the use of midazolam in preterm infants less than 34 weeks' postmenstrual age about potential adverse neurodevelopmental outcomes and worsening hypotension, if present.[2,10]

Adverse events and outcomes are common during neonatal intubation. Foglia and colleagues found that severe desaturation—greater than 20% from baseline—occurred in 51% of intubations.[12] Hatch and colleagues found 40% of intubations had at least 1 adverse outcome and emergent intubations had a fourfold increase in the occurrence of adverse events.[13] Neonatal intubation has a low first-attempt success rate at less than 50% making multiple attempts common,[14] and each successive attempt increases the odds of adverse outcomes.[14,15]

PURPOSE

The aim of this systematic review is to evaluate the effects of providing premedication compared with no medication during nonemergent neonatal intubation. One previous systematic review exists on the topic of premedication for neonatal intubation and was written by Shah and Ohlsson.[16] The decision to proceed with a new systematic review compared with an update was based on 2 factors. First, Shah and Ohlsson[16] evaluated premedication for intubation specific to mechanical ventilation, and in the 18 years since their publication there has been a change in practice focusing on noninvasive ventilation and supporting the spontaneous respiratory effort of babies. Additionally, since fewer babies are mechanically ventilated, many intubations are to administer surfactant via InSurE. Second, Shah and Ohlsson[16] focused on studies testing any premedication regimen, including various premedication regimens against one another, rather than against an unmedicated control. This review specifically looked at the effects of premedication intervention groups compared with an unmedicated control group.

Definitions

For this article, premedication is defined as the use of any analgesic, sedative, anesthetic, vagolytic, or muscle relaxant alone or in combination. Neonate is used broadly in this article to include both neonates from the birth through 28 days of life and older infants who have remained in the NICU since birth and are 28 days to 1 year of age. Intubation is defined as oral or nasal intubation of the trachea. Adverse outcomes are defined as bradycardia, oxygen desaturation, hypotension or hypertension in any system, repeat intubation attempts, prolonged intubation attempts, or trauma of the mouth and/or airway. Bradycardia is defined as a heart rate less than 100 beats per minute.

METHODS

Research question

The research question for this systematic review is: Does the use of premedication decrease adverse outcomes when compared with no medication in infants undergoing nonemergent intubation in the NICU?

Search strategy

The university library was used for an exhaustive search on the topic and used the key words *neonate*, *neonatal, NICU, infant*, *premedication*, *sedation*, and *intubation*. Search words were combined with Boolean phrases as indicated to narrow the focus. CINAHL EBSCOhost, Ovid MEDLINE, PubMed, EMBASE, Google Scholar, Web of Science, grey literature (ClinicalTrials.gov), and Cochrane Collaboration were searched. Additionally, footnotes were searched, and 1 author was contacted. Johanna Briggs Institutes, ERIC, and Dissertations.com were also searched for systematic reviews and dissertations and theses but yielded no new results. The year 1980 to September 2020 was used to refine results, as prior to 1980 it was commonly believed babies did not feel pain.[5] Focus was given to articles in peer-reviewed

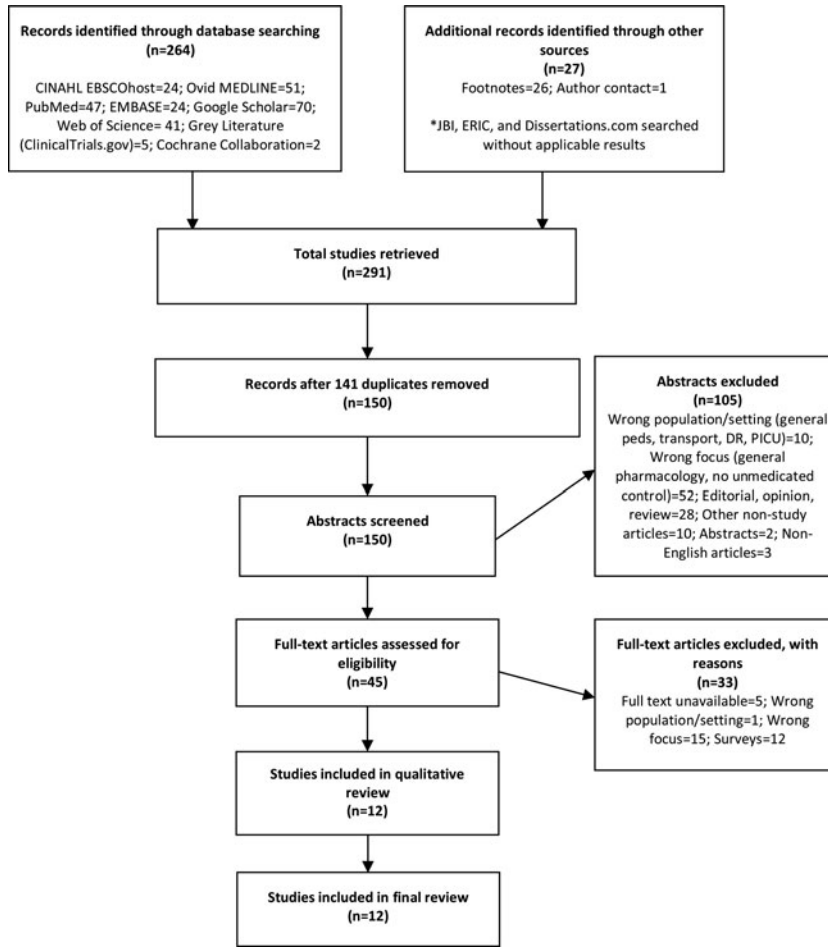

Figure 1. PRISMA flow diagram of literature search for articles included.

journals. The PRISMA flow diagram for the literature search can be seen in Figure 1.

Study selection

Included studies tested one or more medication study group(s) against an unmedicated control group of neonates in the NICU who were undergoing nonemergent intubation. Excluded studies include those whose full text was unavailable and those focusing on general pediatrics, transport, or the delivery room; general pharmacology; comparison of premedication groups without an unmedicated control; editorial, opinion, or review articles; conference abstracts; non-English articles; and surveys regarding general premedication practices.

Data extraction

Data extracted from the included studies can be seen in Table 1. Variables extracted include (1) author(s) and date of publication, (2) study type, (3) country of study and study time frame, (4) purpose of the article, (5) included and excluded subjects, (6) any randomization and blinding, and (7) intervention(s) and control.

Risk of bias assessment

The John Hopkins Evidence Level and Quality Guide[17] tool was used to evaluate level of evidence for each study and can be seen in Table 1. The Critical Appraisal Skills Programme (CASP)[18] tool was used to assess study quality. Four of the older studies appraised lower on the CASP tool, which was deemed to be due to the age of the articles.[19–22] Therefore, no studies were excluded based on level of evidence or quality appraisal.

RESULTS

A summary of results of the included studies can be seen in Table 2. This table includes subgroup sample sizes and types of premedication given and outcome measures. The outcome measures include (1)

Table 1. Literature review summary on premedication for nonemergent intubation in neonates

Author	Study type Study location Time frame	John Hopkins level of evidence	Purpose/aim	Subjects	Exclusion	Randomization? Blinding?	Intervention (I) and control (C)	Outcome variables	Comments
Bhutada et al[27]	RCT New York January 1997 to September 1997	IB	Determine effects of an anesthetic on VS during nonemergent neonatal intubation	$n = 27$ BW >2 kg	Birth weight <2 kg and emergent intubations	Yes No	I: thiopental C: same volume of normal saline	HR changes BP changes Oxygen saturation changes	Inhaled anesthetics in the NICU are uncommon in current practice but may still be used for surgery
Caldwell and Watterberg[28]	Prospective observational study New Mexico January 2012 to July 2013	IIIA	Evaluate the effect of various medications (and combinations) for nonemergent neonatal intubation	$n = 166$	DR intubations, emergent intubations, concurrent analgesia or sedative, airway and other major congenital anomalies, and neuromuscular disorders	No No	I: 5 groups: 1. morphine 2. fentanyl, 3. midazolam, 4. morphine and midazolam, 5. fentanyl and midazolam C: unmedicated	HR changes Oxygen saturation changes # of attempts Bleeding	This study evaluates the 2 most common opioids alone and in combination with midazolam against an unmedicated control
Charlton and Greenhough[19]	RCT Manchester, England 1980s (dates not specified)	IB	Evaluate occurrence of hypertension in medicated vs unmedicated neonatal intubation by comparing pre- and postprocedure VS	$n = 45$ Surgical patients	CHD and CDH	Yes No	I:2 groups: halothane and thiopentone (inhaled anesthetics) C: unmedicated	HR changes BP changes	Study included 3 groups of neonates (<28 d of age) who were born 36 wk and older A fourth group included infants >4 wk, but this group was not included in this analysis
Cook-Sather et al[29]	Prospective observational study Pennsylvania 1990s (dates not specified)	IIIB	Evaluate effect of a muscle relaxant on neonatal intubation	$n = 76$ Pyloric stenosis patients undergoing surgical repair	Known airway or cardiorespiratory problems	No No	I:2 groups: RSI (thiopental and succinylcholine for paralysis) and modified RSI (thiopental and 1 of 4 muscle relaxants) C: "awake" group	HR changes Oxygen saturation changes # of attempts Duration of attempts	The "awake" control still received atropine if indicated

(*continues*)

Table 1. **Literature review summary on premedication for nonemergent intubation in neonates (*Continued*)**

Author	Study type Study location Time frame	John Hopkins level of evidence	Purpose/aim	Subjects	Exclusion	Randomization? Blinding?	Intervention (I) and control (C)	Outcome variables	Comments
Friesen et al[20]	RCT Colorado 1980s (dates not specified)	IIIB	Evaluate anterior fontanelle pressure changes during nonemergent neonatal intubation	$n = 12$ Surgical patients <37 wk <2500 g	None noted	Yes No	I: pancuronium for paralysis and either fentanyl, ketamine, or an anesthetic C: "awake" group	BP changes Duration of attempts	All patients received atropine, including the "awake" control group
Hassid et al[30]	RCT France September 2004 to July 2005	IB	Determine the effect of an anesthetic during nonemergent neonatal intubation	$n = 33$	No parental consent, >1 mo of age, emergent intubation	Yes No	I: servoflurane (inhaled anesthetic) C: unmedicated	HR changes Oxygen saturation changes BP changes # of attempts	Inhaled anesthetics are uncommon inside the NICU
Kelly and Finer[21]	RCT Canada July 1982 to March 1983	IB	Determine effect of a vagolytic with and without paralysis during neonatal intubation	$n = 30$	Emergent intubations	Yes No	I: 2 groups: atropine and atropine with pancuronium C: unmedicated	HR changes Oxygen saturation changes	
Le et al[24]	Retrospective cohort study California July 2003 to June 2010	IIIA	Determine whether premedication affects success rate for nonemergent neonatal intubation	$n = 2694$	Emergent intubations	No No	I: opioid, atropine, and optional muscle relaxant C: unmedicated	Success rate per provider	This study focused on inexperienced intubating providers Atropine alone was classified as unmedicated
Lemyre et al[25]	RCT Canada December 1999 to September 2000	IB	Determine whether morphine improves VS stability and number and duration of attempts for neonatal intubation	$n = 34$	No IV access, upper airway anomaly, cyanotic CHD, upper GI obstruction, concurrent opioid use	Yes Yes	I: morphine C: placebo saline	HR changes Oxygen saturation changes BP changes # of attempts Duration of attempts	This is the only blinded RCT in this analysis These findings do not support the use of premedication as hypothesized

(*continues*)

Table 1. **Literature review summary on premedication for nonemergent intubation in neonates (*Continued*)**

Author	Study type Study location Time frame	John Hopkins level of evidence	Purpose/aim	Subjects	Exclusion	Randomization? Blinding?	Intervention (I) and control (C)	Outcome variables	Comments
Millar and Bissonnette[22]	RCT Canada 1980s to 1990s (dates not specified)	IB	Determine the effect of premedication on anterior fontanelle pressure during nonemergent intubation	$n = 13$ Surgical patients	Known intracranial, cardiovascular, or laryngeal pathologies	Yes No	I: thiopentone and succinylcholine C: "awake"	HR changes BP changes Cerebral blood flow velocity	All patients, including the "awake" group, received atropine
Oei et al[26]	RCT Australia July 1999 to October 1999	IB	Determine whether premedication reduces the number of attempts and duration of attempts during nonemergent intubation for inexperienced providers	$n = 20$	Outborn infants who were intubated upon arrival	Yes No	I: morphine, atropine, and suxamethonium (muscle relaxant) C: unmedicated	HR changes Oxygen saturation changes # of attempts Duration of attempts Trauma	One infant had cyanotic CHD and her oxygen saturation was excluded from analysis Noted trauma was bleeding in the nose without structural trauma
Ozawa et al[23]	Retrospective cohort study United States October 2014 to June 2017	IIIA	Determine whether premedication improves VS and procedure outcomes	$n = 2260$	Repeat intubation encounters (not repeat attempts), DR intubations, and tube changes	No No	I: 2 groups: premedication with and without a muscle relaxant C: unmedicated	HR changes Oxygen saturation changes # of attempts	National Emergency Airway Registry for Neonates (NEAR4NEOS) study Large study

Abbreviations: BP, blood pressure; BW, birth weight; CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; DR, delivery room; HR, heart rate; IV, intravenous; GI, gastrointestinal; NICU, neonatal intensive care unit; RCT, randomized control trial; RSI, rapid sequence intubation; VS, vital signs.

Table 2. **Outcome results of the literature review on premedication for nonemergent intubation in neonates**

Reference and study design	Sample(s)	Premedication(s) used	Heart rate changes	Oxygen saturation changes	Blood pressure changes	Number of attempts	Duration of attempts	Trauma
Bhutada et al[27]	$n_S = 14$ $n_C = 13$	Thiopental (inhaled barbiturate anesthetic)	During intubation: • Decrease in HR ($P = .03$) • Change in HR variability ($P = .01$)	No significant changes between the groups	Significant increase in mean BP noted during intubation ($P = .002$)		Time to intubate was longer in the control group ($P = .04$)	
Caldwell and Watterberg[28]	$n_{S1} = 31$ $n_{S2} = 23$ $n_{S3} = 17$ $n_{S4} = 19$ $n_{S5} = 32$ $n_C = 44$	1. Morphine (opioid) 2. Fentanyl (opioid) 3. Midazolam (benzodiazepine) 4. Morphine and midazolam 5. Fentanyl and midazolam	Fentanyl with midazolam had the most (10%) bradycardia (HR <100) The control group was in the middle of the set with 8% having bradycardia Fentanyl with midazolam had the highest rate (57%) of no complications	Morphine with midazolam (35%) and midazolam (34%) experienced the most desaturation <80% The control group was average		The control group had the highest number of total attempts with 122/521 (23%), with the intervention groups ranging 12% for morphine and midazolam to 21% for morphine only		The most instances (7) and highest percent (6) occurred in the control group
Charlton and Greenhough[19]	$n_{S1} = 15$ $n_{S2} = 15$ $n_C = 15$	1. Halothane 2. Thiopentone (inhaled anesthetics)	Pulse rose with intubation in all 3 groups but did not quite reach significance (NS) in the awake group ($P = .06$)		The halothane group experienced a significant rise in SBP of 10.0 points ($P = .007$) and DBP of 6.2 points ($P = .017$).			
Cook-Sather et al[29]	$n_{S1} = 28$ $n_{S2} = 26$ $n_C = 22$	1. RSI (thiopental and succinylcholine for paralysis) 2. Modified RSI (thiopental and 1 of 4 muscle relaxants)	All groups experienced bradycardia, but differences were NS	All 3 groups experienced a similar and significant ($P < .001$) decrease in saturations, with no intergroup differences		First attempt success was more likely in the study groups ($P = .028$)	Time to intubate in the control group was twice that of the study groups ($P = .004$)	

(*continues*)

Table 2. **Outcome results of the literature review on premedication for nonemergent intubation in neonates (*Continued*)**

Reference and study design	Sample(s)	Premedication(s) used	Heart rate changes	Oxygen saturation changes	Blood pressure changes	Number of attempts	Duration of attempts	Trauma
Friesen et al[20]	$n_S = 6$ $n_C = 6$	Pancuronium (muscle relaxant) and fentanyl, ketamine, or an anesthetic			AFP increased significantly in the awake group ($P <$ .05) and the increase was up to 197% SBP increased significantly ($P <$ .05) in the awake group and by an average of 20%		Similar in both groups	
Hassid et al[30]	$n_S = 19$ $n_C = 14$	Servoflurane (inhaled anesthetic)	More bradycardia ($P = .01$) and the minimum HR was significantly lower in the control group ($P = .03$) Duration of bradycardia was NS but trended toward improved stability with medication	Desaturation was more common in the control group but NS	Hypotension occurred in 37.5% of both groups HTN was double in the control ($P = .04$) with a maximal mean BP higher in the control ($P = .02$)	Intubation attempts NS		
Kelly and Finer[21]	$n_{S1} = 10$ $n_{S2} = 10$ $n_C = 10$	1. Atropine (vagolytic) 2. Atropine with pancuronium (muscle relaxant)	Infants receiving atropine in either study group showed a small but significant increase in HR ($P = .05$) compared with the control group No infant receiving atropine experienced HR <80, but 3/10 in the control group did ($P = .035$)	All 3 groups experienced similar and significant desaturations ($P = .02$)	All groups experienced an increase in BP, but it was NS			
Le et al[24]	$n_S = 1558$ $n_C = 1136$	Opioid, atropine, and optional muscle relaxant				Overall success rate was 36% and increased with training (25% for pediatric interns and 50% for third-year fellows)		

(*continues*)

Table 2. **Outcome results of the literature review on premedication for nonemergent intubation in neonates (*Continued*)**

Reference and study design	Sample(s)	Premedication(s) used	Heart rate changes	Oxygen saturation changes	Blood pressure changes	Number of attempts	Duration of attempts	Trauma
Lemyre et al[25]	$n_S = 17$ $n_C = 17$	Morphine	Less bradycardia in the control group but NS	Duration of hypoxemia was longer in the study group ($P = .04$)	Increased in both groups, control greater than study but NS	NS	The control group had shorter procedure average but NS	
Millar and Bissonnette[22]	$n_S = 6$ $n_C = 7$	Thiopentone and succinylcholine	Decrease in HR was more significant in the control group ($P = .05$)	No decreases in either group	Both groups had significant increases in BP ($P = .05$) Rise in AFP was 254% in the control group compared with 44% in the study group			
Oei et al[26]	$n_S = 10$ $n_C = 10$	Morphine, atropine, and suxamethonium (muscle relaxant)	Lowest mean HR was lower in the control group ($P = .04$)	Differences were NS		More than twice the number of attempts was needed in the control group ($P = .035$)	Time to intubate was shorter in the study group ($P = .016$)	5 infants had trauma in the control group and only 1 in the study group (NS)
Ozawa et al[23]	$n_{S1} = 394$ $n_{S2} = 1058$ $n_C = 808$	1. Premedication 2. Premedication with a muscle relaxant		The premedication group had the highest occurrence ($P < .001$) of desaturation The premedication with a muscle relaxant group and control groups was similar		Control group required more attempts compared with the premedication with a muscle relaxant group ($P < .001$)		

Abbreviations: AFP, anterior fontanelle pressure; C, control group; DBP, diastolic blood pressure; HR, heart rate; N/A, outcome not measured in the study; NS, no (statistical significance); RSI, rapid sequence intubation; S, study group; SBP, systolic blood pressure.

changes in heart rate (bradycardia, lowest heart rate), (2) changes in oxygen saturation (desaturation), (3) changes in blood pressure (hypertension or hypotension), (4) number of attempts to intubate, (5) duration of intubation attempts, and (6) trauma during intubation.

Description of studies

The initial electronic search yielded 264 articles and footnotes and author contact added 27 sources for a total of 291. One hundred and forty-one duplicates were removed, and the remaining 150 articles were assessed by abstract or full text for inclusion. After inclusion and exclusion criteria were applied, 12 articles met the aim of this review and were evaluated for level of evidence and critiqued for study quality.[19–30] Studies are from 5 countries, including 1 in the UK, 1 in France, 1 in Australia, 3 in Canada, and 6 in the United States, with 5 being local studies and 1 being national in scope. Seven studies were completed in the last 20 years and the oldest study was published in 1984.[21,23–28,30] This information is summarized in Table 2.

Sample characteristics

A total of 5410 infants were included in the 12 studies. Settings included both academic and nonacademic NICUs of various levels from 5 countries. All studies excluded emergent intubations except for one.[23] Ozawa and colleagues[23] included unplanned extubation with reintubation, which is often emergent; however, they excluded delivery room intubations, which are almost always emergent for resuscitation. Sample sizes varied from 12[20] to 2694,[24] with gestational ages, when specified, ranging 24 to 44 weeks and birth weights ranging 580 g[21] to approximately 4000 g. Most studies reported the mean with standard deviation as the metric for gestational age and weight, whereas 3 studies used median gestational age and weight.[23,25,26] Three of the studies used gestational age and birth weight as their metric,[21,25,27] whereas 6 of the studies used postmenstrual age and current weight at time of the intubation.[19,20,22,23,28,29] Two studies reported both birth and current metrics.[26,30] The last study reported a median; however, they evaluated intubation success rate as their variable rather than a demographic metric.[24]

Intervention and control characteristics

All studies included at least 1 medication as the intervention for the study group(s) and an unmedicated control group. Five of the studies included multiple study groups as opposed to a single study group.[19,21,23,28,29] Medication interventions included anesthetics (thiopental, halothane, sevoflurane, and ketamine),[19,21,22,27,29,30] opioid analgesics (fentanyl or morphine),[20,23–26,28] the benzodiazepine midazolam for adjuvant sedation,[23,28] the vagolytic atropine,[20–22,24,26,29] and various muscle relaxants (succinylcholine, vecuronium, rocuronium, atracurium, pancuronium, mivacurium, cisatracurium, or suxamethonium) for paralysis.[19,20,22,24,26,29] Seven studies used a combination of medications.[20–24,26,28,29]

Outcome measures

Six outcomes were identified in the 12 articles included in this review. They include heart rate changes during intubation, oxygen saturation changes during intubation, blood pressure changes during intubation, number of attempts to intubate, duration of attempts to intubate, and trauma during intubation.

Heart rate changes during intubation

Nine studies evaluated the change in heart rate during intubation. The most common heart rate change during intubation was bradycardia due to a vagal response of passing the laryngoscope blade and endotracheal tube into the throat.[2,21] Bradycardia was significantly worse in the control group in 3 studies.[22,27,30] Cook-Sather and colleagues[29] found bradycardia in all 3 groups, but the difference between groups was not significant. Kelly and Finer[21] found that no infant who received atropine experienced a heart rate less than 80 beats per minutes, whereas 3/10 infants in the control group did, which was significant. Lemyre and colleagues[25] actually found less bradycardia in the control group, although the difference was not significant. Caldwell and Waterberg[28] found the highest incidence of bradycardia (10%) in one of the study groups (those who received both fentanyl and midazolam) and that the incidence of bradycardia in the control group to be 8%, which was in the middle of the range for all groups.

The lowest heart rate was significantly lower in the control group in 2 studies.[26,30] Hassid et al[30] evaluated the duration of bradycardia, and while it did not reach the level of significance, it trended toward improved heart rate stability in the premedication group. Kelly and Finer[21] found a small, but significant heart rate increase in both study groups compared with the control group due to the use of atropine.

Oxygen saturation changes during intubation

Nine studies evaluated the change in oxygen saturation during intubation. Desaturation was common in both study and control groups. Desaturation was found to be significantly more likely in the control group in 2 studies and more likely, but not significant in 3 more studies.[19,21,26,27,30] One study found no desaturation in either the study or control group.[22]

Two studies found more desaturation in the study groups.[23,28] In the first study the highest occurrence of desaturation was in the premedication without a muscle relaxant study group and was very significant ($P < .001$) and the premedication with a muscle relaxant study group and control groups was similar.[23] In the second study, 35% of the morphine and midazolam group and 34% of the midazolam group experienced desaturation, whereas the control group experienced less and was average across the 6 groups.[28]

Blood pressure changes during intubation

Seven studies evaluated the change in blood pressure during intubation. Blood pressure changes are important, especially in the more preterm infants, as changes in cerebral blood flow and intracranial blood pressure have been known to cause IVH.

Hypertension was noted in both the study and control groups in 4 studies, but the intergroup differences were significant in only 2 of the studies.[20,22] Friesen and colleagues[20] found an average increase of 20% in blood pressure in their control group. Hypertension was found to be significant in the control group in 2 studies.[27,30] In the Charlton and Greenhough[19] study, the halothane experimental group found significant changes in both systolic blood pressure ($P = .007$) and diastolic blood pressure ($P = .017$). Hassid and colleagues[30] found hypertension occurred more than double in the control group ($P = .04$), and the maximal increase in mean arterial blood pressure was also significantly higher in the control group ($P = .02$).

Two studies evaluated anterior fontanelle pressure changes as a gauge of cerebral blood flow.[20,22] Friesen et al[20] found a significant increase in the control group with the increase up to 197%, and Millar and Bissonnette[22] found the increase to be 254% in the control group compared with 44% in the study group.

Hypotension is also problematic, as it too changes cerebral blood flow, which can increase the risk of IVH. One study found hypotension in both groups, but the difference was not significant as the incidence was identical (37.5%) in the study and control groups.[30]

Number of attempts to intubate

Seven studies evaluated the number of attempts to intubate. Repeat attempts are more likely to cause distress and physiologic decompensation as well as trauma. Two studies found the differences were not significant.[25,30] Two other studies found the number of attempts to intubate to be significantly more for the control group, including more than double that of the study group in one of the studies.[24,30]

Since first-pass success is obviously the goal with intubation, Le and colleagues[24] evaluated first-pass success rate. Results showed the overall success rate was only 36% but tended to increase with experience (25% success for pediatric interns compared with 50% for third-year neonatal fellows).[24] Cook-Sather and colleagues[29] also found first-attempt success to be significantly more likely in the study group ($P = .028$).

Duration of attempts to intubate

Five studies evaluated the duration of attempts to intubate. Friesen et al[20] found a similar duration between groups. Three studies found that the control groups took longer to intubate with significant differences.[26,27,29] The last study showed a longer duration for the study group although the difference was not significant.[25]

Trauma during intubation

Two studies noted trauma during intubation. The first study found the most instances and the highest percentage of trauma in the control group.[28] The second study found 5 instances of trauma during intubation in the control group compared with 1 instance in the study group; however, this difference was not significant and the trauma was bleeding without structural damage.[26]

DISCUSSION

Premedication for neonatal intubation started in the 1980s and has become increasingly common.[5] However, there is still great variability in the use of premedication even when it is given despite the 2010 AAP recommendations.[10] Several medications have been used for premedication, including anesthetics, opioids, sedatives, vagolytics, and muscle relaxants. Each medication in the included studies has shown benefit during neonatal intubation; however, not all of these medications are best given what we now know about neonatal pain control and brain development. Nine studies demonstrated beneficial effects of the use of premedication for at least 1 outcome variable.[20,22,23,25–30]

The use of anesthetics has become an uncommon practice inside the NICU. These medications do improve intubating conditions but are generally only used as an induction agent for surgery.[27,30] The use of opioids provides analgesia during intubation and should be given for pain control.[2,10] Opioids with a quicker onset of action and shorter half-life such as fentanyl instead of morphine are preferable, especially for InSurE.[2,10] The use of benzodiazepines provides adjuvant sedation and decreases distress during intubation.[2,10] There are concerns about the safety of midazolam in preterm infants and those with hypotension, so caution should

be used.[2,10] The use of vagolytics is generally well-tolerated and buffers vagal-related bradycardia during intubation[2]; therefore, should be given. There are some concerns that vagolytic agents mask hypoxia-induced bradycardia, but this is less likely than vagal-induced bradycardia during intubation and transient.[10]

The use of combination therapy has become increasingly common. At a minimum an opioid and vagolytic improve physiologic stability and should be given. The use of muscle relaxants without the concurrent use of sedation and/or analgesia was common in the older studies from the 1980s[20,21,29]; however, due to the understanding that babies indeed feel pain, this would now be considered inhumane.[5] Paralysis does improve intubating conditions and should be considered in certain cases where the patient will remain mechanically ventilated, but sedation and analgesia *must* be coadministered.[31] It is important to analyze the situation and need for possible paralysis. Reversal agents should be readily available for opioids and muscle relaxants. Naloxone and muscle relaxants can be used to reverse chest wall rigidity with opioids and naloxone also reverses prolonged, unintended respiratory depression.[2,10,31] Atropine can be used to reverse paralysis with some muscle relaxants (pancuronium, vecuronium, and rocuronium).[10]

Findings across the studies show that, in general, heart rate was more stable when any premedication was given. Findings across studies were mixed regarding oxygen saturation, as desaturation was still prevalent despite premedication and findings were inconclusive regarding whether study or control groups were more likely to experience desaturation. Findings across studies show that premedication stabilizes blood pressure and decreases the risk of IVH development.

Limitations

There are a few limitations of this review to acknowledge. The first limitation of this review is that there is variability across studies in the types of medications and dosages that were used as well as the outcome metrics. Variability of medications and dosages and outcome measures make it difficult to aggregate and statistically analyze data for effect. The second limitation of this review is the variability in the age of the studies. The broad age of articles acknowledges the change in opinions and practices over time. The third limitation of this review is that some studies had small sample sizes. Small sample size *potentially* results in underpowered studies and may lead to weak or incorrect conclusions. Two studies specifically addressed their sample size as being small in their study limitations,[25,26] and Lemyre and colleagues[25] note this small sample size precluded their ability to eliminate type 2 error. The fourth limitation of this review is that atropine was given to the control group as well as the study groups in 4 studies.[20,22,24,29] This practice may have skewed the results since atropine mitigates the effect of procedure-related bradycardia although the off-label use may have controlled for this bias.

No language bias was noted as all studies, including non-American, were published in English language and peer-reviewed journals.

CONCLUSION

The aim of this review was to evaluate whether premedication for nonemergent intubation improves outcomes compared with unmedicated intubation. The findings of the articles included in this review add to the evidence supporting the use of premedication for nonemergent intubation in neonates. In general, premedication of any type tends to improve the patient's physiologic stability resulting in less fluctuation in heart rate, oxygen saturation, and blood pressure. Increased physiologic stability provides for better intubating conditions and decreases the number and duration of attempts to intubate and decreases the occurrence of trauma during intubation; therefore, improving patient outcomes.

It is imperative that neonatal units and providers adopt a culture of providing premedication. Since the AAP recommendations are now a decade old, further evidence is needed. Recommendations for future study include evaluating newer sedatives such as dexmedetomidine to see whether there are safer options for preterm and hypotensive infants when midazolam is cautioned.

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