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ARTICLE

Premedication for Nonemergent Neonatal Intubations: A Randomized, Controlled Trial Comparing Atropine and Fentanyl to Atropine, Fentanyl, and Mivacurium

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ABSTRACT

OBJECTIVE. The purpose of this work was to investigate whether using a muscle relaxant would improve intubation conditions in infants, thereby decreasing the incidence and duration of hypoxia and time and number of attempts needed to successfully complete the intubation procedure.

PATIENTS/METHODS. This was a prospective, randomized, controlled, 2-center trial. Infants requiring nonemergent intubation were randomly assigned to receive atropine and fentanyl or atropine, fentanyl, and mivacurium before intubation. Incidence and duration of hypoxia were determined at oxygen saturation thresholds of ≤85%, ≤75%, ≤60%, and ≤40%. Videotape was reviewed to determine the time and number of intubation attempts and duration of action of mivacurium.

RESULTS. Analysis of 41 infants showed that incidence of oxygen saturation ≤60% of any duration was significantly less in the mivacurium group (55% vs 24%). The incidence of saturation level of any duration ≤85%, 75%, and 40%; cumulative time ≥30 seconds; and time below the thresholds were not significantly different. Total procedure time (472 vs 144 seconds) and total laryngoscope time (148 vs 61 seconds) were shorter in the mivacurium group. Successful intubation was achieved in ≤2 attempts significantly more often in the mivacurium group (35% vs 71%).

CONCLUSIONS. Premedication with atropine, fentanyl, and mivacurium compared with atropine and fentanyl without a muscle relaxant decreases the time and number of attempts needed to successfully intubate while significantly reducing the incidence of severe desaturation. Premedication including a short-acting muscle relaxant should be considered for all nonemergent intubations in the NICU.

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Key Words
intubation, premedication, atropine, fentanyl, mivacurium, muscle relaxant, hypoxia, infant, neonate

Abbreviations
ETT—endotracheal tube
BP—blood pressure
ICP—intracranial pressure
HR—heart rate
Sa_{O_2}—arterial oxygen saturation
NNP—neonatal nurse practitioner
F_{IO_2}—fraction of inspired oxygen
SBP—systolic blood pressure

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RECOGNITION AND MANAGEMENT of pain are important aspects of neonatal intensive care. In 2000, the American Academy of Pediatrics and the Canadian Paediatric Society published a consensus statement on the prevention and management of pain and stress in the neonate. The statement recommends that "health care professionals . . . use appropriate environmental, nonpharmacologic (behavioral), and pharmacologic interventions to prevent, reduce, or eliminate the stress and pain of neonates".[1]

Endotracheal intubation is a procedure frequently performed in NICUs. In addition to causing discomfort, placing an endotracheal tube (ETT) without premedication is associated with adverse physiologic effects. These effects include bradycardia,[2,3] fluctuations in blood pressure (BP),[2–8] hypoxia,[2,3,7,9–11] and increases in intracranial pressure (ICP).[3,4,6,8,12,13] Previous studies have shown that these potentially adverse effects can be attenuated by using pharmacologic agents. Anticholinergic medication can attenuate the decrease in heart rate (HR),[3,6–8,14] potent analgesics or anesthetic agents can attenuate the hypertensive response,[11] and muscle relaxants have been shown to attenuate the increase in ICP.[3,4,6,8,12] Studies have also shown that using premedication may decrease the time and number of attempts needed to successfully intubate.[5,7,8,11,15–17]

Despite the potential advantages, premedication for nonemergent intubations is not routinely used in most NICUs.[18–22] Reasons why this practice has not been widely adopted may include lack of familiarity with the medications, fear of adverse effects, insufficient evidence for efficacy and safety, or lack of consensus regarding optimal combination of medications. It is also difficult to apply previous study results to current practice because many of the medications studied, such as thiopental,[6,11,15] pethidine,[7] or anesthetic agents,[9,12] are not commonly used in the NICU. In addition, succinylcholine, one of the more frequently studied muscle relaxants, is no longer recommended for routine use in children.[23,24]

We designed a prospective, randomized, controlled, 2-center study to compare 2 premedication strategies for nonemergent intubations occurring in the NICU. Both strategies included an anticholinergic agent (atropine) and an analgesic agent (fentanyl). The groups were randomly assigned based on whether a short-acting muscle relaxant (mivacurium) was also used. We hypothesized that the use of a muscle relaxant would improve intubating conditions, thereby decreasing the incidence of hypoxia for ≥30 seconds below an arterial oxygen saturation (Sao_2) of 75% and secondarily reducing the time and number of attempts needed to complete the intubation procedure.

METHODS

Patients

All infants admitted to the NICUs at the Children's Hospital at Dartmouth and the University of California San Diego Medical Center who required endotracheal intubation on a nonemergent basis were screened for eligibility. Intubations that occurred in the delivery room, on an emergent basis, for a planned ETT change, or when <2 senior providers were present on the unit were not eligible. Senior providers were defined as neonatology attendings, neonatology fellows, or experienced neonatal nurse practitioners (NNPs). Other exclusion criteria included (1) absence of intravenous access, (2) abnormalities of the airway, (3) known or family history of a neuromuscular disorder or pseudocholinesterase deficiency, (4) renal insufficiency (urine output <0.6 mL/kg per hour or creatinine >1.7 mg/dL if >1 day of age), or (5) known hepatic insufficiency (abnormal liver function or coagulation laboratory results). Two senior providers were required because of the research nature of the interventions and the use of paralytic agents that were not familiar to all of the staff. In an effort to simulate common practice in the participating teaching hospitals, intubations were performed by all levels of housestaff or faculty, and there was no requirement for previous intubation experience.

Infants who had multiple intubations during their hospital stay were allowed to be in the study for only a single intubation. The protocol was approved by the institutional review boards at the participating institutions; written informed parental consent was obtained before enrollment.

Randomization was stratified by study center and weight at the time of intubation (≤1000 g, 1001–2000 g, and ≥2001 g) using a permuted-blocks scheme with blocks of 10 within each stratum. Randomization envelopes were provided to each study institution in sealed, opaque envelopes. Twins were randomly assigned separately. Designation of the providers who would perform the intubation (both initial and subsequent attempts) was made before randomization. Blinding to group assignment was not possible given the obvious effects of a muscle relaxant.

Study Protocol

A staff member not directly involved with the procedure recorded data and operated the computer-based data acquisition system, which included a pulse-oximeter (Masimo, Irvine, CA) and video camera (Sony USA, New York, NY). Data obtained for each study infant included birth weight, gestational age, adjusted age, gender, 5-minute Apgar score, history of previous intubation, fraction of inspired oxygen (Fio_2) requirement before intubation, age and weight at the time of procedure, and reason for intubation. Randomization group, level of training of the person performing the endotracheal intubation, number of attempts for each individual attempting intubation, total number of attempts needed to successfully complete the procedure, and any complications were also recorded. Video recordings were started

before the infant was positioned for intubation and stopped 5 minutes after the intubation procedure was completed. In the mivacurium group, video recording continued until spontaneous movement was observed (with a minimum of 5 minutes after completion of the procedure). HR, Sao_2, and BP were obtained for 5 minutes before administration of study medications and continued until 5 minutes after completion of the procedure. HR and oxygen saturation were recorded every 1 second. BPs were recorded every 1 minute.

Baseline values were obtained for 5 minutes before administration of medication. When premedication was begun, oxygen was administered with a flow-inflating resuscitation bag with FIO_2 adjusted to maintain Sao_2 ≥95%. Atropine (0.02 mg/kg) was administered intravenously over 1 minute followed by fentanyl (2 μg/kg) intravenously administered over 5 minutes. During the fentanyl infusion, infants received continuous positive airway pressure by mask (if spontaneously breathing) or bag-mask ventilation (if hypopneic or apneic). At the completion of the fentanyl infusion, FIO_2 was increased to 100%. Infants randomly assigned to the mivacurium group received mivacurium (0.2 mg/kg) via intravenous rapid infusion. Intubation was attempted once spontaneous movements ceased. For infants randomly assigned to the control group, intubation was attempted after the fentanyl infusion was complete. Mivacurium was available at the bedside for infants randomly assigned to the control group for use in the event of chest wall rigidity with the fentanyl infusion. All of the intubations were by the oral route.

For both groups, the study protocol required termination of the intubation attempt if Sao_2 fell below 75% or the attempt exceeded 30 seconds. A repeat attempt was initiated once Sao_2 was ≥95%. Less experienced individuals were allowed 2 attempts at intubation before yielding to a more experienced practitioner. An intubation was considered successful when there was confirmation of good breath sounds, visible vapor present in the ETT, increases in HR and Sao_2, and end tidal CO_2 detection.

Data Acquisition and Analysis

A custom-designed data acquisition system was used to simultaneously record video information and analog physiologic data. Digital video data obtained from a 3CCD digital video camera (Model TRV-950, Sony Electrics, Oradell, NJ) and analog signals from the oximeter (Radical, Masimo Corporation, Irvine, CA) were processed through a data acquisition board (Model PCI-6014, National Instruments, Austin, TX) and analyzed using a process-specific program that links them in time. The actual data sampling rate was 16 Hz per channel. Data collection was initiated 5 minutes before any drug administration and ended 5 minutes after completion of the procedure. Both the video signal and physiology data could be played back and viewed on the same screen, thereby allowing accurate identification of the initiation and completion of any intervention to the nearest second. For HR and oxygen saturation, the exact duration of any change from baseline, with medians, means, maxima, and minima, was calculated and stored for subsequent analysis (ProFox software, Escondido, CA). BP data, obtained by oscillometry or transduction of an arterial line, were printed from bedside monitors and entered into a database.

Incidence and duration of hypoxia were determined at oxygen saturation thresholds of Sao_2 ≤85%, ≤75%, ≤60%, and ≤40%. For each threshold we recorded: (1) whether any saturation level occurred below threshold value (dichotomous), (2) whether the cumulative amount of time below threshold value exceeded 30 seconds (dichotomous), and (3) total duration below threshold value.

HR and BP measurements were analyzed as the absolute change from baseline. Baseline values were those obtained for 5 minutes before atropine administration. Procedural values were those obtained beginning with the administration of atropine and ending 5 minutes after successful intubation.

Videotape of the procedure was reviewed to determine total duration of the intubation procedure, duration of time that the laryngoscope was in the mouth for each attempt, and number of attempts needed to successfully complete the intubation procedure. Total procedure time was defined as the duration from first insertion of the laryngoscope until the laryngoscope was removed from the mouth after successful intubation. If the intubation attempt was not successful, time accumulated continuously until successful intubation was achieved. Total laryngoscope time was defined as the sum of time that the laryngoscope was in the mouth during each attempt. An intubation attempt was defined as placement of the laryngoscope in the mouth, regardless of whether an attempt was made to pass an ETT.

In the mivacurium group, videotapes were also reviewed to determine the duration of action of mivacurium. Duration of action was defined as the time from administration of the mivacurium until first observed spontaneous movement.

Sample Size and Statistical Analysis

At the onset of the trial, previously published literature provided insufficient data on the incidence and duration of hypoxia to allow formal calculation of sample size. Therefore, analysis of the incidence of hypoxia (Sao_2 ≤75% for ≥30 seconds) blinded to group assignment was planned after enrollment of 30 infants. Blinding to group assignment was achieved by providing the statistician a spreadsheet created from the data file with durations of desaturation without identification of group assignment. Using these data, we determined that a sam-

ple size of 144 infants would be required to detect a 50% difference in the primary outcome of hypoxia as defined above (power = −0.8; $\alpha < .05$). Because this number of subjects was much higher than could be obtained in a reasonable time, the decision was made to stop enrollment and to publish the results as an explorative study. At the time that the decision was made, 45 infants had been enrolled.

Statistical analysis was performed with Stata 7 (Stata Corp, College Station, TX). Infants were analyzed on an intent-to-treat basis. Continuous variables were compared using 2-sample t tests. Dichotomous variables were compared using χ^2 analysis or Fisher's exact test as appropriate. Because the study was randomized and there were no substantial differences in baseline characteristics between treatment groups, only unadjusted analyses are presented. Results are presented as mean ± SD unless otherwise indicated. HR data were analyzed as change from mean baseline values to mean values during procedural time. Peak and mean values for systolic BP (SBP) and mean BP were analyzed as: (1) change between baseline and procedural time, (2) procedural time values only, and (3) regression analysis of values during procedural time including baseline BP and weight at time of the procedure as covariants. Duration of action of mivacurium was summarized using mean and range for the mivacurium group. Regression analysis was used to look for an association between duration of action of mivacurium and the following variables: birth weight, weight at time of procedure, gestational and corrected age, and age at time of procedure. A $P < 0.05$ was considered statistically significant.

RESULTS

During the study period (December 2003 to March 2005), there were a total of 504 intubations, of which 163 were eligible for the study. Of these, 45 infants were enrolled. Four randomly assigned infants were excluded from analysis for the following reasons: clinical deterioration resulting in emergent intubation before equipment setup or the administration of medications (1), inappropriate random assignment of a subject who met exclusion criteria (1), and technical difficulties resulting in no data obtained (2). Therefore, a total of 41 infants were included in the analysis (Fig 1). Two infants in the control group received muscle relaxant before intubation: 1 received mivacurium for presumed chest wall rigidity and a second infant received a dose of vecuronium after 3 unsuccessful intubation attempts. The latter infant was intubated preoperatively and received vecuronium as a deviation from study protocol because of time constraints and the preference of the attending

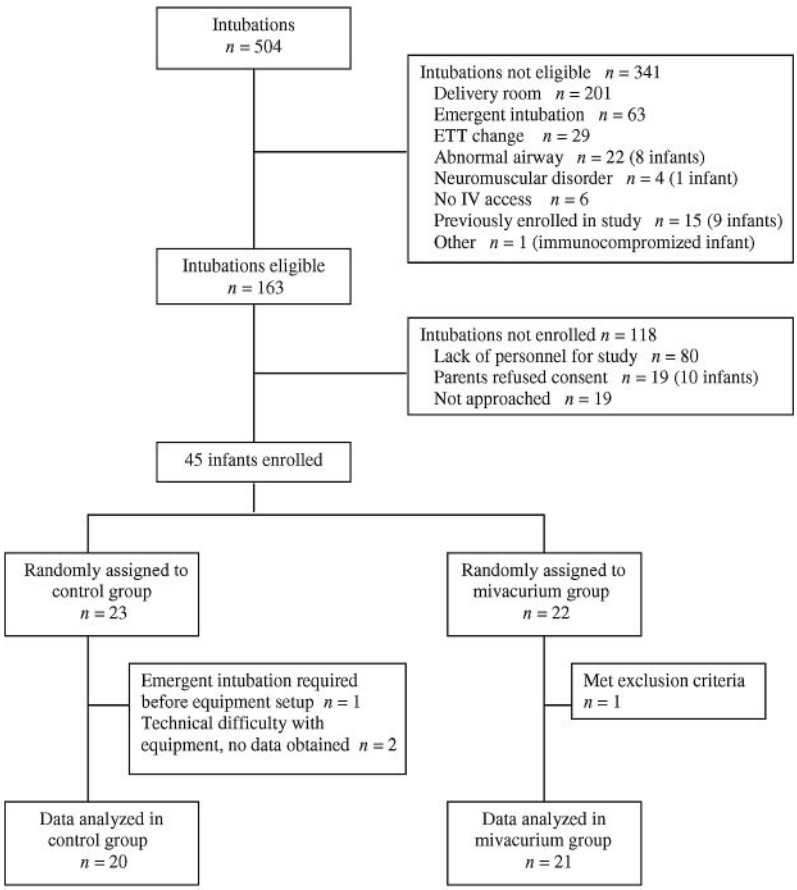

FIGURE 1
Trial profile and participant flow.

anesthesiologist. These infants were analyzed on an intent-to-treat basis. There were no differences in baseline characteristics between the control and mivacurium groups (Table 1).

Results for the primary outcome of hypoxia are presented in Table 2. We did not find a significant difference for the duration of hypoxia with a Sao_2 ≤75% for ≥30 seconds between the study groups. The incidence of oxygen saturation ≤60% for any duration was significantly less in the mivacurium group (11 of 20 [55%] vs 5 of 21 [24%]; $P = .041$). The incidences of oxygen saturation of any duration ≤85%, 75%, and 40% were not significantly different between groups. There were no significant differences between groups for incidence of cumulative time below threshold value ≥30 seconds or total duration of time below the 4 threshold saturation levels. However, for all of the definitions of hypoxia analyzed, low saturation occurred more frequently or for a longer duration in the control group compared with the mivacurium group.

Total procedure time and total laryngoscope time are presented in Fig 2. In the mivacurium group, total procedure time (472 vs 144 seconds; $P = .003$) and total laryngoscope time (148 vs 61 seconds; $P = .002$) were shorter. The number of intubation attempts is presented in Table 3. Although the median number of attempts was not different between groups (4 vs 2; $P = .066$), successful intubation achieved in ≤2 attempts occurred significantly more often in the mivacurium group (7 of 20 [35%] vs 15 of 21 [71%]; $P = .019$).

No difference was found in the change of HR from baseline through intubation (19 ± 11 beats per minute in controls vs 14 ± 10 beats per minute in mivacurium group; $P = .126$). Four patients experienced bradycardia (HR <100 beats per minute), 3 in the mivacurium group and 1 in the control group ($P = .606$). The lowest HR for these 4 infants ranged from 74 to 92 beats per minute.

BP data were available on 31 infants. Data were not available from 10 infants (7 in control group and 3 in mivacurium group) because of technical difficulties with downloading data or failure to initiate BP measurements during the intubation procedure. Peak SBP and change in peak SBP from baseline were similar in both groups (77.3 ± 10.2 vs 73.0 ± 17.5, $P = .434$; 10.1 ± 12.1 vs 5.4 ± 10.2, $P = .267$, respectively). Additional analysis of peak and mean values for SBP and mean blood pressure using several different comparisons as described in the statistical analysis section yielded similar and nonsignificant results.

Complications of the intubation procedure did not differ between groups. One infant in the mivacurium group developed a pneumothorax, mouth or lip lacerations occurred in 2 infants (1 in each group), and aspiration occurred in 1 infant (mivacurium group). Difficulty with bag-mask ventilation occurred in 3 infants: 2 in the control group and 1 in the mivacurium group.

Mean duration of action of mivacurium was 11 minutes and 26 seconds with a range of 5 to 22 minutes. Duration of action was not influenced by birth weight, weight at time of the procedure, gestational or corrected age, or age at time of procedure.

DISCUSSION

Our results show that premedication with a muscle relaxant reduces the time and number of attempts needed to successfully complete the intubation. There was a

TABLE 1 Baseline Characteristics

Variable	Control Group ($n = 20$)	Mivacurium Group ($n = 21$)	P
Birth weight, mean ± SD (range), g	1627 ± 1215 (685–4990)	1420 ± 901 (640–4270)	.538
Weight at time of procedure, mean ± SD (range), g	1687 ± 1187 (754–4990)	1556 ± 912 (660–4270)	.692
Gestational age, mean ± SD (range), wk	30.2 ± 4.9 (24.3–42.0)	29.7 ± 4.3 (24.7–38.1)	.737
Adjusted age, mean ± SD (range), wk	31.6 ± 4.2 (27.1–42.0)	31.0 ± 3.9 (25.0–38.6)	.652
Age at time of procedure, mean ± SD (range), d	9.6 ± 16.7 (0–65)	9.4 ± 16.8 (0–74)	.967
Study center, *n* (%)			.623
Children's Hospital at Dartmouth	8 (40)	10 (48)	
University of California San Diego Medical Center	12 (60)	11 (52)	
Male, *n* (%)	9 (45)	13 (62)	.278
5-min Apgar score, median (range)	9 (3–9)	8 (3–9)	.120
Initial intubation, *n* (%)	13 (65)	12 (57)	.606
FIO_2 before procedure, mean ± SD	0.56 ± 0.30	0.67 ± 0.31	.276
Reason for intubation, *n* (%)			1.000
Respiratory distress	14 (70)	14 (67)	
Apnea	3 (15)	3 (14)	
Self-extubation	0 (0)	1 (5)	
Preoperative	3 (15)	3 (14)	
Level of training of first intubator, *n* (%)			.877
Intern	11 (55)	9 (43)	
Resident	5 (25)	7 (33)	
NNP	1 (5)	1 (5)	
Fellow	3 (15)	4 (19)	

TABLE 2 **Hypoxia Results**

Variable	Control Group ($n = 20$)	Mivacurium Group ($n = 21$)	*P*
Incidence of saturation below threshold, *n* (%)[a]			
$Sao_2 \leq 85\%$	19 (95)	17 (81)	.343
$Sao_2 \leq 75\%$	13 (65)	11 (52)	.530
$Sao_2 \leq 60\%$	11 (55)	5 (24)	.041
$Sao_2 \leq 40\%$	5 (25)	1 (5)	.093
Incidence of saturation exceeding 30 s below threshold, *n* (%)[a]			
$Sao_2 \leq 85\%$	16 (80)	13 (62)	.306
$Sao_2 \leq 75\%$	11 (55)	6 (29)	.086
$Sao_2 \leq 60\%$	3 (15)	3 (14)	1.000
$Sao_2 \leq 40\%$	2 (10)	1 (5)	.606
Duration of saturation below threshold, mean ± SD (range), s			
$Sao_2 \leq 85\%$	135 ± 166 (0–736)	108 ± 126 (0–386)	.571
$Sao_2 \leq 75\%$	63 ± 108 (0–476)	38 ± 65 (0–190)	.368
$Sao_2 \leq 60\%$	25 ± 59 (0–256)	12 ± 33 (0–138)	.389
$Sao_2 \leq 40\%$	11 ± 31 (0–126)	4 ± 17 (0–76)	.342

[a] Incidence is defined as ≥1 event meeting definition during intubation procedure.

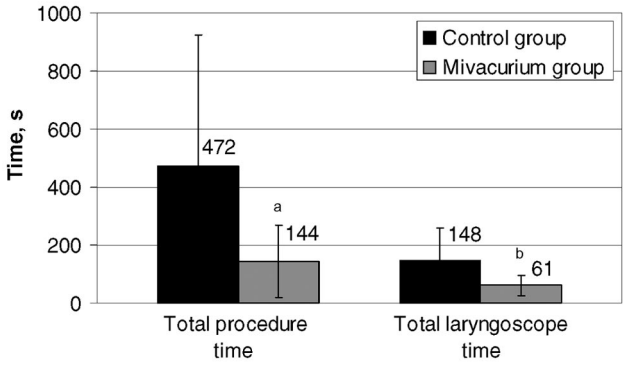

FIGURE 2
Time results. [a] $P = .003$. [b] $P = .002$.

TABLE 3 **Number of Intubation Attempts**

Variable	Control Group ($n = 20$)	Mivacurium Group ($n = 21$)	*P*
No. of attempts, median (range)[a]	4 (1–9)	2 (1–4)	.066
Attempts ≤2, *n* (%)	7 (35)	15 (71)	.019

[a] Attempt was defined as placement of the laryngoscope in the mouth regardless of whether an attempt was made to pass an ETT.

threefold decrease in total procedure time and twofold decrease in total laryngoscope time in the mivacurium group. Intubation was successfully completed in ≤2 attempts more than twice as often when a muscle relaxant was used. These results are consistent with previously published literature. Cook-Sather et al[15] studied awake intubation (no medication) compared with premedication with thiopental/succinylcholine and found a decrease in time of 54% and an increase in the number of successful first attempts (64% vs 87%) with the use of premedication. Similarly, Barrington et al[8] (atropine alone versus atropine/succinylcholine) and Khammash et al[5] (atropine alone versus atropine/fentanyl/succinylcholine) found a 41% and 48% decrease in time, respectively, with the use of a muscle relaxant.

Decreasing time and number of attempts needed to complete the intubation procedure reduces the time that the infant is subjected to the stress and adverse physiologic effects of the procedure. A previous study of preterm infants intubated without premedication found that the intubation procedure resulted in a 47% increase in the SBP and a 41% decrease in Sao_2. In addition, bradycardia (HR <100 beats per minute) occurred in 60% of the infants.[2] Similarly, Friesen and Thieme found that preterm infants intubated using atropine alone experienced a 20% increase in SBP and a 197% increase in ICP.[4]

Previous studies have shown that premedication attenuates potentially adverse physiologic effects. Atropine has been shown to attenuate the bradycardic response to vagal stimulation and to help maintain HR during periods of hypoxia. All of the infants enrolled in our study received atropine. HR was maintained at >100 beats per minute throughout the entire procedure in 37 (90%) of 41 of the patients. Of the 4 infants who experienced bradycardia, 3 were in the mivacurium group and 1 in the control group. The duration of bradycardia ranged from 7 to 46 seconds. The lowest HR was 74 beats per minute in an infant whose lowest Sao_2 was 79%. Atropine may have also helped maintain the HR during periods of low oxygen saturation level in 6 infants who experienced Sao_2 ≤40%. HR was maintained at >100 beats per minute for 5 of the 6 infants, with the remaining infant having a lowest HR of 92 beats per minute, demonstrating that atropine is useful for preventing bradycardia during intubation.

BP data were analyzed by using several different approaches, none of which showed significant differences between groups. Because both the control and mivacurium group received fentanyl, our findings are consistent

with a previous study that showed that analgesic agents attenuate the hypertensive response to intubation.[11]

There is no consensus about the degree or duration of hypoxia that is clinically significant. We chose to investigate hypoxia at 4 different saturation ranges. We found no differences in the total amount of time, incidence of any hypoxia, or incidence of hypoxia for ≥30 seconds at saturation levels of ≤85%, ≤75%, or ≤40%. However, the incidence of any Sao_2 ≤60% was significantly less with the use of a muscle relaxant (55% vs 24%; P = .041). The study protocol required that an intubation attempt be stopped for Sao_2 ≤75%, at which time the infant was to be manually ventilated until a saturation of ≥95% was achieved, and each attempt was limited to 30 seconds (a limit that was exceeded in 64 of 117 [55%] attempts: 44 of 75 [59%] in control group vs 20 of 42 [48%] in mivacurium group; P = .249). Therefore, duration of hypoxia as an outcome in this study may be a function of: (1) how well the team was able to follow the protocol and (2) how well the team was able to effectively bag-mask ventilate the infant. A true comparison of duration of hypoxia with and without a muscle relaxant would require a protocol that did not have a saturation threshold at which to stop the attempt, a design that we felt would be unethical. Choosing the degree of hypoxia as the primary outcome created challenges in the design of this trial. The lack of available data on the incidence of hypoxia during intubation made it difficult to determine the sample size for the trial. We chose to do an analysis of the incidence of hypoxia blinded to group after enrollment of 30 infants. The projected sample size of 144 infants was based on a 50% difference between groups in the incidence of Sao_2 ≤75% for ≥30 seconds. This outcome was chosen as a saturation level and duration that we felt to be relevant to clinical practice. The actual observed difference for this outcome was 47% (55% in control and 29% in study; P = .086), compatible with our hypothesis. This finding, together with the fact that all of the measures of hypoxia favored the mivacurium group, strongly suggests that a study of larger sample size would support the hypothesis that muscle relaxation, when used in addition to atropine and fentanyl, reduces hypoxia risk during intubation.

The overall incidences of any desaturation in the entire population of patients were: Sao_2 ≤85%: 36 of 41 (88%); Sao_2 ≤75%: 24 of 41 (59%); Sao_2 ≤60%: 16 of 41 (39%); and Sao_2 ≤40%: 6 of 41 (15%). For the 6 infants who experienced Sao_2 ≤40% during the intubation procedure, the low saturation was not correlated with weight, age, or adjusted age at time of the procedure. Five of the 6 infants were in the control group; 1 infant experienced muscle rigidity and desaturation before intubation, 2 were associated with prolonged intubation attempts and multiple attempts without substantial recovery time between attempts, 1 infant had a prolonged period of suctioning without time for recovery before an attempt, and 1 occurred without any obvious associated factor. One infant in the mivacurium group experienced Sao_2 ≤40%. This infant had a prolonged period of time between cessation of spontaneous respiration and placement of the laryngoscope and a prolonged intubation attempt. We believe that loss of lung volume is the most likely cause of the desaturations. These cases illustrate the importance of minimizing the loss of lung volume by avoiding prolonged suctioning, limiting intubation attempts to <30 seconds, and providing adequate recovery time between attempts.

Previous literature supports using premedication to prevent the adverse physiologic effects and pain associated with intubation. For this reason we chose not to use a control group where infants would be intubated without any premedication. However, clinicians must be aware that using medication involves potential risks of adverse effects and be prepared to handle them. Muscle rigidity involving the chest wall, abdominal muscles, and larynx is a known complication of fentanyl and may lead to difficulty with bag-mask ventilation. Despite this known complication, fentanyl was chosen for this study because it was an analgesic frequently used in both study centers before the initiation of this trial, previous surveys have shown that fentanyl is commonly used in other NICUs,[19,21,22] and fentanyl seems to have fewer adverse effects than morphine, especially hypotension.[25,26] The muscle rigidity associated with fentanyl is generally thought to occur with rapid infusions and high doses of the medication. Therefore, our study protocol was designed to provide a dose of fentanyl of 2 μg/kg infused on a pump over 5 minutes, and mivacurium was required to be at the bedside for patients in the control group. Despite the slow infusion and relatively low dose of fentanyl, 2 instances of difficulty with bag-mask ventilation occurred (1 in each group) shortly after the completion of the fentanyl infusion. Both instances were associated with decreased chest wall movement that did not respond to repositioning but resolved with the administration of mivacurium. Difficulty with bag-mask ventilation occurred in a third infant (control group) after an intubation attempt and was most likely because of positional airway obstruction. Ventilation improved in this infant after repositioning without administration of a muscle relaxant.

Mivacurium is a recently developed short-acting muscle relaxant from the class of nondepolarizing muscle relaxants. It was chosen for the study because of its rapid onset, short duration of action, and relative lack of adverse effects. We found that mivacurium provided acceptable intubating conditions and had a mean duration of action of 11 minutes and 26 seconds (range: 5–22 minutes). These results are similar to the only other known study which has reported the use of mivacurium

for newborn intubation that found a mean duration of 15 minutes and 37 seconds (range: 8–30 minutes).[27] There were no instances where muscle relaxation was not achieved, nor were there any cases of prolonged duration of action. No adverse effects, such as bronchospasm, wheezing, flushing, or rash were observed.

Four randomly assigned infants were not included in the analysis. Data were not obtained for 3 of the infants, making it impossible to include them on an intent-to-treat basis. One of the 3 infants required emergent intubation between the time of randomization and setting up study data acquisition equipment. In 2 infants (1 at each study site), technical problems resulted in an absence of any recorded data. The fourth infant was randomly assigned despite meeting the exclusion criteria of the intubation being performed for an ETT change. ETT changes were excluded from the study because common practice in the study centers was to leave the ETT in place during the placement of the laryngoscope and change the ETT on direct visualization of the vocal cords. Therefore, the infant would be continuously ventilated during the placement of the laryngoscope and would not be a true comparison of hypoxia with infants not receiving continuous ventilation during this time period. Review of the individual cases revealed them to be similar to the infants analyzed.

An advantage of this study is the accuracy of the data collection. Oxygen saturation and HR data were collected continuously every second and downloaded directly into a computer program for analysis. These data were synchronized with the video recording, allowing the reviewer to accurately measure times and number of attempts, as well as assigning values to the appropriate phases of the procedure. This study design represents an improvement over previous studies measuring times using a stopwatch with the potential for human error. In addition, oximeter values were obtained using a 2-second averaging interval. This provided a more accurate measure of the true saturation level as compared with oximeters that average values over longer intervals of time.

Over the past 25 years, several researchers have investigated premedication for nonemergent intubations in the NICU. Relevance to current practice, however, is limited by the medications used or the design of the study. In many studies, succinylcholine has been used as the muscle relaxant. However, succinylcholine has many undesirable adverse effects, including bradycardia, muscle fasciculations, malignant hyperthermia, and increased intraocular pressure. In addition, rare reports of acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death after the administration of succinylcholine to apparently healthy pediatric patients who were subsequently found to have undiagnosed skeletal myopathies led to the recommendation that "the use of succinylcholine in pediatric patients be reserved for emergency intubation or instances where immediate securing of the airway is necessary."[24] In addition, many of the previous studies were designed such that the study authors or other experienced personnel performed the intubations, thereby making it difficult to generalize the results to institutions where people of many different levels of training perform the procedure.

Our study was designed to overcome the limitations of previous studies. We chose to use fentanyl, an analgesic agent commonly used in the NICU, and mivacurium, a muscle relaxant from the new generation of nondepolarizing muscle relaxants that does not have the adverse side effect profile of succinylcholine. This study was also conducted in 2 university-affiliated teaching hospitals where intubations were performed by pediatric interns, residents, NNPs, perinatal-neonatal fellows, and attendings, thus making the results more applicable to teaching NICU environments.

CONCLUSIONS

Our study shows that premedication with atropine, fentanyl, and mivacurium compared with atropine and fentanyl without a muscle relaxant results in limited changes in oxygenation, HR, and BP during the intubation procedure while decreasing the time and number of attempts needed to successfully intubate. We believe that premedication including a short-acting muscle relaxant should be considered for all nonemergent intubations in the NICU.

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