Premedication for endotracheal intubation in the newborn infant

KJ Barrington; Canadian Paediatric Society, Fetus and Newborn Committee

Canadian Paediatric Society

Endotracheal intubation, a common procedure in newborn care, is associated with pain and cardiorespiratory instability. The use of premedication reduces the adverse physiological responses of bradycardia, systemic hypertension, intracranial hypertension and hypoxia. Perhaps more importantly, premedication decreases the pain and discomfort associated with the procedure. All newborn infants, therefore, should receive analgesic premedication for endotracheal intubation except in emergency situations. Based on current evidence, an optimal protocol for premedication is to administer a vagolytic (intravenous [IV] atropine 20 µg/kg), a rapid-acting analgesic (IV fentanyl 3 µg/kg to 5 µg/kg; slow infusion) and a short-duration muscle relaxant (IV succinylcholine 2 mg/kg). Intubations should be performed or supervised by trained staff, with close monitoring of the infant throughout.

Key Words: *Bradycardia; Endotracheal intubation; Hypertension; Hypoxia; Newborn; Pain; Premedication*

La prémédication en vue de l'intubation trachéale du nouveau-né

L'intubation trachéale, courante dans les soins au nouveau-né, s'associe à de la douleur et à une instabilité cardiorespiratoire. Le recours à une prémédication réduit les réponses physiologiques indésirables de bradycardie, d'hypertension systémique, d'hypertension intracrânienne et d'hypoxie. Fait peut-être plus important, la prémédication réduit la douleur et l'inconfort associés à l'intervention. Tous les nouveau-nés devraient donc recevoir une prémédication analgésique avant l'intubation trachéale, sauf en situation d'urgence. Selon les données probantes à jour, un protocole optimal de prémédication consiste à administrer un vagolytique (20 µg/kg d'atropine par voie intraveineuse [IV]), un analgésique à action rapide (de 3 µg/kg à 5 µg/kg de fentanyl IV en perfusion lente) et un myorelaxant de courte durée (2 mg/kg de succinylcholine IV). Les intubations devraient être effectuées ou supervisées par du personnel formé, qui assure une surveillance étroite du nourrisson tout au long de l'intervention.

Endotracheal intubation is a common procedure in newborn care. There is great variation in the frequency of premedication use for intubation, and in the medications used (1,2). The experience of being intubated is unpleasant (3) and painful (3,4), and seriously disturbs the cardiovascular and respiratory status of the newborn. Reducing pain is an ethical obligation for those providing care for newborn infants (5); although nurses and physicians recognize that tracheal intubation of the newborn is a very painful procedure (4), they still frequently fail to provide any pain relief (4).

The use of such agents does not require indisputable proof that they improve the long-term outcomes of the infants; it is possible that they do not do so. There is no absolute proof that awake intubation adversely affects long-term outcomes in adults undergoing endotracheal intubation, but that is not used as an excuse for performing this painful and unpleasant act without premedication. The infants under our care are more likely to feel pain (6) and more likely to have adverse long-term outcomes as a result of the serious pain that they experience during intensive care (6), than an adult in similar circumstances. A humane and ethical approach to neonatal intensive care procedures demands the use of preemptive analgesia before planned painful procedures (7).

The purpose of the present statement is to review the literature regarding appropriate premedications for intubation and produce evidence-based recommendations for their use.

METHODS OF STATEMENT DEVELOPMENT

The literature review included a Medline search last updated in June 2010 using PubMed. The following search terms were used: intubation, endotracheal and newborn. The search was limited to human studies in English, French, German or Spanish. The abstracts of the Pediatric Academic Societies were searched for the years 1995 through 2007. A search of Embase was performed for the years 1966 through 2007. The hierarchy of evidence from the Centre for Evidence-Based Medicine was applied using levels of evidence for treatment and prognosis (go to www.cebm.net and click on the EBM Tools tab, or go directly to www.cebm.net/index.aspx?o=1025).

In addition, the principal author searched his personal data files, as well as the reference lists of published studies for further potential articles. A published systematic review was also examined for references (8).

The following questions were asked:

- What are the physiological responses to intubation?
- What are the effects of premedication on the physiological responses?
- How can the pain and discomfort of intubation be reduced?
- What are the complications of premedicating an infant for intubation?
- Under what clinical circumstances is it acceptable to intubate an infant without the use of premedication?

Correspondence: Canadian Paediatric Society, 2305 St Laurent Boulevard, Ottawa, Ontario K1G 4J8. Telephone 613-526-9397, fax 613-526-3332, websites www.cps.ca, www.caringforkids.cps.ca

- Which premedications have been studied?
- What are the characteristics of an acceptable protocol for premedication?

WHAT ARE THE PHYSIOLOGICAL RESPONSES TO INTUBATION?

The majority of studies have not separated the physiological responses to intubation from those of laryngoscopy. This is only of importance because laryngoscopy is sometimes performed for other reasons such as checking tube position or examining the upper airway. In such an instance, it should be remembered that laryngoscopy by itself causes adverse physiological changes (9). Intubation/laryngoscopy causes systemic and pulmonary hypertension (10), bradycardia, intracranial hypertension (11) and hypoxia. The bradycardia and hypoxia appear to be independent. Hypoxia can be reduced or avoided by the use of preoxygenation, and by the use of a laryngoscope blade that allows continuous oxygen insufflation into the pharynx during the procedure. The bradycardia is largely vagal in origin, and it is not prevented by preoxygenation and avoidance of hypoxia (12). The intracranial pressure increase appears to be the result of the coughing and struggling of the infant (13). Systemic arterial hypertension has been investigated extensively in hypertensive adults, and appears to be due to an increase in systemic vascular resistance (14), probably due to catecholamine release in response to the intense pain (9). Pulmonary hypertension leading to right ventricular failure during intubation has been well described in adults (15), but pulmonary artery pressures have not been measured in newborn infants during intubation.

WHAT ARE THE EFFECTS OF PREMEDICATION ON THE PHYSIOLOGICAL RESPONSES?

The physiological responses to intubation can be reduced or eliminated by the administration of vagolytics, muscle relaxants, analgesics, preoxygenation and gentle technique. Specifically, bradycardia can be largely prevented by the use of atropine (12); systemic hypertension can be reduced by adequate analgesia, which also reduces endocrine and endorphin responses (16); and intracranial hypertension can be avoided by the use of muscle relaxants (13) (all evidence level 1b). Intubation is much faster when the infant is paralyzed (13,17,18), whether performed by experienced neonatologists (13), anesthetists (18) or paediatric residents (17) (evidence level 1b), which leads to reduced hypoxia. Fewer attempts are also required (19,20).

Two recent studies (19,20) that gave potent analgesics to all infants, randomly assigned the infants to receive muscle relaxants or no relaxants. Both studies demonstrated additional benefits of giving a muscle relaxant.

HOW CAN THE PAIN AND DISCOMFORT OF INTUBATION BE REDUCED?

It is ethically imperative to administer analgesia before planned painful interventions unless it can be proven harmful to do so; the reduction of the short-term physiological sequelae is probably, at least in part, secondary to the reduction in pain and discomfort.

Opiates

Morphine appears not to reduce the occurrence of severe hypoxia with bradycardia during intubation, in comparison with placebo, probably because of the delayed onset of action (21). It is likely that fentanyl is more effective because of the more rapid onset of action. Other newer agents that are even faster acting may also be more effective. An example of such an agent is remifentanil, which in older subjects, has an onset of action within seconds and a duration of only a few minutes (22,23). Limited neonatal pharmacokinetic (PK) and pharmacodynamic (PD) data are available for morphine and fentanyl, but much less are available for remifentanil. A blinded randomized trial (16) showed that meperidine reduced the endocrine responses to intubation. The very limited PK or PD data that are available in the neonate show marked interindividual variability of clearance (24).

Barbiturates

A small randomized trial in term and late preterm infants (25) showed that thiopental, an anesthetic barbiturate, reduced apparent pain in newborn infants undergoing intubation compared with no premedication. However, the very prolonged elimination of thiopental in the neonate raises concern (average elimination half-life 14.9 h) (26). Methohexital, a barbiturate that is very short acting in older subjects, was associated with smooth intubating conditions and no apparent distress during intubation in an uncontrolled study (27). Currently, there appears to be no PK or PD data for the newborn.

Propofol

A recent randomized controlled trial (28) compared the use of propofol with morphine, atropine and succinylcholine for intubation of newborn infants. Intubation was faster, oxygen saturations better maintained, and recovery time shorter in the propofol group. Concern has been raised that propofol is a hypnotic agent without analgesic effect and that the combination of propofol with an analgesic such as an opioid may be required. Limited PK data show extreme variability in clearance, suggesting that methods for individualizing dosage may be required. In older subjects, propofol commonly causes hypotension (29), and prolonged or repeated use can lead to serious adverse effects; thus, further investigation of single-dose use is required before recommending its widespread use.

Midazolam

Nonanalgesic sedatives, by definition, do not reduce pain and, thus, their use alone for intubation is inappropriate. Midazolam appears to be the most commonly used medication in this category (30). It has not been shown to reduce any physiological changes of intubation and has been associated with serious adverse effects during intubation (31). It causes hypotension (31-35), decreased cardiac output (32) and decreased cerebral blood flow velocity (31,34), has variable kinetics with a half-life that can exceed 22 h (36,37) and, when used as a prolonged infusion, has been associated with an increase in adverse neurological outcomes (38). Midazolam should not be used for intubation purposes in the newborn (29,39).

WHAT ARE THE COMPLICATIONS OF PREMEDICATING AN INFANT FOR INTUBATION?

The risk of complications is one reason frequently given for not using premedications (40). None of the randomized controlled trials, however, have demonstrated serious complications from premedication given before intubation. A multicentre observational study in France (30) showed no increase in the frequency of complications when infants were premedicated. The use of potent short-acting opiates is occasionally followed by increased muscle tone including increased tone in the chest wall musculature. This result appears to be relatively infrequent if the medication is given slowly (41), and can be treated by administering a muscle relaxant or opioid antagonist.

Infants are now frequently intubated for the purpose of administering surfactant, with a plan to extubate as soon as they have responded adequately. In such a circumstance, one priority for a premedication regimen should be to avoid prolonged adverse respiratory effects. Although fentanyl has a prolonged serum half-life in the newborn, averaging 10 h or more, it causes only short-lasting respiratory depression, and infants can be safely extubated less than 1 h after its administration. One potential advantage of ultrashort-acting agents such as remifentanil is a very short serum half-life of only a few minutes and, thus, there is less concern about potential residual effects. Future premedication research should examine the effects of the regimen on extubation success.

UNDER WHAT CLINICAL CIRCUMSTANCES IS IT ACCEPTABLE TO INTUBATE AN INFANT WITHOUT THE USE OF PREMEDICATION?

If the risks of the medications exceed the risks to the infant of being intubated without premedication, it would be acceptable to proceed without premedication. This may occur during resuscitation, either in the delivery room, or during acute deterioration or critical illness after the delivery room but during the neonatal period or the neonatal intensive care unit stay. While establishing an airway, procuring adequate ventilation and ensuring a good heart rate, administration of premedication would be inappropriate. However, an infant successfully resuscitated by face mask, who requires intubation because of an ongoing need for respiratory support, should receive premedication as soon as appropriate vascular access has been established, which could be by peripheral intravenous (IV) access, central access or the umbilical vein.

Infants with extremely difficult vascular access, in whom multiple IV attempts with consequent discomfort are likely, could be considered for an alternative route of medication administration. Alternatives include via the nasal mucosa (eg, fentanyl is effective by this route) or by inhalation (such as with nitrous oxide [42] or sevoflurane [43]); rarely, awake intubation can be considered. Infants with severely abnormal airways who are likely to be difficult to intubate and need to breath on their own should not receive premedication. Bronchoscopic intubation (44) or use of a laryngeal mask airway (45) may be necessary; if the centre does not have experience with these techniques, transfer to an experienced centre, using bag and mask ventilation as backup, should be considered.

WHICH PREMEDICATIONS HAVE BEEN STUDIED?

See Table 1 for a summary of the premedications that have been studied.

WHAT ARE THE CHARACTERISTICS OF AN ACCEPTABLE PROTOCOL FOR PREMEDICATION?

From the above review, it appears that given the current level of knowledge, the optimal protocol is to administer a vagolytic, an analgesic and a muscle relaxant. Further research of hypnotic/anesthetic agents such as propofol will be required before recommending their use.

Vagolytic

Glycopyrrolate and atropine are both effective and have not been directly compared. Dose requirements of glycopyrrolate in small preterm infants are not known (46). Atropine has not been associated with significant adverse effects when given once in the correct dosage. It should be noted that there is no minimum total dose – 10 µg/kg to 20 µg/kg is effective and safe.

Analgesia

The optimal analgesic for intubation would have a very rapid onset, no effect on respiratory mechanics, a short duration of action with good sedation, and reliable kinetics. None of the currently available agents fit this profile. Fentanyl, the most widely used analgesic agent, blunts physiological disturbance during intubation in adults and older children, and has a good safety profile. No randomized trials of fentanyl as a premedication for intubation compared with other agents are available. Chest wall rigidity is a rare phenomenon at the doses usually given. It can be reversed with naloxone or the immediate administration of a rapid-acting muscle relaxant, or perhaps prevented by coadministration of the relaxant. Fentanyl may reduce respiratory drive; therefore, the team must be ready to maintain an open airway and support the respiration of the infant whenever the drug is given.

According to a number of studies (1,4), morphine is the most commonly used drug for intubation; however, it does not improve physiological stability during intubation when used alone. This may well be because at least 10 min are required for good analgesia after IV administration, suggesting it may not be the optimal drug for analgesia before intubation. The very rapid onset and short duration of action of remifentanil is attractive; it should be further investigated in the newborn. Methohexital and thiopental have only been studied in larger preterm and term infants, but warrant further investigation.

Muscle relaxation

The optimal muscle relaxant for intubation would have a rapid onset, short duration of action and few side effects. Succinylcholine has been most widely used, but has rare serious side effects and causes an increase in blood pressure after use, simultaneously with the depolarization. Hyperkalemia may occur, but major elevations are uncommon and usually seen in association with significant tissue injury (47). Succinylcholine may trigger malignant hyperthermia, a rare autosomal dominant disorder of skeletal muscle that remains asymptomatic unless triggering substances are given. Succinylcholine should not be used in infants with hyperkalemia or a family history of malignant hyperthermia.

Of the nondepolarizing agents, mivacurium most closely fits the ideal profile. The duration of action of approximately 8 min to 12 min is reasonable for allowing tube fixation after intubation, and will allow rapid weaning and extubation if the infant was intubated for a brief procedure such as surfactant administration. However, mivacurium is not currently available in North America and alternative agents (eg, cisatracurium) should be investigated. Rocuronium has been investigated and has the advantage of a rapid onset of action, but for most purposes, the duration of muscle relaxation (of up to 1 h) is too long and would not be appropriate.

If the decision is made to intubate using a potent opiate but without muscle relaxation, we recommend that a muscle relaxant be drawn up in the correct dosage and be available for use in case of chest wall rigidity. For this purpose, succinylcholine, which has the most rapid onset of action, would be appropriate.

OTHER ASPECTS OF ENDOTRACHEAL INTUBATION

Endotracheal intubation is a stressful and potentially dangerous procedure that requires careful monitoring, excellent technique and every effort made to reduce its hazards, in addition to consideration of premedication. Preoxygenation to reduce hypoxia, limiting the duration of attempts to a reasonable maximum duration (such as 30 s), careful observation and monitoring during the procedure (in particular with pulse oximetry), and confirmation of appropriate tube placement with exhaled carbon dioxide detection are required. The procedure should be performed or supervised by individuals with adequate training and experience.

TABLE 1
Premedication for neonatal endotracheal intubation – published studies

Drug	Advantages	Disadvantages	Evidence			
			Type of study	n	Subjects	Findings
Vagal blockade						
Atropine	Dose requirements known	Potential for CNS complications in overdose	RCT; atropine vs no therapy (12)	30	Term and preterm newborns	Prevention of bradycardia compared with no therapy
Glycopyrrolate	Does not cross the blood-brain barrier	Uncertain dose requirements in the very preterm infant	RCT; given to both groups (16)	20	Term and preterm newborns	No bradycardia
Analgesia/anesthesia						
Fentanyl	Potent opiate; PK data available (43) Good analgesic effect	Dose requirements for intubation unknown in the newborn, rare occurrence of chest wall rigidity (44), unpredictable sedative effect (45)	Cohort study (40) Used in both arms of numerous small RCTs	253	Term and preterm newborns	Showed safety of a protocol including fentanyl and succinylcholine
Alfentanil	Potent opiate	Dose requirements and kinetics unknown	RCT; in combination with succinylcholine vs meperidine without muscle relaxant (20)	20	Term and preterm newborns	Shorter intubation and reduced duration of hypoxia with alfentanil/succinylcholine
Morphine	Opiate; PK data available Sedative effect	Dose requirements unknown for this purpose, delayed onset of action limits efficacy for this purpose	RCT; morphine vs no premedication (21)	60	Term and preterm newborns	No effect on severity of physiological disturbance during intubation
			RCT; in combination with succinylcholine and atropine (17) vs nothing	20	Term and preterm newborns	Reduced time to intubate, (60 s vs 590 s), fewer attempts and less bradycardia
Meperidine	Opiate with sedative effect	Causes nausea in older patients	RCT; meperidine vs alfentanil and succinylcholine (16)	20	Term and preterm newborns	More hypoxia than comparison group
Remifentanil	Potent opiate Rapid acting, very rapid clearance and short duration of action, provides good levels of anesthesia	May cause chest wall rigidity, hemodynamic effects uncertain in the newborn, limited PK data in the newborn	RCT; remifentanil vs morphine (48)	20	Preterm newborns	Improved intubating conditions with remifentanil
			Cohort study (49)	21	Preterm newborns 29 to 32 wks' gestation	Good intubation conditions, rapid extubation
			RCT; remifentanil vs fentanyl plus succinylcholine (23)	30	Term and preterm newborns	Similar intubation conditions and complications, longer intubations and more chest wall rigidity with remifentanil alone, not statistically significant
Methohexital	Barbiturate analogue Rapid acting, provides good levels of sedation	Unfamiliar to many neonatologists, no PK data	Cohort study (27)	18	Newborns >32 wks' gestation	Good sedation and intubating conditions
Propofol	Very rapid acting, provides good levels of anesthesia	May cause hypotension, toxicity unknown in the newborn, little data on PK but reduced clearance in the newborn	Cohort study (50)	100	Newborns and infants 2.1 kg to 9.2 kg under halothane anesthesia	Short intubation time, excellent intubating conditions
			RCT; propofol vs morphine, succinylcholine and atropine (28)	63	Term and preterm newborns	Shorter intubation and less hypoxia with propofol
Thiopental	Rapid-acting anesthetic agent	Causes hypotension in older children, prolonged and extremely variable clearance	RCT (25); thiopental vs no therapy	30	Newborn infants >2 kg	Blunts hypertensive response
Muscle relaxation						
Pancuronium	Nondepolarizing agent, few side effects	Prolonged duration	RCT; atropine alone vs atropine plus pancuronium vs no therapy (12)	30	Term and preterm newborns	Smaller increase in intracranial pressure and less hypoxia during intubation
Succinylcholine	Rapid acting, short duration of action	Depolarizing agent, rare serious complications, malignant hyperthermia, hyperkalemia, rhabdomyolysis	4 RCTs (1 only partly randomized) (13,16-18)	81	Term and preterm newborns	Reduces intracranial pressure increase, shortens duration of the procedure, reduces number of attempts, reduces trauma
Mivacurium	Nondepolarizing agent, few side effects, brief duration of action		Cohort study of use in combination with fentanyl and atropine (51)	34	Term and preterm newborns	Rapid onset (1–3 min), brief duration of action (5–15 min), very stable intubation conditions
			RCT; mivacurium vs no mivacurium (all infants received fentanyl and atropine) (19)	41	Term and preterm newborns	Much shorter intubations and less hypoxemia with mivacurium
Rocuronium	Nondepolarizing agent with rapid onset	Prolonged and variable duration (up to 1 h)	RCT; rocuronium vs no relaxant (all infants received fentanyl and atropine) (48)	44	Preterm newborns	Much more likely to be intubated on first attempt compared with controls

CNS Central nervous system; PK Pharmacokinetic; RCT Randomized controlled trial; vs Versus; wks Weeks

TABLE 2
Suggested protocol for administration of premedication

Medication	Suggested dosage
Atropine	20 µg/kg intravenously
Fentanyl	3 µg/kg to 5 µg/kg intravenously (slow infusion)
Succinylcholine	2 mg/kg intravenously

None of these drugs are currently labelled for neonatal use

RECOMMENDATIONS

- Intubations should be performed (or supervised) by trained staff with knowledge about the effects of the intubation process and the medications used.

- During intubation, the infant should be monitored closely – pulse oximetry is usually the minimum monitoring required.

- All newborn infants should receive analgesic premedication for endotracheal intubation, except for emergency intubations during resuscitation or infants in whom instrumentation of the airway is likely to be extremely difficult (recommendation grade A).

- Vagolytic agents should be strongly considered; atropine at a dose of 20 µg/kg (there is no absolute minimum dose) is effective and safe if given once. 10 µg/kg may be sufficient. (recommendation grade A).

- Rapid-acting analgesic agents should be given; the current best choice is fentanyl (recommendation grade B).

- Infants should receive fentanyl by slow IV infusion (1 min appears to be adequate) and muscle relaxants should be available when fentanyl is given to a nonintubated infant. Alternatively, routine use of a muscle relaxant following fentanyl administration could be considered.

- Rapid-onset muscle relaxants should be considered. Agents of short duration will usually be preferable; succinylcholine in a dose of 2 mg/kg is currently considered to be the best choice (recommendation grade A).

- A suggested protocol is described in Table 2.

- Further research is needed to determine the most appropriate medications and sequence. Newer very rapid-acting agents with short durations of action should be further investigated. Long-term outcomes should be assessed.

REFERENCES

1. Whyte S, Birrell G, Wyllie J. Premedication before intubation in UK neonatal units. Arch Dis Child Fetal Neonatal Ed 2000;82:F38-41.
2. Vogel S, Gibbins S, Simmons B, Shah V. Premedication for endotracheal intubation (EI) in neonates: A Canadian perspective [Abstract]. Pediatric Academic Societies and American Academy of Pediatrics Joint Meeting. Boston, May 12 to 16, 2000.
3. Topulos GP, Lansing RW, Banzett RB. The experience of complete neuromuscular blockade in awake humans. J Clin Anesth 1993;5:369-74.
4. Sarkar S, Schumacher RE, Baumgart S, Donn SM. Are newborns receiving premedication before elective intubation? J Perinatol 2006;26:286-9.
5. American Academy of Pediatrics, Committee on Fetus and Newborn, Section on Surgery and Section on Anesthesiology and Pain Management; Canadian Paediatric Society, Fetus and Newborn Committee. Prevention and management of pain and stress in the neonate: An update. Paediatr Child Health 2007;12:137-8.
6. Anand KJ. Clinical importance of pain and stress in preterm neonates. Biol Neonate 1998;73:1-9.
7. Anand KJ; International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. Arch Pediatr Adolesc Med 2001;155:173-80.
8. Shah V, Ohlsson A. The effectiveness of premedication for endotracheal intubation in mechanically ventilated neonates. A systematic review. Clin Perinatol 2002;29:535-54.
9. Shribman AJ, Smith G, Achola KJ. Cardiovascular and catecholamine responses to laryngoscopy with and without tracheal intubation. Br J Anaesth 1987;59:295-9.
10. Marshall TA, Deeder R, Pai S, Berkowitz GP, Austin TL. Physiologic changes associated with endotracheal intubation in preterm infants. Crit Care Med 1984;12:501-3.
11. Friesen RH, Honda AT, Thieme RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. Anesth Analg 1987;66:874-8.
12. Kelly MA, Finer NN. Nasotracheal intubation in the neonate: Physiologic responses and effects of atropine and pancuronium. J Pediatr 1984;105:303-9.
13. Barrington KJ, Finer NN, Etches PC. Succinylcholine and atropine for premedication of the newborn infant before nasotracheal intubation: A randomized, controlled trial. Crit Care Med 1989;17:1293-6.
14. Moorthy SS, Greenspan CD, Dierdorf SR, Hillier SC. Increased cerebral and decreased femoral artery blood flow velocities during direct laryngoscopy and tracheal intubation. Anesth Analg 1994;78:1144-8.
15. Hickey PR, Retzack SM. Acute right ventricular failure after pulmonary hypertensive responses to airway instrumentation: Effect of fentanyl dose. Anesthesiology 1993;78:372-6.
16. Pokela ML, Koivisto M. Physiological changes, plasma beta-endorphin and cortisol responses to tracheal intubation in neonates. Acta Paediatr 1994;83:151-6.
17. Oei J, Hari R, Butha T, Lui K. Facilitation of neonatal nasotracheal intubation with premedication: A randomized controlled trial. J Paediatr Child Health 2002;38:146-50.
18. Cook-Sather SD, Tulloch HV, Cnaan A, et al. A comparison of awake versus paralyzed tracheal intubation for infants with pyloric stenosis. Anesth Analg 1998;86:945-51.
19. Roberts KD, Leone TA, Edwards WH, Rich WD, Finer NN. Premedication for nonemergent neonatal intubations: A randomized, controlled trial comparing atropine and fentanyl to atropine, fentanyl, and mivacurium. Pediatrics 2006;118:1583-91.
20. Feltman DM, Weiss MG, Nicoski P, Sinacore J. Does premedication with rocuronium facilitate successful endotracheal intubation in premature infants [Abstract]. Pediatric Academic Societies Annual Meeting. Toronto, May 5 to 8, 2007.
21. Lemyre B, Doucette J, Kalyn A, Gray S, Marrin ML. Morphine for elective endotracheal intubation in neonates: A randomized trial. BMC Pediatr 2004;4:20.
22. Davis PJ, Galinkin J, McGowan FX, et al. A randomized multicenter study of remifentanil compared with halothane in neonates and infants undergoing pyloromyotomy. I. Emergence and recovery profiles. Anesth Analg 2001;93:1380-6.
23. Choong K, AlFaleh K, Doucette J, et al. Remifentanil for endotracheal intubation in neonates: A randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2010;95:F80-F84.
24. Pokela ML, Olkkola KT, Koivisto M, Ryhänen P. Pharmacokinetics and pharmacodynamics of intravenous meperidine in neonates and infants. Clin Pharmacol Ther 1992;52:342-9.
25. Bhutada A, Sahni R, Rastogi S, Wung JT. Randomised controlled trial of thiopental for intubation in neonates. Arch Dis Child Fetal Neonatal Ed 2000;82:F34-7.
26. Bach V, Carl P, Ravlo O, et al. A randomized comparison between midazolam and thiopental for elective cesarean section anesthesia: III. Placental transfer and elimination in neonates. Anesth Analg 1989;68:238-42.
27. Naulaers G, Deloof E, Vanhole C, Kola E, Devlieger H. Use of methohexital for elective intubation in neonates. Arch Dis Child Fetal Neonatal Ed 1997;77:F61-4.
28. Ghanta S, Abdel-Latif ME, Lui K, Ravindranathan H, Awad J, Oei J. Propofol compared with the morphine, atropine, and suxamethonium regimen as induction agents for neonatal

endotracheal intubation: A randomized, controlled trial. Pediatrics 2007;119:e1248-55.

29. Vardi A, Salem Y, Padeh S, Paret G, Barzilay Z. Is propofol safe for procedural sedation in children? A prospective evaluation of propofol versus ketamine in pediatric critical care. Crit Care Med 2002;30:1231-6.

30. Simon L, Trifa M, Mokhtari M, Hamza J, Treluyer JM. Premedication for tracheal intubation: A prospective survey in 75 neonatal and pediatric intensive care units. Crit Care Med 2004;32:565-8.

31. Harte GJ, Gray PH, Lee TC, Steer PA, Charles BG. Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates. J Paediatr Child Health 1997;33:335-8.

32. Shekerdemian L, Bush A, Redington A. Cardiovascular effects of intravenous midazolam after open heart surgery. Arch Dis Child 1997;76:57-61.

33. Jacqz-Aigrain E, Daoud P, Burtin R, Desplanques L, Beaufils F. Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. Lancet 1994;344:646-50.

34. van Straaten HL, Rademaker CM, de Vries LS. Comparison of the effect of midazolam or vecuronium on blood pressure and cerebral blood flow velocity in the premature newborn. Dev Pharmacol Ther 1992;19:191-5.

35. McCarver-May DG, Kang J, Aouthmany M, et al. Comparison of chloral hydrate and midazolam for sedation of neonates for neuroimaging studies. J Pediatr 1996;128:573-6.

36. Lee TC, Charles BG, Harte GJ, Gray PH, Steer PA, Flenady VJ. Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: Midazolam neonatal pharmacokinetics. Anesthesiology 1999;90:451-7.

37. Jacqz-Aigrain E, Daoud P, Burtin P, Maherzi S, Beaufils F. Pharmacokinetics of midazolam during continuous infusion in critically ill neonates. Eur J Clin Pharmacol 1992;42:329-32.

38. Anand KJ, Barton BA, McIntosh N, et al. Analgesia and sedation in preterm neonates who require ventilatory support: Results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. Arch Pediatr Adolesc Med 1999;153:331-8.

39. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Cochrane Database Syst Rev 2003;(1):CD002052.

40. Ziegler JW, Todres ID. Intubation of newborns. Am J Dis Child 1992;146:147-9.

41. Barrington KJ, Byrne PJ. Premedication for neonatal intubation. Am J Perinatol 1998;15:213-6.

42. Milesi C, Pidoux O, Sabatier E, Badr M, Cambonie G, Picaud JC. Nitrous oxide analgesia for intubating preterm neonates: A pilot study. Acta Paediatr 2006;95:1104-8.

43. Hassid S, Nicaise C, Michel F, et al. Randomized controlled trial of sevoflurane for intubation in neonates. Pediatric Anesth 2007;17:1053-8.

44. Scheller JG, Schulman SR. Fiber-optic bronchoscopic guidance for intubating a neonate with Pierre-Robin syndrome. J Clin Anesth 1991;3:45-7.

45. Paterson SJ, Byrne PJ, Molesky MG, Seal RF, Finucane BT. Neonatal resuscitation using the laryngeal mask airway. Anesthesiology 1994;80:1248-53.

46. Rautakorpi P, Manner T, Kanto J. A survey of current usage of anticholinergic drugs in paediatric anaesthesia in Finland. Acta Anaesthesiol Scand 1999;43:1057-9.

47. Motoyama EK, Davis PJ. Smith's Anesthesia for Infants and Children, 7th edn. Philadelphia: Mosby/Elsevier, 2006.

48. Pereira e Silva Y, Gomez RS, de Oliveira Marcatto J, Maximo TA, Barbosa RF, Simões e Silva AC. Morphine versus remifentanil for intubating preterm neonates. Arch Dis Child Fetal Neonatal Ed 2007;92:F293-4.

49. Welzing L, Kribs A, Huenseler C, Eifinger F, Mehler K, Roth B. Remifentanil for INSURE in preterm infants: A pilot study for evaluation of efficacy and safety aspects. Acta Paediatr 2009;98:1416-20.

50. Schippel P, Wild L, Burkhardt U, Olthoff D. [Propofol for intubation of infants after halothane induction.] Anaesthesist 1999;48:317-24.

51. Dempsey EM, Al Hazzani F, Faucher D, Barrington KJ. Facilitation of neonatal endotracheal intubation with mivacurium and fentanyl in the neonatal intensive care unit. Arch Dis Child Fetal Neonatal Ed 2006;91:F279-82.

FETUS AND NEWBORN COMMITTEE

Members: *Drs Robert I Hilliard, The Hospital for Sick Children, Toronto, Ontario (Board Representative); Ann L Jefferies, Mount Sinai Hospital, Toronto, Ontario (Chair); Abraham Peliowski-Davidovich, Royal Alexandra Hospital, Edmonton, Alberta; S Todd Sorokan, New Westminster, British Columbia; Hilary EA Whyte, The Hospital for Sick Children, Toronto, Ontario; Robin K Whyte, IWK Health Centre, Halifax, Nova Scotia*

Liaisons: *Dr Michael S Dunn, Sunnybrook Health Sciences Centre, Toronto, Ontario (Canadian Paediatric Society, Neonatal-Perinatal Medicine Section); Ms Sandra Dunn, Children's Hospital of Eastern Ontario, Ottawa, Ontario (Canadian Perinatal Programs Coalition); Drs Andrée Gagnon, Blainville, Quebec (College of Family Physicians of Canada); Robert Gagnon, Royal Victoria Hospital, Montreal, Quebec (Society of Obstetricians and Gynaecologists of Canada); Catherine M McCourt, Public Health Agency of Canada, Ottawa, Ontario (Health Canada); Ms Patricia A O'Flaherty, Children's Hospital of Eastern Ontario, Ottawa, Ontario (Canadian Association of Neonatal Nurses); Dr Lu-Ann Papile, Texas Children's Hospital, Houston, Texas (American Academy of Pediatrics, Committee on Fetus and Newborn)*

Consultants: *Drs Keith James Barrington, Sainte Justine UHC, Montreal, Quebec; Haresh M Kirpalani, McMaster Children's Hospital, Hamilton, Ontario*

Principal author: *Dr Keith James Barrington, Montreal, Quebec*