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ABSTRACT

Objective To evaluate the efficacy and safety of remifentanil as a premedication in neonates undergoing elective endotracheal intubation.

Design A double-blind randomised controlled trial.

Setting Tertiary care neonatal intensive care unit.

Patients Haemodynamically stable term and preterm neonates requiring elective endotracheal intubation.

Interventions Infants in the intervention arm received remifentanil (3 μg/kg) and normal saline placebo. The control group received fentanyl (2 μg/kg) and succinylcholine (2 mg/kg). Both groups also received atropine (20 μg/kg) as part of the premedication regime.

Main outcome measures The primary outcome was time to successful intubation. Secondary outcomes included time to return of spontaneous respirations, oxygen saturation, heart rate and blood pressure changes during the procedure, adverse events and a survey of intubation conditions.

Results A total of 15 infants were randomised to each group. Baseline characteristics were similar in both groups. The median time to successful intubation was not statistically different (247 s in the remifentanil group vs 156 s in the fentanyl group, p=0.88). The intubation conditions were rated more favourably with fentanyl by the intubators. Although not statistically significant, chest wall rigidity was observed more commonly with remifentanil.

Conclusions Although remifentanil is comparable to fentanyl and succinylcholine in attenuating adverse physiologic responses during neonatal intubation, muscle rigidity is a concern at doses of 3 μg/kg. Further trials are required to evaluate ideal dosing regimens and combinations of agents for use with remifentanil in neonates.

What is already known on this topic

- Remifentanil is an ultra-short-acting, potent selective μ-opioid receptor agonist that has been proposed for use in neonatal intubation.
- There is a paucity of prospective data on the safety and efficacy of remifentanil in the neonatal population.

What this study adds

- Premedication with remifentanil attenuates physiologic responses during intubation comparable to fentanyl and succinylcholine in neonates.
- There are concerns of muscle rigidity with remifentanil and the potential for medication errors particularly when reconstituting for administration in small babies.

It is now acknowledged that neonates have adequately developed functional nociceptive and pain pathways.[1] The physiologic responses to painful stimuli not only have short-term detrimental effects such as altered systemic blood pressure, cerebral blood flow and increased risk for intracranial haemorrhage, but poor pain control in early life can also predispose these infants to hypersensitive pain perception with future experiences and long-term psychophysical sequelae.[2 3] As a result, increasing attention is being paid to procedural sedation and analgesia in the newborns.[4] Premedication for semi-urgent and elective endotracheal intubation has thus become an increasingly accepted standard of care in this population.[5] However, compared with paediatric critical care, the experience with the variety of premedication regimens available is limited in neonates. The most commonly used regimens are currently limited to benzodiazepines or opioids such as morphine or fentanyl, either alone or in combination with atropine and a muscle relaxant.[6 7] Growing concerns with respect to prolonged muscle relaxation, duration of action and the potential adverse effects of succinylcholine has lead to a search for alternative drugs with the objective of providing adequate procedural sedation and analgesia with minimal side effects.[5 8] Furthermore, in order to allow a rapid return of spontaneous respiration and airway reflexes, especially with the increasing use of brief tracheal intubation and extubation for the sole purpose of surfactant administration in neonates with respiratory distress syndrome,[9 10] the evaluation of ultra-short-acting agents to facilitate these objectives is of great interest.

Remifentanil is a potent selective μ-opioid receptor agonist that has a unique pharmacokinetic profile characterised by a rapid and uniform clearance by unspecific esterases and a highly predictable onset and offset of effect.[11] Remifentanil has a rapid onset of action (60–90 s) and at adequate doses renders the patient apnoeic and motionless, thus reducing the need for a muscle relaxant.[12] The experience with remifentanil in the neonatal literature to date is extremely limited; however, earlier reports suggest that remifentanil may provide adequate sedation,

analgesia and intubation conditions in this population.[13–15] The objective of this trial was to evaluate the safety and efficacy of remifentanil in term and preterm neonates undergoing non-urgent endotracheal intubation. We hypothesised that the combination of remifentanil and atropine would result in more favourable physiologic intubation conditions when compared with a traditional premedication regimen of fentanyl, atropine and succinylcholine.

METHODS

Patients

Haemodynamically stable neonates of any gestational age with existing intravenous access admitted to the neonatal intensive care unit at McMaster Children's Hospital were eligible if an elective endotracheal intubation was anticipated. All consecutive patients were screened. We excluded the following patients: emergent intubations, cyanotic congenital heart lesions, anticipated difficult airway (eg, airway anomaly or obstruction), concurrent or recent intravenous opioid infusions administered within 3 h of the procedure, pre-existing hyperkalemia, family history of malignant hyperthermia and previous enrolment in this trial. In compliance with the Division 5 of the Health Canada Food and Drug regulations, a clinical trials application was submitted with no objection for the off-label use of remifentanil, which is otherwise not yet approved for use in this age group. This trial received approval from the Hamilton Health Sciences Research Ethics Board. Written informed consent was obtained from the substitute decision makers of all eligible patients before enrolment.

Randomisation and treatment protocol

Patients were randomised to one of two treatment groups in a 1:1 allocation ratio using a random numbers table. All patients, caregivers, medical and nursing staff, outcome assessors and investigators were masked to the study group assignment. Only the research pharmacist who prepared the study drugs was aware of the group allocation and ensured that the preparations in each study group could not be differentiated. Each study drug was identical, colourless and odourless in appearance and was reconstituted to similar volumes for intravenous administration in the respective groups in order to maintain allocation concealment. They were prepared and administered sequentially in identical clear syringes marked as drug 1, 2 and 3 for each study patient. For the control arm (fentanyl group), these drugs were assigned as follows: drug 1, atropine (20 μg/kg); drug 2, fentanyl (2 μg/kg administered over 60 s); drug 3, succinylcholine (2 mg/kg). The remifentanil group received the premedication in the following order: drug 1, atropine (20 μg/kg); drug 2, remifentanil (3 μg/kg) administered over 60 s; drug 3, normal saline placebo. Remifentanil was prepared for the purposes of this trial in the following manner: a 1-mg powder vial was diluted with 1 ml of sterile water, and 0.08 ml of this mixture was subsequently added to 9.9 ml of sterile water, such that 0.4 ml/kg of this mixture was equal to a dose of 3 μg/kg. Fentanyl 1 ml (50 μg) was diluted in 9 ml sterile water such that 0.4 ml/kg was equal to a dose of 2 μg/kg. This method of dilution enabled us to prepare both study drugs in similar volumes for the purposes of maintaining blinding. The protocol for study drug administration is illustrated in Appendix A. In the event that intubation conditions were considered suboptimal by the intubator after receiving all three drugs, additional open-label medications could be administered at their discretion.

Each participant was prepared for endotracheal intubation according to standard of practice with the necessary intubation equipment, positioning and pre-oxygenated to achieve oxygen saturation (SpO_2) ≥95%. The following physiologic variables were measured at baseline and throughout the procedure: continuous heart rate and intermittent blood pressure measurements were obtained by the Siemens SC 7000 monitor (Siemens Medical Systems, Danvers, Massachusetts, USA); continuous pulse oximetry was measured by Masimo Radical (Masimo, Irvine, California, USA). The study drugs were administered by qualified personnel in accordance with unit policy. Intubation commenced 30 s after drug 3 was administered in all study patients. Each patient could be intubated nasally or orally by certified staff who had accomplished at least five previous successful intubations. If the intubation was unsuccessful after two attempts, the procedure would thereafter be performed by a more senior member of the team. The endotracheal tube (ETT) was secured after confirmation of appropriate position.

Outcome measures

The primary outcome was the time to successful intubation, as defined by the total time in seconds from the first insertion of the laryngoscope blade into the mouth until final confirmation of ETT placement by clinical examination (auscultation, visible vapour in the ETT, adequate chest rise with bag and mask ventilation, and increase in SpO_2). This measurement was timed by a blinded assessor who was not involved in the intubation procedure. The total laryngoscopic time was also measured, which was the sum of time spent (in seconds) at laryngoscopy during each intubation attempt. Secondary outcomes included comparisons in time to return of spontaneous respirations, SpO_2, heart rate and blood pressure changes related to the procedure and adverse events in the two groups. Anticipated adverse events directly related to the trial interventions included chest wall rigidity (defined by an acute onset of stiffness of the chest wall despite adequate positive pressure ventilation, temporally related to study drug administration) and evidence of trauma (as defined by direct visualisation or evidence of blood in the airway secretions). The intubation conditions were rated immediately following each procedure independently by the intubator and bedside nurse respectively, using a seven-point, Likert scale self-reported survey.

Statistical analyses

Estimates of the time to successful intubation reported in the literature in neonates who have received premedication are in the range of 53–472 s.[16–19] We chose to use data from our previous trial, which reported the median of 94 s, to estimate the sample size for this trial.[8] We calculated that 30 infants were required to achieve 90% power to detect a 30% relative reduction in the time to successful intubation, at a significance level of 5%. Descriptive summaries of demographic and clinical characteristics were generated for all participants at baseline. Primary and secondary outcomes were analysed according to the intention-to-treat principle. Continuous data were summarised using medians (interquartile range (IQR)) and means (SD) for normally distributed data. Differences between groups were evaluated using Student t test for means and Mann–Whitney U test for group medians. χ^2 and Fisher's exact tests, where appropriate, were applied for binary outcomes. We reported two-sided 95% confidence intervals and p values. Data were analysed using the statistical package SPSS V.13.0 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

From January 2006 to February 2008, 925 neonates admitted to the neonatal intensive care unit required endotracheal intubation. Of these, 103 potentially eligible patients were approached for consent, of whom a total of 30 patients were randomised, 15 to each study group (fig 1). None of the patients were withdrawn after randomisation, and there were no protocol violations. Patients in both study groups had similar demographic characteristics at baseline (table 1). The most frequent indication for elective intubation was respiratory failure secondary to respiratory distress syndrome (47%). There were four patients in the remifentanil group who could not be oxygenated to $SpO_2 \geq 95\%$ because of chest wall rigidity (n=2), persistent respiratory effort (n=1) and unclear reasons (n=1). The baseline SpO_2, however, was not statistically different between the two groups (p=0.1; table 1).

The median time to successful intubation was not statistically different (247 s in the remifentanil group vs 156 s in the fentanyl group, p=0.87) (table 2). Nine patients (60%) in the remifentanil group were intubated on their first attempt, compared with 6 (40%) of the fentanyl group (p=NS). The total number of attempts at intubation was not statistically different in the two groups. Comparisons of the time to intubation in those successfully intubated on the first attempt were also not statistically significant (104 vs 45 s; p=0.19). Four patients in the remifentanil group received additional open-label succinylcholine for intubation: one for chest wall rigidity and desaturation, another for persistent spontaneous respirations despite premedication and two for repeated intubation attempts. None of the patients in the fentanyl group required additional open-label medications. The degree of SpO_2, heart rate and blood pressure changes, were not significantly different between the two groups (fig 2). The time to return of spontaneous respirations was not statistically different between the remifentanil and fentanyl groups (452 vs 300 s; p=0.356). In the 11 neonates in the remifentanil group who did not receive open-label succinylcholine, the median time to return of spontaneous respiration was 210 s, compared with the four patients who did require additional succinylcholine (756 s; p=0.003). However, the

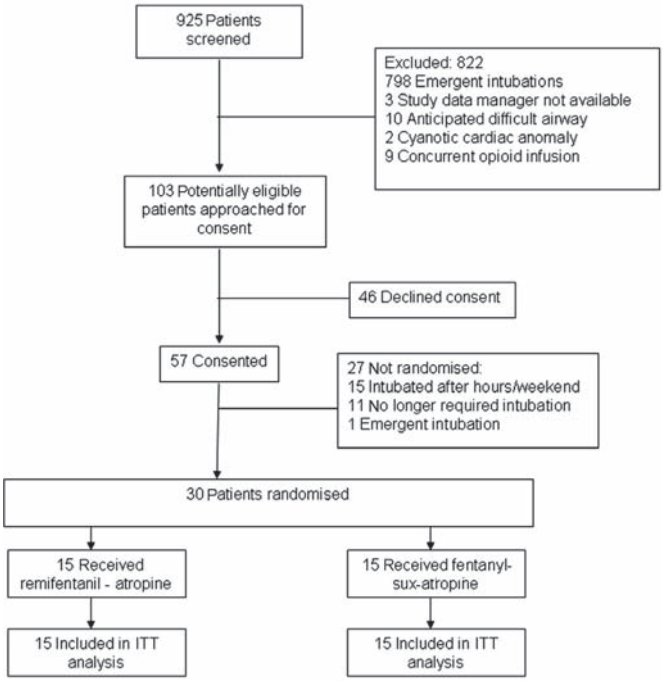

Figure 1 Patient flow. IIT, intention-to-treat; sux, succinylcholine.

Table 1 Baseline characteristics of participants

	Fentanyl (n=15)	Remifentanil (n=15)
Gestational age at birth (weeks), median (IQR)	27.1 (25.6 to 28.7)	28.0 (25.0 to 30.0)
Birth weight (g), median (IQR)	940 (735 to 1342.5)	995 (750 to 1190)
Male, n (%)	10 (66.7)	7 (46.7)
Age at intubation (days), median (IQR)	11.0 (2.4 to 19.5)	9.0 (3.0 to 24.5)
Baseline vitals, mean (SD)		
Heart rate (beats per minute)	163.0 (17.9)	149.6 (9.5)
Mean blood pressure (mm Hg)	43.3 (9.5)	43.9 (9.9)
Spo_2 (%)	93.8 (3.8)	89.7 (8.5)
Reason for intubation, n (%)		
Respiratory distress syndrome	8 (53.3)	6 (40.0)
Elective ETT change	2 (13.3)	3 (20.0)
Surgery	2 (13.3)	2 (13.3)
Sepsis	2 (13.3)	1 (6.7)
Chronic lung disease	0	2 (13.3)
Apnoea of prematurity	1 (6.7)	0
Atelectasis	0	1 (6.7)
Intubator, n (%)		
Clinical nurse practitioner	11 (73.3)	8 (53.3)
Neonatal fellow	1 (6.7)	6 (40.0)
Neonatal attending	1 (6.7)	0
Transport nurse	1 (6.7)	0
Resident: paediatrics/anaesthesia	0	1 (6.7)
Respiratory therapist	1 (6.7)	0

ETT, endotracheal tube.

Table 2 Outcomes of interest

	Fentanyl (n=15)	Remifentanil (n=15)	p Value
Time to successful intubation (s), median (IQR)	156 (46 to 395)	247 (48 to 349)	0.88
Total laryngoscopic time (s), median (IQR))	106 (30 to 425)	208 (46 to 445)	0.39
Time to return of spontaneous respirations (s), median (IQR)	300 (221 to 422)	452 (179 to 649)	0.356
Number of intubation attempts	1.8 (0.8)	1.7 (0.9)	0.67
Intubated on first attempt, n (%)	6 (40)	9 (60)	0.47
Intubated on second attempt, n (%)	6 (40)	2 (13.3)	0.21
Intubated on third attempt, n (%)	3 (20)	4 (26.7)	1.0
Additional open-label succinylcholine given, n (%)	0	4 (26.7)	0.1
Change in Spo_2 (%)	−47 (25)	−55 (27)	0.42
Change in blood pressure (mm Hg)	4.3 (7.5)	4.3 (15.9)	0.98
Change in heart rate	−52 (29)	−52 (31.6)	0.98
Adverse events			
Trauma	2	2	1.0
Chest wall rigidity	0	2	0.48
Total number of adverse events,* n (%, 95% CI)	2 (13, 1.66 to 40.46)	4 (27, 7.79 to 55.10)	0.17

Values are presented as mean (SD) unless otherwise described.
*Number of adverse events per total number of patients allocated to that group.

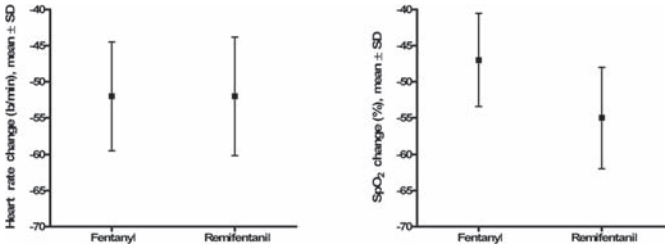

Figure 2 Heart rate (HR) and oxygen saturation (Spo_2) change during procedure.

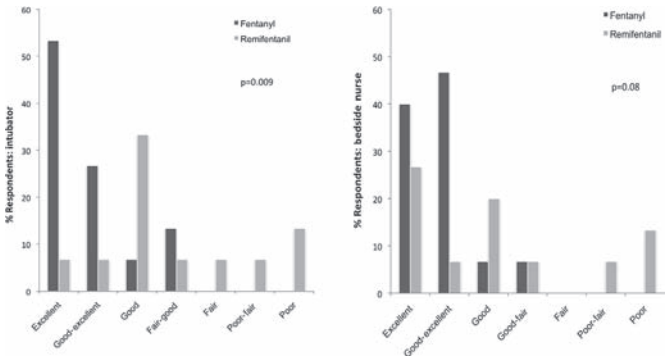

Figure 3 Intubation conditions as rated by the intubator and bedside nurse, respectively.

comparison of this outcome in this subgroup of 11 remifentanil patients and the fentanyl group was not significant (p=0.66).

The overall adverse event ratio was not statistically different in the two groups (27% vs 13%, p=0.17). There were two patients in the remifentanil group who experienced chest wall rigidity, one of whom required administration of succinylcholine as described above, while the other spontaneously resolved without further intervention. Intubation conditions were considered "excellent" by eight (53.3%) respondents in the fentanyl group, compared with 1 (6.7%) of the intubators in the remifentanil group (p=0.009) (fig 3). Two (13.3%) intubators reported poor intubation conditions with remifentanil compared with none in the fentanyl group. The intubation conditions were not statistically different between the two groups when rated by the bedside nurse (p=0.08).

DISCUSSION

Premedication before endotracheal intubation is evolving as a standard of care for critically ill neonates.[4 5 19] Unfortunately, many premedication regimens are not well evaluated in prospective trials in the neonate, and hence the most appropriate selection and indeed the safety of some of these medications in this population remain unclear. This double-blind randomised controlled trial adds to a growing body of evidence on the use of remifentanil in neonates and very low birthweight infants, which, to date, has been very limited.[10 13–15 20 21] While our results demonstrate that remifentanil combined with atropine maintained haemodynamic and oxygenation parameters comparable to the traditional regimen of fentanyl, succinylcholine and atropine, the intubation conditions reported by intubators were felt to be less optimal with remifentanil. Two cases of muscle rigidity in this small trial, while not statistically significant, are nevertheless of concern, given that it resulted in prolongation of the procedure and additional medications in these patients. It is undetermined whether a trial with a larger sample size would demonstrate a significant difference in this adverse event, as fentanyl itself is also associated with muscle rigidity.[22] Opioid-associated muscular rigidity is well recognised and is dose- and rate-dependent.[23] Therefore, both remifentanil and fentanyl were administered over 60 s in this trial in accordance with current recommendations.[18 24] Furthermore, we cannot rule out that the lack of chest wall rigidity may have been related to the use of succinylcholine in the fentanyl group. The addition of succinylcholine to fentanyl, by ensuring apnoea, motionlessness and complete muscle relaxation, may in turn have influenced the subjective favourable rating of intubation conditions in this group.

As a result of perceived suboptimal intubation conditions, repeated attempts and an observed adverse event, four of the remifentanil patients required additional premedication with open-label succinylcholine. These factors collectively contributed to the trend towards a longer time to successful intubation in the remifentanil group. While the differences in the outcomes of interest between the two groups were not statistically significant, the trends observed in this trial are clinically significant and highlight potential safety concerns that the use of 3 μg/kg remifentanil as the sole sedative/analgesic agent in neonatal intubation may result in less than optimal Spo_2 at baseline, requirement for redosing of medication, a potential for chest wall rigidity and subsequently longer procedural and recovery times. The results of this trial are in contrast to previous publications where remifentanil was found to result in better intubation conditions when compared with longer-acting opioids such as morphine,[14] without an increase in side effects such as muscle rigidity.[10 14]

The dose response for remifentanil is reportedly similar in infants and children, as it is in adults; however, there is a marked variation in acceptable intubating conditions at different doses.[12] While the effective dose in adults ranges from 2.0 to 5.0 μg/kg, the dosage in this trial was based on paediatric literature that suggests that intubating conditions are optimised with incremental dosages of remifentanil and a dose of 3 μg/kg provides similar intubation conditions to muscle relaxants with minimal side effects.[12 24–26] However, lower doses of 1–2 μg/kg may be equally effective in neonates, with potentially fewer side effects.[14] Furthermore, the addition of benzodiazepines or a combination of propofol followed by remifentanil may minimise the occurrence of muscle rigidity.[12 24] Propofol is currently not approved for use under the age of 3 months in North America. The dosage of remifentanil may also influence the time taken to return of spontaneous respirations, although this has been debated.[24] One of the advantages of remifentanil is that it has a context-sensitive half-time of approximately 3 min and thus a rapid termination of action, independent of dosage and infusion time.[27] The return of spontaneous respirations is thus reported to be comparable to succinylcholine. Paediatric studies report apnoea times ranging from 158 to 347 s with 1 μg/kg of remifentanil, albeit when given in combination with propofol.[24 28] We chose to administer remifentanil with atropine only in this trial to minimise the period of respiratory depression. Nevertheless, we observed that the time to return of spontaneous respirations while not statistically significant tended to be longer in the remifentanil group. This was influenced by the patients in this group who required repeated intubation attempts and redosing of medication, as the subgroup of remifentanil patients who did not receive additional succinylcholine demonstrated a shorter time to return of spontaneous respirations.

This trial is limited by the small sample size. The definition used for the primary outcome in this trial was a pragmatic one, in keeping with current clinical standards of practice for identifying appropriate placement of ETTs. This outcome has been measured by a variety of methods in the neonatal literature; nevertheless, our observations are within the range previously identified in trials of this nature.[8 16 17 19 29] The survey of overall intubation conditions used in this trial was likely too subjective and did not enable discrimination between mechanical versus patient-related factors. From a practical standpoint, there are additional safety concerns during the administration of remifentanil in the very low birthweight infant. Remifentanil is available as a vial containing 1 or 2 mg of powder that has to be reconstituted and then further diluted to a measurable concentration before its use in neonates of variable sizes. Remifentanil may, therefore, not be a practical bolus medication to administer in small babies given the potential for error during dilution.

CONCLUSION

Premedication before intubation in the neonate should not be limited to only a single drug or drug regimen, as the most appropriate agent(s) should be individualised and dictated by the individual case-specific objectives. As is often the case, given the lack of neonatal-specific data, the use of many premedication regimens is extrapolated from the experience in older children and adults. However, this should not negate the need for safety and efficacy evaluation of these drugs in neonates. Muscle rigidity is a potential risk with remifentanil. While there is a role for remifentanil in neonates, based on the results of this trial, we do not currently recommend its routine use as a premedication until further studies of optimum dosing, either alone or in combination with other medications, as well as its safety, have been further evaluated in this population.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Hamilton Health Sciences Research Ethics Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

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