National Institute for Health and Care Excellence

Specialist neonatal respiratory care for babies born preterm

[E] Evidence reviews for sedation and analgesia

NICE guideline <TBC at publication>

Evidence reviews

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Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

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Contents

Sedation and analgesia

This evidence report contains information on 2 reviews relating to sedation and analgesia.

- Review question 5.1 What is the effectiveness of morphine during respiratory support?
- Review question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

Review question 5.1 What is the effectiveness of morphine during respiratory support?

Introduction

Preterm babies can experience pain and, due to the high level of support that may be required (such as the use of invasive ventilation), may experience significant discomfort or pain. This may have adverse consequences on their well-being and recovery. Pharmacological and non-pharmacological pain management strategies may be employed but there is currently variation in practice. This review aims to explore the effectiveness of morphine (the most commonly used opioid) during respiratory support and to determine if morphine improves outcomes in babies requiring respiratory support compared to no intervention, non-pharmacological interventions, other opioids, non-opioid analgesics and sedatives.

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Preterm babies requiring respiratory support **Exclusions:** • Preterm babies with any congenital abnormalities except patent ductus arteriosus • Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, necrotising enterocolitis, neurological disorders.
Intervention	Morphine
Comparison	• **Control** ○ Placebo/no intervention • **Other non-opioid analgesics** ○ Paracetamol • **Other opioids** ○ Fentanyl • **Sedatives** ○ Midazolam • **Non-pharmacological interventions** ○ Sucrose (EBM, non-nutritive sucking) ○ Postural support ○ Positioning aids ○ Swaddling ○ Containment holding ○ Skin to skin contact • **Comparisons** ○ Morphine versus each comparator listed, inter-group comparisons will not be considered
Outcomes	**Critical outcomes:** • Mortality prior to discharge

	• Severe IVH (grade 3 or 4) • Pain and comfort scores **Important outcomes:** • Unplanned or accidental extubation • Days to achieve full enteral feeding • Hypotension which requires intervention • Parental satisfaction

RCT: randomised controlled trial; EBM, expressed breast milk; IVH: intraventricular haemorrhage

For full details see the review protocol in appendix A.

Clinical evidence

Included studies

Eight RCTs were identified (Anand 1999; Anand 2004; Carbajal 2005; Cignacco 2008; Dyke 1999; Quinn 1993; Saarenmaa 1999; Simons 2003). One publication (Menon 2008 [Anand 2004]) that reported additional outcomes from the Anand 2004 trial data was also included. .

Seven RCTs compared morphine to placebo (Anand 2004; Carbajal 2005; Cignacco 2008; Dyke 1995; Menon 2008 [Anand 2004]; Quinn 1993; Simons 2003).

One RCT compared morphine to fentanyl (Saarenmaa 1999).

One 3-armed RCT compared morphine to placebo and midazolam (Anand 1999).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies.

Table 2: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
RCTs and follow-up publications				
Anand 2004 France, Sweden, United Kingdom, United States	N= 898 Preterm infants born at 23-32 weeks gestation who were intubated within 72 hrs of birth and had been ventilated < 8 hrs at enrolment	Loading dose of morphine (100 µg/kg infused over 1 hr), followed by continuous infusions of 10 µg/kg/hr for those of gestational age 23–26 weeks, 20 µg/kg/hr for those of 27–29 weeks' gestation, or 30 µg/kg/hr for those of 30–32 weeks' gestation vs	• Mortality prior to discharge • Severe IVH (Grade 3 or 4) • Days to full enteral feeding*	1 follow up study: Menon 2008*

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
		placebo (type of placebo infusion not specified) Infants in both arms could receive open-label morphine after the start of the study if the attending nurse or physician deemed the infant to be in pain		
Anand 1999 Menon 2008 Canada, Germany, United Kingdom and United States	N= 67 Preterm infants born at 24-32 weeks gestation who were intubated and required ventilatory support for < 8hr at the time of enrolment	Morphine sulphate (0.05 mg/mL in 10% dextrose) infusions vs midazolam hydrochloride (0.1/mg/mL in 10% dextrose) infusions or placebo (10% dextrose) infusions Infants in both arms could receive open-label morphine after the start of the study if the attending nurse or physician deemed the infant to be in pain	• Mortality prior to discharge • Severe IVH (Grade 3 or 4) • Pain and comfort scores (COMFORT scale and PIPP scale) • Days to full enteral feeding	
Carbajal 2005 France	N= 42 Preterm infants born at 23-32 weeks gestation who were intubated within 72hr of birth and had been ventilated < 8hr at enrolment	Morphine loading dose of 100 µg/kg, followed by infusions of 10–30 µg/kg per hour according to gestation vs placebo (5% dextrose infusions)	• Pain and comfort scores (DAN scale, PIPP scale)	
Cignacco 2008 Switzerland	N= 30 Preterm neonates born at 24-37 weeks	Dose of 0.1 mg/kg of morphine administered before ETS vs placebo (type of	• Mortality prior to discharge • Pain and comfort scores (BPSN scale, PIPP scale)	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	postmenstrual age who were intubated and invasively ventilated	placebo infusion not specified) Infants in both arms could receive open-label morphine after the start of the study if the attending nurse or physician deemed the infant to be in pain		
Dyke 1995 Australia	N= 26 Preterm infants born between 29-36 weeks gestation who required intermittent mandatory ventilation	Loading dose of morphine 100 µg/kg over 30 min followed by a continuous intravenous infusion at 10 µg/kg per hour was given vs placebo (5% dextrose infusion)	• Mortality prior to discharge	
Quinn 1993 United Kingdom	N= 41 Preterm infants born at a gestational age of < 34 weeks and who required invasive ventilation as well as who received Curosurf for respiratory distress syndrome	Loading infusion of 100 µg/kg per hr for 2 hr followed by 25 µg/kg per hr as a continuous infusion of morphine vs placebo (5% dextrose infusion)	• Mortality prior to discharge • IVH (Grade not specified)	
Saarenmaa 1999 Finland	N= 163 Preterm infants born at a gestational age > 24 weeks who were on invasive ventilation at least 1 day and had an indwelling arterial line and no chromosomal aberrations or	Loading dose of 10.5 µg/kg fentanyl or 140 µg/kg morphine in 1 hour. Infusion was continued at a maintenance rate of 1.5 µg/kg/hr fentanyl or 20 µg/kg/hr morphine for at least 24 hours	• Mortality prior to discharge • Severe IVH (Grade 3 or 4) • Days to full enteral feeding	

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	major anomalies			
Simons 2003 The Netherlands	N= 150 Neonates whose postnatal age was < 3 days admitted to the NICU who required invasive ventilation, were on artificial ventilation < 8 hours at the start of the study and who had an indwelling arterial catheter	Loading dose (100µg/kg) of morphine hydrochloride followed by a continuous infusion (10µg/kg per hour) vs placebo (sodium chloride dissolved in 5% glucose infusion) Infants in both arms could receive open-label morphine after the start of the study if the attending nurse or physician deemed the infant to be in pain	• Mortality prior to discharge • Severe IVH (Grade 3 or 4) • Pain and comfort scores (NIPS scale)	

BPSN: Bernese Pain Scale for Neonates; COMFORT scale: developed by Ambuel et al (1992), it is a non-intrusive method of assessing distress in mechanically ventilated patients in NICUs; DAN: Douleur Aiguë Nouveau-Né; ETS: endotracheal suctioning; hr, hour; IVH: intraventricular haemorrhage; NICU: neonatal intensive care unit; NIPS: Neonatal Infant Pain Scale; PIPP: Premature Infant Pain Profile; vs, versus

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

No economic evidence on the cost effectiveness of morphine during respiratory support was identified by the literature searches of the economic literature undertaken for this guideline.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Clinical evidence statements

Comparison 1. Morphine versus placebo

Critical Outcomes

Mortality prior to discharge

All babies

- Very low quality evidence from 5 RCTs (n=1065) showed no clinically significant difference in mortality prior to discharge among preterm babies of all gestational ages on respiratory support who received morphine compared to those who received placebo.

<u>Babies 23-26 weeks</u>

- Very low quality evidence from 1 RCT (n=350) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of 23-26 weeks on respiratory support who received morphine compared to those who received placebo.

<u>Babies 23-32 weeks</u>

- Very low quality evidence from 1 RCT (n=898) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of 23-32 weeks gestation on respiratory support who received morphine compared to those who received placebo.

<u>Babies 24-33 weeks</u>

- Very low quality evidence from 1 RCT (n=45) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of 24-33 weeks gestation on respiratory support who received morphine compared to those who received placebo.

<u>Babies 24-37 weeks</u>

- Very low quality evidence from 1 RCT (n=30) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of 24-27 weeks gestation on respiratory support who received morphine compared to those who received placebo.

<u>Babies 27-29 weeks</u>

- Very low quality evidence from 1 RCT (n=380) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of 27-29 weeks gestation on respiratory support who received morphine compared to those who received placebo.

<u>Babies 27-32 weeks</u>

- Very low quality evidence from 1 RCT (n=150) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of 32-26 weeks gestation on respiratory support who received morphine compared to those who received placebo.

<u>Babies 29-34 weeks</u>

- Very low quality evidence from 1 RCT (n=26) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of 32-26 weeks gestation on respiratory support who received morphine compared to those who received placebo.

<u>Babies 30-32 weeks</u>

- Very low quality evidence from 1 RCT (n=168) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of 32-26 weeks gestation on respiratory support who received morphine compared to those who received placebo.

Severe intraventricular haemorrhage (IVH) (Grade 3 or 4)

<u>All babies</u>

- Very low quality evidence from 4 RCTs (n=1065) showed no clinically significant difference in severe IVH (Grade 3 or 4) before discharge among preterm babies of all gestational ages on respiratory support who received morphine compared to those who received placebo.

Babies 23-26 weeks

- Very low quality evidence from 1 RCT (n=318) showed no clinically significant difference in severe IVH (Grade 3 or 4) among preterm babies with a gestational age of 23-26 weeks on respiratory support who received morphine compared to those who received placebo.

Babies 24-33 weeks

- Very low quality evidence from 1 RCT (n=45) showed no clinically significant difference in severe IVH (Grade 3 or 4) among preterm babies with a gestational age of 24-33 weeks on respiratory support who received morphine compared to those who received placebo.

Babies 24-37 weeks

- Very low quality evidence from 1 RCT (n=30) showed no clinically significant difference in severe IVH (Grade 3 or 4) among preterm babies with a gestational age of 24-37 weeks on respiratory support who received morphine compared to those who received placebo.

Babies 27-29 weeks

- Very low quality evidence from 1 RCT (n=363) showed a clinically significant decrease in severe IVH (Grade 3 or 4) among preterm babies with a gestational age of 27-29 weeks on respiratory support who received morphine compared to those who received placebo.

Babies 27-32 weeks

- Very low quality evidence from 1 RCT (n=150) showed no clinically significant difference in severe IVH (Grade 3 or 4) among preterm babies with a gestational age of 27-32 weeks on respiratory support who received morphine compared to those who received placebo.

Babies 30-32 weeks

- Very low quality evidence from 1 RCT (n=161) showed no clinically significant difference in severe IVH (Grade 3 or 4) among preterm babies with a gestational age of 30-32 weeks on respiratory support who received morphine compared to those who received placebo.

Pain and comfort scores

Change in level of sedation from baseline during endotracheal suctioning (ETS) (COMFORT scale)

During drug infusion

- Very low quality evidence from 1 RCT (n=45) showed a clinically significant increase in level of sedation from baseline during ETS during drug infusion among preterm babies with a gestational age of 24-32 weeks on respiratory support who received morphine compared to those who received placebo.

After drug infusion

- Low quality evidence from 1 RCT (n=45) showed no clinically significant difference in the change in the level of sedation during ETS after stopping drug infusion among preterm babies with a gestational age of 24-32 weeks on respiratory support who received morphine compared to those who received placebo.

Change in pain scores from baseline during ETS (PIPP scale)

During drug infusion

- Moderate quality evidence from 1 RCT (n=45) showed a clinically significant decrease in pain scores during ETS during drug infusion among preterm babies with a gestational age of 24-32 weeks on respiratory support who received morphine compared to those who received placebo.

After stopping drug infusion

- Very low quality evidence from 1 RCT (n=45) showed no clinically significant difference in the change in the level of pain during ETS after stopping drug infusion among preterm babies with a gestational age of 24-32 weeks on respiratory support who received morphine compared to those who received placebo.

<u>Pain scores as a result of ETS (NIPS scale)</u>

30 minutes after start of drug infusion

- Moderate quality evidence from 1 RCT (n=150,) showed no difference 30 minutes after the loading dose in pain scores in preterm babies who received morphine compared to placebo.

Before ETS

- Moderate quality evidence from 1 RCT (n=150) showed no difference before ETS in pain scores in preterm babies who received morphine arm compared to placebo.

During ETS

- Moderate quality evidence from 1 RCT (n=150, low risk of bias) showed no difference during ETS in pain scores in preterm babies who received morphine compared to placebo.

30 minutes after ETS

- Moderate quality evidence from 1 RCT (n=150) showed no difference 30 minutes after ETS in pain scores in preterm babies who received morphine compared to placebo.

<u>Change in pain scores from baseline during ETS (BPSN scale)</u>

After administering analgesia, 5 min before ETS

- Low quality evidence from 1 RCT (n=30) showed a clinically significant increase in pain scores from baseline among preterm babies with a gestational age of 24-37 weeks on respiratory support who received morphine compared to those who received placebo.

During ETS

- Very low quality evidence from 1 RCT (n=30) showed no clinically significant difference in the change in pain scores from baseline among preterm babies with a gestational age of 24-37 weeks on respiratory support who received morphine compared to those who received placebo.

<u>Change in pain scores from baseline during heel stick (DAN scale)</u>

Pain score from heel stick 2-3 hours after loading dose

- Low quality evidence from 1 RCT (n=42) showed no clinically significant difference in the change in pain scores from baseline among preterm babies with a gestational age of 24-32 weeks on respiratory support who received morphine compared to those who received placebo.

Pain score from heel stick 20-28 hours after loading dose

- Very low quality evidence from 1 RCT (n=42) showed no clinically significant difference in the change in pain scores from baseline among preterm babies with a gestational age of 24-32 weeks on respiratory support who received morphine compared to those who received placebo.

<u>Change in pain scores from baseline during heel stick (PIPP scale)</u>

Pain score from heel stick 2-3 hours after loading dose

- Very low quality evidence from 1 RCT (n=42) showed no clinically significant difference in the change in pain scores from baseline among preterm babies with a gestational age of 24-32 weeks on respiratory support who received morphine compared to those who received placebo.

Pain score from heel stick 20-28 hours after loading dose

- Low quality evidence from 1 RCT (n=42) showed no clinically significant difference in the change in pain scores from baseline among preterm babies with a gestational age of 24-32 weeks on respiratory support who received morphine compared to those who received placebo.

Important Outcomes

Unplanned or accidental extubation

- There was no evidence for this important outcome.

Days to achieve full enteral feeding

Infants 23-32 weeks gestation

- Low quality evidence from 1 RCT (n=898) showed a clinically significant difference between 20 (13-29) days to achieve full enteral feeding in the morphine arm and 17 (12-26) in the control arm among preterm babies on respiratory support.

Infants 24-33 weeks gestation

- Low quality evidence from 1 RCT (n=45) showed no clinically significant difference in the days to achieve full enteral feeding among preterm babies on respiratory support who received morphine compared to those who received placebo.

Hypotension which requires intervention

- There was no evidence for this important outcome.

Parental satisfaction

- There was no evidence for this important outcome.

Comparison 2. Morphine versus paracetamol

- There was no evidence for this comparison

Comparison 3. Morphine versus fentanyl

Critical Outcomes

Mortality prior to discharge

- There was no evidence for this critical outcome

Severe IVH (Grade 3 or 4)

- Low quality evidence from 1 RCT (n=163) showed no clinically significant difference in severe IVH (Grade 3 or 4) among preterm babies with a gestational age of > 24 weeks on respiratory support who received morphine compared to those who received fentanyl.

Pain and comfort scores

- There was no evidence for this critical outcome

Important Outcomes

Unplanned or accidental extubation

- There was no evidence for this important outcome

Days to achieve full enteral feeding

- There was no evidence for this important outcome

Hypotension which requires intervention

- There was no evidence for this important outcome

Parental satisfaction

- There was no evidence for this important outcome

Comparison 4. Morphine versus midazolam

Critical Outcomes

Mortality prior to discharge

- Very low quality evidence from 1 RCT (n=46) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of 23-32 weeks on respiratory support who received morphine compared to those who received midazolam.

Severe IVH (Grade 3 or 4)

- Very low quality evidence from 1 RCT (n=46) showed there may be a clinically significant decrease in severe IVH (Grade 3 or 4) among preterm babies with a gestational age of 23-32 weeks on respiratory support who received morphine compared to those who received midazolam, but there is uncertainty around the estimate.

Pain and comfort scores

Change in level of sedation during ETS (COMFORT scale)

During drug infusion

- Low quality evidence from 1 RCT (n=46) showed no clinically significant difference in the level of sedation during ETS during drug infusion among preterm babies with a gestational age of 23-32 weeks on respiratory support who received morphine compared to those who received midazolam.

After stopping drug infusion

- Low quality evidence from 1 RCT (n=46) showed there may be a clinically significant decrease in the level of sedation during ETS after stopping drug infusion among preterm babies with a gestational age of 23-32 weeks on respiratory support who received morphine compared to those who received midazolam, but there is uncertainty around this estimate.

Change in pain scores during ETS (PIPP scale)

During drug infusion

- Low quality evidence from 1 RCT (n=46) showed a clinically significant decrease in pain scores during ETS during drug infusion among preterm babies with a gestational age of 23-32 weeks on respiratory support who received morphine compared to those who received midazolam.

After stopping drug infusion

- Low quality evidence from 1 RCT (n=46) showed no clinically significant difference in the level of pain during ETS after drug infusion among preterm babies with a gestational age of 23-32 weeks on respiratory support who received morphine compared to those who received midazolam.

Important Outcomes

Unplanned or accidental extubation

- There was no evidence for this important outcome

Days to achieve full enteral feeding

- Low quality evidence from 1 RCT (n=46) showed no clinically significant difference in the days to achieve full enteral feeding among preterm babies with a gestational age of 23-32 weeks on respiratory support who received morphine compared to those who received midazolam.

Hypotension which requires intervention

- There was no evidence for this important outcome

Parental satisfaction

- There was no evidence for this important outcome

Comparison 5: Morphine versus non-pharmacological interventions

- There was no evidence for this comparison

See appendix E for Forest plots.

Economic evidence statements

- No economic evidence on the cost effectiveness of morphine during respiratory support was available.

Recommendations

E1.1 Do not routinely use morphine for preterm babies on respiratory support.

E1.2 Consider morphine[a] if the baby is in pain, using a validated pain score.

E1.3 Reassess babies on morphine regularly to ensure that morphine is stopped as soon as possible.

Research recommendations

What is the effectiveness of morphine compared with containment holding for preterm babies receiving respiratory support?

a Although this is common in UK clinical practice, at the time of consultation (October 2018), morphine did not have a UK marketing authorisation for children under 12 years (intravenous administration) or under 1 year (oral administration). The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Rationale and impact

Why the committee made the recommendations

The evidence showed that there was no difference in mortality prior to discharge in babies who received morphine compared to placebo. Babies receiving morphine took longer to achieve full enteral feeding, and babies born at 27–29 weeks' gestation had an increased risk of severe intraventricular haemorrhage (IVH). There was some evidence that, when compared with placebo, morphine improves sedation and pain scores in preterm babies who need invasive respiratory support during infusion. However, moderate quality evidence from a larger study showed no difference in pain scores during endotracheal suctioning between babies who received morphine compared to placebo.

The only evidence available comparing morphine to fentanyl showed no clinically significant difference in rates of severe IVH.

There was some evidence that when compared with midazolam, babies receiving morphine may have decreased rates of severe IVH.

Babies receiving morphine experienced less pain during infusion, but less sedation after infusion.

Because of the mixed evidence regarding the effectiveness of morphine and taking into account the risks, the committee agreed that morphine should not be used routinely, but may be considered when it is clear the baby is in pain (using a validated pain score).

The committee discussed other concerns about using morphine, such as suppressed respiratory drive and opioid dependency. They agreed that regular reassessments are important to ensure that morphine is stopped as soon as appropriate.

The committee did not make any recommendations for paracetamol or non-pharmacological interventions because there was no evidence available. Instead, the committee recommended that further research be done to compare morphine with containment holding during respiratory support, because the committee agreed that containment holding may improve outcomes in preterm babies, with a reduced risk of adverse events compared to pharmacological therapy.

Impact of the recommendations on practice

Use of sedation and analgesia currently varies among units. The recommendations will have little impact in units that do not routinely use morphine, but other units may need to change practice and this may lead to a reduction in the use of morphine. The recommendations will make practice more consistent across the NHS.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that morphine use in preterm babies on respiratory support is mainly intended to alleviate discomfort and distress, but that it might also influence critical outcomes such as the incidence of severe IVH and even overall mortality. A major concern with the use of respiratory support with preterm babies is pain and discomfort due to invasive ventilation techniques and the long-term effects of pain, thus pain and comfort scores were also considered critically important outcomes for decision making.

The committee prioritised mortality occurring prior to first discharge as being of primary importance. Incidence of severe IVH was second in importance because of its associated risk of mortality, post-haemorrhagic hydrocephalus, cerebral palsy and developmental delays in preterm babies and pain and comfort scores was considered third in importance. Unplanned or accidental extubation (which may indicate discomfort or distress) was considered an important outcome. Days to achieve full enteral feeding, hypotension that requires intervention and parental satisfaction were also considered as important outcomes in decision-making and in considering the balance of benefit and harm.

The quality of the evidence

Evidence was available from 8 RCTs that compared morphine with placebo, 1 RCT that compared morphine and midazolam and 1 RCT that compared morphine with fentanyl that only reported one relevant outcome. No evidence was found comparing morphine to paracetamol or non-pharmacological interventions. Additionally, no evidence was found for outcomes pertaining to unplanned or accidental extubation, hypotension requiring intervention, or parental satisfaction. The quality of the evidence in this review ranged from moderate to very low although the majority for all comparisons and outcomes was of low and very low quality.

The quality of evidence was most often downgraded because of the uncertainty around the risk estimate, heterogeneity in the population and methodological limitations affecting the risk of bias.

Uncertainty around the risk estimate was generally attributable to low event rates and small sample sizes.

Considerable heterogeneity was observed in the studies assessing pain and comfort scores, which may be attributed to the subjectivity of the outcome and variation in validated pain scales used. In view of this, studies were not meta-analysed, but rather assessed individually. Furthermore, approximately half of the studies did not report the number of days on ventilation as means, but rather as medians so imprecision could not be assessed for these studies.

Methodological limitations affecting the risk of bias were generally attributed to the majority of the trials giving open-label morphine to preterm babies in both arms and several of the trials containing less than 15 participants in 1 or both of the arms.

Benefits and harms

Evidence regarding the efficacy of morphine compared to placebo in reducing pain and achieving sedation was limited, with inconsistency between study findings in babies undergoing potentially uncomfortable or painful procedures such as endotracheal suction and heel prick blood sampling. No evidence was found indicating that sedation or improved pain scores were achieved with morphine in those on respiratory support in other contexts. There was no difference in mortality rate between those given morphine compared with placebo. There was no evidence of overall difference in the risk of severe IVH with morphine versus placebo, but the guideline committee did note that in a subgroup analysis, there was low quality evidence suggesting a significantly higher rate of severe IVH in babies born between 27-29 weeks gestation. They also noted that there was a small (3 day) but statistically significant difference in the time to achieving full enteral feed in one study with a high risk of bias, those receiving morphine taking longer than a control group. Additionally, the committee were aware of side effects of morphine from their clinical knowledge, which include reduced gut motility, suppression of respiratory drive and dependency. Althought the evidence was of low quality, the committee felt that the balance of benefit versus harms was strong enough for them to make a recommendation to not use morphine.

The committee agreed that adverse effects associated with morphine could outweigh the benefits if it was used without evidence of pain. The committee discussed the potential consequences of under-treatment with morphine in preterm babies, but agreed that over-treatment would be more likely to lead to harms. However, the committee agreed that a recommendation to consider using morphine in preterm babies in whom pain had been identified would allow it to be used if required. However, as the committee agreed that even in this situation the harms may outweigh the benefits they made a recommendation to reassess its use regularly and minimise as far as possible.

The committee did not recommend the use of the synthetic opioid fentanyl because there was no evidence to suggest any advantage compared with morphine. Low quality evidence from 1 RCT did not find a difference in incidence of severe IVH with fentanyl compared to morphine. The committee were also aware of its greater potency, shorter duration of action but that it may cause chest wall rigidity in a small number of cases.

There was insufficient evidence regarding paracetamol or non-pharmacological methods to make any recommendations. However the committee did not feel this was a priority to recommend for further research.

The committee believed that non-pharmacological interventions, such as containment holding, non-nutritive sucking and skin to skin contact may be useful and are likely to have fewer associated harms, but given the lack of evidence to support their use, they prioritised containment holding and made a research recommendation for a RCT to assess the effectiveness of morphine compared with containment holding for preterm babies on respiratory support.

Cost effectiveness and resource use

There was no economic evidence on the cost effectiveness of morphine during respiratory support.

The committee discussed the potential costs and benefits associated with morphine. The committee noted that despite its low acquisition cost morphine may increase the risk of severe IVH in preterm babies born at 27-29 weeks gestation. The committee explained that all babies that survive severe IVH are expected to suffer long-term consequences including cerebral palsy and neurodevelopmental problems that may require expensive long-term care. The committee also noted a number of other side effects of morphine including reduced gut motility, suppression of respiratory drive and dependency that may potentially prolong the hospital stay and incur additional costs to the NHS.

Overall, the committee was of a view that morphine should be used only in cases where there is a clear evidence of pain and that babies on morphine should be reassessed regularly. The committee noted that regular reassessments would not incur significant extra resource implications to the healthcare system since these babies are already very closely monitored.

Due to a lack of clinical evidence the committee could not draw conclusions pertaining to the cost effectiveness of other treatment options used to manage pain in babies receiving respiratory support.

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Review question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

Introduction

Intubation is a potentially painful and distressing procedure. It has been suggested that the physiological distress caused by awake intubation may increase neonatal morbidity. However, while premedication for intubation with opioids or anaesthetic agents and muscle relaxants is routinely used for children and infants, it is not a common practice in babies. This review aims to explore the effectiveness of using premedication and to determine if there is an optimal premedication regimen for intubation in preterm babies.

Summary of the protocol

See Table 3 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review

Table 3: Summary of the protocol (PICO table)

Population	Preterm babies undergoing intubation: **Exclusions:** • Preterm babies with congenital abnormalities excluding patent ductus arteriosus • Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, necrotising enterocolitis, neurological disorders, congenital heart disease
Intervention	**Anticholinergics:** • Atropine **Analgesics:** • Fentanyl • Remifentanyl • Morphine • Alfentanyl **Sedatives:** • Midazolam **Anaesthetics:** • Propofol **Neuromuscular blockers:** • Suxamethonium • Atracurium • Rocuronium
Comparison	• Any premedication versus placebo/nothing • Any premedication including neuromuscular blockers (single agent or combination of agents) versus any premedication • Any premedication including atropine (single agent or combination of agents) versus any premedication

	Comparisons will be limited to intra-class and not include inter-class comparisons.

Outcome	**Critical outcomes:**
	• Ease of intubation (e.g. number of intubation attempts, time to successful intubation, failed intubation)
	• Pain and comfort scores during intubation
	• Adverse physiological response during intubation (e.g. hypoxia, heart rate and blood pressure changes, cortisol, catecholamines)
	
	Important outcomes:
	• Neurodevelopmental outcome ≥18 months:
	  o Cerebral palsy (CP) (reported as presence or absence of condition, **not** severity of condition)
	  o Neurodevelopmental delay (reported as dichotomous outcomes, **not** continuous outcomes such as mean change in score)
	    - Severe (score of >2 SD below normal on validated assessment scales, **or** on Bayley's assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay)
	    - Moderate (score of 1-2 SD below normal on validated assessment scales, **or** on Bayley's assessment scale of MDI or PDI 70-84)
	  o Neurosensory impairment (reported as presence or absence of condition, **not** severity of condition)
	    - Severe hearing impairment (for example, deaf)
	    - Severe visual impairment (for example blind)
	• Days on ventilation
	• Adverse drug reactions (e.g. atropine-induced tachycardia and viscid respiratory and gastrointestinal secretions, neuroblocker-induced hyperkalaemia and respiratory depression)
	• Mortality prior to discharge

CP: cerebral palsy; MDI: mental development index; PDI: psychomotor developmental index; RCT: randomised controlled trial; SD: standard deviation

For full details see review protocol in appendix A

Clinical evidence

Included studies

For preterm babies on respiratory support, 6 randomised controlled trials (RCTs) were identified (Choong 2010; Durrmeyer 2018; Feltman 2011; Ghanta 2007; Lemyre 2004; Norman 2011).

One study (Lemyre 2004) compared any premedication versus placebo/nothing.

Three studies (Choong 2010; Durrmeyer 2018; Feltman 2011) compared any premedication including neuromuscular blockers (single agent or combination of agents) versus any premedication.

No studies compared any premedication including atropine (single agent or combination of agents) versus any premedication.

Two studies (Ghanta 2007; Norman 2011) compared neuromuscular blocker and atropine combinations.

See the literature search strategy in appendix B and study selection flow chart in appendix C. No meta-analyses were conducted for this review question as all the studies include different combination of drugs so there are no forest plots in appendix E.

Excluded studies

Studies not included in this review, with reasons for their exclusion, are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 4 provides a brief summary of the included studies.

Table 4: Summary of included studies

Study details	Participants	Interventions	Outcomes and Results	Comments
Choong 2010 Canada	N= 30 Preterm babies who were haemodynamically stable, had existing IV access and for whom elective endotracheal intubation was anticipated	Atropine+remifentanyl+saline vs atropine+fentanyl Intervention: drug 1, atropine (20 mcg/kg); drug 2, remifentanyl (3 mcg/kg) administered over 60 s; drug 3, normal saline placebo. Control: drug 1, atropine (20 mcg/kg); drug 2, fentanyl (2 mcg/kg administered over 60 s); drug 3, succinylcholine (2 mg/kg).	Time to successful intubation, number of intubation attempts, number intubated on first attempt Change in SpO_2, change in blood pressure, change in heart rate Adverse events (trauma, chest wall rigidity)	Open-label suxamethonium administered to some babies in the intervention arm
Durrmeyer 2018 France	N= 171 Hospitalised in the NICU, corrected PMA < 45 weeks, IV access, and required non-emergency or planned intubation	Atropine+atracurium+sufentanyl vs atropine+propofol Intervention: 15 ug/kg atropine, 0.3 mg/kg atracurium (additional doses 0.1 mg/kg), 0.1 ug/kg sufentanyl in babies < 1000 g or 0.2 ug/kg in babies > 1000 g Control: 15 ug/kg atropine, 2.5 mg/kg	Number of intubation attempts, duration of intubation, intubated on first attempt Prolonged hypoxia, change in heart rate, MABP, SPO_2, transcutaneous partial carbon dioxide Adverse events	Open-label study drugs administered to babies in each arm

Study details	Participants	Interventions	Outcomes and Results	Comments
		propofol in babies > 1000 or 1 mg/kg in babies < 1000 g		
Feltman 2011 US	N= 44 All infants < 25^{+6} weeks corrected gestational age	Atropine+fentanyl+rocuronium vs atropine+fentayl Intervention: Atropine 0.02 mg kg^{-1} followed by fentanyl 2 mg kg-1 followed by rocuronium 0.5mg kg^{-1} Control: Atropine 0.02 mg kg-1 followed by fentanyl 2 mg kg^{-1}	Success rate on first attempt	N/A
Ghanta 2007 Australia	N= 66 Newborn babies requiring elective or semi-elective intubation, sufficient time to obtain informed parental consent and had a subsequent need for semi-elective intubation	Propofol vs morphine+atropine+suxamethonium Intervention: single 2.5 mg/kg IV dose propofol to a maximum of 2 doses. Default to morphine + atropine + suxamethonium if sleep not achieved in 3 minutes or after second dose of propofol Control: morphine, 100 ug/kg; atropine, 10 ug/kg; and suxamethonium, 2 mg/kg. Two repeat doses of suxamethonium at 1 mg/kg each (maximum total dose of 4 mg/kg per intubation attempt) were administered if muscle relaxation was not achieved in 3 to 5 minutes. Repeat applications of suxamethonium up to a maximum total of 4 mg/kg were allowed	Time to successful intubation, multiple attempts to achieve successful intubation Intubation-related trauma (oropharyngeal trauma) Increase in serum lactate levels >2.2 mmol/L before and after intubation	N/A
Lemyre 2004 Canada	N= 34 Preterm babies likely to need an elective oral or nasotracheal	Morphine vs placebo Intervention: morphine 0.2 mg/kg IV given over 1 minute, followed 5 minutes later by the intubation	Number of intubation attempts, intubation achieved at first attempt, intubation needing rescue intubator, duration of procedure	N/A

Study details	Participants	Interventions	Outcomes and Results	Comments
	intubation, was less than 30 weeks gestation, was already ventilated, or was on nCPAP for respiratory distress	Control: placebo (0.9% NaCl), given over 1 minute, followed 5 minutes later by the intubation	Experienced some degree of severe hypoxemia, experienced hypoxemia, duration of severe hypoxemia, duration of hypoxemia Maximum increase in MABP from baseline, bradycardia during procedure	
Norman 2011 Sweden	N= 34 Preterm babies with a GA < 37 weeks, had no administration of analgesics or sedative drugs during the previous 24 hours	Glycopyrrolate+suxamethonium+remifentanyl vs atropine+morphine Intervention: glycopyrrolate 5 mcg/kg; thiopental 2 mg/kg < 1000g or 3 mg/kg ≥ 1000g; suxamethonium 2 mg/kg; remifentanyl 1 mcg/kg Control: atropine 0.01 mg/kg; morphine 0.3 mg/kg	Total duration of intubation procedure, number of intubation attempts needed MABP	N/A

GA: gestational age; IV: intravenous; MABP: mean arterial blood pressure; NaCl: sodium chloride (salt); nCPAP: nasal continuous positive airway pressure; NICU: neonatal intensive care unit; PMA: postmenstrual age; RCT: randomised controlled trial; SpO_2: peripheral oxygen saturation; s: seconds

See appendix D for full clinical evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

No economic evidence on the cost effectiveness of premedication regimens for intubation in preterm babies was identified by the literature searches of the economic literature undertaken for this guideline.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Clinical evidence statements

Comparison 1. Any premedication versus placebo/nothing

Critical outcomes

Ease of intubation

Number of intubation attempts

Morphine versus placebo (babies < 30 weeks)

- Moderate quality evidence from 1 RCT (n=34) showed no clinically significant difference in the number of intubation attempts among preterm babies with a gestational age of < 30 weeks who received morphine compared to those who received placebo.

Time to achieve intubation

Morphine versus placebo (babies < 30 weeks)

- Moderate quality evidence from 1 RCT (n=34) showed no clinically significant difference in the time to achieve intubation among preterm babies with a gestational age of < 30 weeks who received morphine compared to those who received placebo.

Number of intubation attempts needing rescue intubation

Morphine versus placebo

- Low quality evidence from 1 RCT (n=34) showed no clinically significant difference in the number of intubations needing rescue intubation among preterm babies with a gestational age of < 30 weeks who received morphine compared to those who received placebo.

Successfully intubated on first attempt

Morphine versus placebo (babies < 30 weeks)

- Low quality evidence from 1 RCT (n=34) showed no clinically significant difference in the number of preterm babies who were successfully intubated on the first attempt among preterm babies with a gestational age of < 30 weeks who received morphine compared to those who received placebo.

Pain and comfort scores during intubation

- No studies reported on this critical outcome

Adverse physiological response during intubation

Hypoxemia

Morphine versus placebo (babies < 30 weeks)

- Moderate quality evidence from 1 RCT (n=34) showed no clinically significant difference in the number of preterm babies developed hypoxemia during intubation among preterm babies with a gestational age of < 30 weeks who received morphine compared to those who received placebo.

Duration of hypoxemia

Morphine versus placebo (babies < 30 weeks)

- Moderate quality evidence from 1 RCT (n=34) showed a clinically significant increase in the duration of hypoxemia for preterm babies with a gestational age of < 30 weeks who received morphine compared to those who received placebo.

Severe hypoxemia

Morphine versus placebo (babies < 30 weeks)

- Low quality evidence from 1 RCT (n=34) showed no clinically significant difference in the number of preterm babies with a gestational age of < 30 weeks who developed severe hypoxemia among preterm babies who received morphine compared to those who received placebo.

<u>Duration of severe hypoxemia</u>

Morphine versus placebo (babies < 30 weeks)

- Moderate quality evidence from 1 RCT (n=34) showed no clinically significant difference in the duration of severe hypoxemia for preterm babies with a gestational age of < 30 weeks who received morphine compared to those who received placebo.

<u>Maximum increase in mean blood pressure</u>

Morphine versus placebo (babies < 30 weeks)

- Moderate quality evidence from 1 RCT (n=34) showed no clinically significant difference in maximum increase in mean blood pressure in mm Hg in preterm babies with a gestational age of < 30 weeks who received morphine compared to those who received placebo.

<u>Bradycardia</u>

Morphine versus placebo (babies < 30 weeks)

- Moderate quality evidence from 1 RCT (n=34) showed there may be a clinically significant increase in the number of preterm babies experiencing bradycardia during intubation among preterm babies with a gestational age of < 30 weeks who received morphine compared to those who received placebo, however there is uncertainty around the risk estimate.

Important outcomes

Neurodevelopmental outcomes ≥ 18 months

- No studies reported on this important outcome

Days on invasive ventilation

- No studies reported on this important outcome

Adverse drug reactions

- No studies reported on this important outcome

Mortality prior to discharge

- No studies reported on this important outcome

Comparison 2. Any premedication including neuromuscular blockers (single agent or combination of agents) versus any premedication

Critical outcomes

Ease of intubation

<u>Intubated on first attempt</u>

Fentanyl + suxamethonium + atropine versus remifentanyl + placebo + atropine (babies 25-30 weeks)

- Low quality evidence from 1 RCT (n=30) showed no clinically significant difference in the number of preterm babies intubated on the first attempt among preterm babies with a gestational age of 25-30 weeks who received fentanyl + suxamethonium + atropine compared to those who received remifentanyl + placebo + atropine.

Rocuronium + atropine + fentanyl versus atropine + fentanyl (babies < 36 weeks)

- Very low quality evidence from 1 RCT (n=44) showed there may be a clinically significant increase in the number of preterm babies intubated on the first attempt among preterm babies with a gestational age of < 36 weeks who received rocuronium + atropine + fentanyl compared to those who received atropine + fentanyl, however there is uncertainty around the estimate.

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=168) showed no clinically significant difference in the number of preterm babies intubated on the first attempt among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Duration of intubation</u>

Fentanyl + suxamethonium + atropine versus remifentanyl + placebo + atropine (babies 25-30 weeks)

- Moderate quality evidence from 1 RCT (n=30) showed no clinically significant difference in the duration of intubation among preterm babies with a gestational age of 25-30 weeks who received fentanyl + suxamethonium + atropine compared to those who received remifentanyl + placebo + atropine.

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=164) showed no clinically significant difference but a statistically significant decrease in the duration of intubation among preterm babies who with a gestational age of 26-32 weeks received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Number of intubation attempts</u>

Fentanyl + suxamethonium + atropine versus remifentanyl + placebo + atropine (babies 25-30 weeks)

- Moderate quality evidence from 1 RCT (n=30) showed no clinically significant difference in the number of intubation attempts among preterm babies with a gestational age of 25-30 weeks who received fentanyl + suxamethonium + atropine compared to those who received remifentanyl + placebo + atropine.

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=171) showed no clinically significant difference in the number of intubation attempts among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

Pain and comfort scores during intubation

- No studies reported on this critical outcome

Adverse physiological response during intubation

<u>Prolonged hypoxia</u>

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Very low quality evidence from 1 RCT (n=163) showed no clinically significant difference in the number of prolonged periods of hypoxia among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

Change in SpO_2 (peripheral capillary oxygen saturation) from baseline during intubation, %

Fentanyl + suxamethonium + atropine versus remifentanyl + placebo + atropine (babies 25-30 weeks)

- Moderate quality evidence from 1 RCT (n=30) showed no clinically significant difference in the change in SpO_2 from baseline during intubation among preterm babies with a gestational age of 25-30 weeks who received compared to those who received fentanyl + suxamethonium + atropine compared to those who received remifentanyl + placebo + atropine.

Atropine + atracurium + sufentanyl versus atropine + propofol, 1 minute after injection to 6 minutes after (babies 26-32 weeks)

- Moderate quality evidence from 1 RCT (n=165) showed no clinically significant difference in the change in SpO_2 1 minute after the first injection to 6 minutes after among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

Atropine + atracurium + sufentanyl versus atropine + propofol, 1 minute after injection to 9 minutes after (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=164) showed there may be a clinically significant increase in the change in SpO_2 1 minute after the first injection to 9 minutes after among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol but there is uncertainty around the risk estimate.

Change in blood pressure from baseline during intubation, mm Hg

Fentanyl + suxamethonium + atropine versus remifentanyl + placebo + atropine (babies 25-30 weeks)

- Low quality evidence from 1 RCT (n=30) showed no clinically significant difference in the change in blood pressure from baseline during intubation among preterm babies with a gestational age of 25-30 weeks who received fentanyl + suxamethonium + atropine compared to those who received remifentanyl + placebo + atropine.

Atropine + atracurium + sufentanyl versus atropine + propofol, 1 minute after injection to 15 minutes after (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=157) showed a clinically significant decrease in the change in blood pressure after the first injection to 15 minutes after among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

Atropine + atracurium + sufentanyl versus atropine + propofol, 1 minute after injection to 30 minutes after (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=150) showed a clinically decrease in the change in blood pressure 1 minute after the first injection to 30 minutes after among preterm babies who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

Change in heart rate from baseline during intubation, beats/minute

Fentanyl + suxamethonium + atropine versus remifentanyl + placebo + atropine (babies 25-30 weeks)

- Low quality evidence from 1 RCT (n=30) showed no clinically significant difference in the change in heart rate from baseline during intubation among preterm babies with a gestational age of 25-30 weeks who received fentanyl + suxamethonium + atropine compared to those who received remifentanyl + placebo + atropine.

Atropine + atracurium + sufentanyl versus atropine + propofol, 1 minute after injection to 6 minutes after (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=166) showed no clinically significant difference but a statistically significant increase in the change in heart rate 1 minute after the first injection to 6 minutes after among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

Atropine + atracurium + sufentanyl versus atropine + propofol, 1 minute after injection to 9 minutes after (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=166) showed a clinically significant increase in the change in heart rate 1 minute after the first injection to 9 minutes after among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Change in partial carbon dioxide pressure from baseline during intubation, mm Hg</u>

Atropine + atracurium + sufentanyl versus atropine + propofol, 1 minute after injection to 15 minutes after (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=59) showed no clinically significant difference in the change in partial carbon dioxide pressure after the first injection to 15 minutes after among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

Atropine + atracurium + sufentanyl versus atropine + propofol, 1 minute after injection to 30 minutes after (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=59) showed a clinically significant increase in the change in partial carbon dioxide pressure 1 minute after the first injection to 30 minutes after among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

Important outcomes

Neurodevelopmental outcomes ≥ 18 months

- No studies reported on this important outcome

Days on invasive ventilation

- No studies reported on this important outcome

Adverse drug reactions

<u>Chest wall rigidity</u>

Fentanyl + suxamethonium + atropine versus remifentanyl + placebo + atropine (babies 25-30 weeks)

- Low quality evidence from 1 RCT (n=30) showed no clinically significant difference in the number of preterm babies who experienced chest wall rigidity during intubation among preterm babies with a gestational age of 25-30 weeks who received fentanyl + suxamethonium + atropine compared to those who received remifentanyl + placebo + atropine.

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Low quality evidence from 1 RCT (n=163) showed a clinically significant decrease in the number of preterm babies who experienced chest wall rigidity among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Viscid respiratory excretions</u>

Fentanyl + suxamethonium + atropine versus remifentanyl + placebo + atropine (babies 25-30 weeks)

- Low quality evidence from 1 RCT (n=30) showed no clinically significant difference in the number of preterm babies with a gestational age of 25-30 weeks who experienced trauma during intubation among preterm babies who received fentanyl + suxamethonium + atropine compared to those who received remifentanyl + placebo + atropine.

<u>Pneumothorax</u>

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Very low quality evidence from 1 RCT (n=163) showed no clinically significant difference in the number of preterm babies who experienced pneumothorax among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Digestive tract perforation</u>

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Very low quality evidence from 1 RCT (n=163) showed no clinically significant difference in the number of preterm babies who experienced digestive tract perforation among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Pulmonary haemorrhage</u>

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Very low quality evidence from 1 RCT (n=160) showed no clinically significant difference in the number of preterm babies who experienced pulmonary haemorrhage among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Cardiac arrest</u>

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Very low quality evidence from 1 RCT (n=163) showed no clinically significant difference in the number of preterm babies with a gestational age of 26-32 weeks who experienced cardiac arrest among preterm babies who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Supraventricular tachycardia</u>

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Very low quality evidence from 1 RCT (n=163) showed no clinically significant difference in the number of preterm babies who experienced supraventricular haemorrhage among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Pulmonary hypertension</u>

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Very low quality evidence from 1 RCT (n=163) showed no clinically significant difference in the number of preterm babies who experienced pulmonary hypertension among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Aspiration syndrome</u>

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Very low quality evidence from 1 RCT (n=163) showed no clinically significant difference in the number of preterm babies who experienced aspiration syndrome with a gestational age of 26-32 weeks among preterm babies who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

<u>Hyponatremia</u>

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Very low quality evidence from 1 RCT (n=163) showed no clinically significant difference in the number of preterm babies with a gestational age of 26-32 weeks who experienced hyponatremia among preterm babies who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

Mortality prior to discharge

Atropine + atracurium + sufentanyl versus atropine + propofol (babies 26-32 weeks)

- Very low quality evidence from 1 RCT (n=163) showed no clinically significant difference in mortality prior to discharge among preterm babies with a gestational age of 26-32 weeks who received atropine + atracurium + sufentanyl compared to those who received atropine + propofol.

Comparison 3. Any premedication including atropine (single agent or combination of agents) versus any premedication

- There were no studies with this comparison

Comparison 4. Comparisons comparing neuromuscular blocker and atropine combinations

Critical outcomes

Ease of intubation

<u>Time to successful intubation</u>

Propofol versus morphine + atropine + suxamethonium (babies 25-31 weeks)

- Moderate quality evidence from 1 RCT (n=63) showed a clinically significant decrease in the time to achieve intubation in preterm babies with a gestational age of 25-31 weeks who received propofol compared to those who received morphine + atropine + suxamethonium.

Glycopyrrolate + thiopental + suxamethonium + remifentanyl versus atropine + morphine (babies < 37 weeks)

- Low quality evidence from 1 RCT (n=34) showed a clinically significant decrease in the time to achieve intubation for preterm babies with a gestational age of < 37 weeks who received glycopyrrolate + thiopental + suxamethonium + remifentanyl compared to those who received atropine + morphine.

<u>Intubated on first attempt</u>

Propofol versus morphine + atropine + suxamethonium (babies 25-31 weeks)

- Moderate quality evidence from 1 RCT (n=63) showed no clinically significant difference in the number of preterm babies intubated on the first attempt among preterm babies with a gestational age of 25-31 weeks who received propofol compared to those who received morphine + atropine + suxamethonium.

<u>Number of attempts needed to achieve intubation</u>

Glycopyrrolate + thiopental + suxamethonium + remifentanyl versus atropine + morphine (babies < 37 weeks)

- Low quality evidence from 1 RCT (n=34) showed no clinically significant difference in the number of attempts needed to achieve successful intubation in preterm babies with a gestational age of < 37 weeks who received glycopyrrolate + thiopental + suxamethonium + remifentanyl compared to those who received atropine + morphine.

Pain and comfort scores during intubation

- No studies reported on this critical outcome

Adverse physiological response during intubation

<u>Plasma cortisol concentrations</u>

Glycopyrrolate + thiopental + suxamethonium + remifentanyl versus atropine + morphine (babies < 37 weeks)

- Low quality evidence from 1 RCT (n=34) showed no clinically significant difference 20 minutes after intubation in plasma cortisol concentrations (nmol/L) for preterm babies with a gestational age of < 37 weeks who received glycopyrrolate + thiopental + suxamethonium + remifentanyl compared to those who received atropine + morphine.
- Low quality evidence from 1 RCT (n=34) showed no clinically signficant difference 6 hours after intubation in plasma cortisol concentrations (nmol/L) for preterm babies with a gestational age of < 37 weeks who received glycopyrrolate + thiopental + suxamethonium + remifentanyl compared to those who received atropine + morphine.
- Low quality evidence from 1 RCT (n=34) showed no clinically significant difference 24 hours after intubation in plasma cortisol concentrations (nmol/L) for preterm babies with a gestational age of < 37 weeks who received glycopyrrolate + thiopental + suxamethonium + remifentanyl compared to those who received atropine + morphine.

<u>Mean arterial blood pressure relative change from baseline during intubation</u>

Glycopyrrolate + thiopental + suxamethonium + remifentanyl versus atropine + morphine (babies < 37 weeks)

- Low quality evidence from 1 RCT (n=34) showed a clinically significant decrease in the mean arterial blood pressure relative change from baseline during intubation among preterm babies with a gestational age of < 37 weeks who received glycopyrrolate + thiopental + suxamethonium + remifentanyl compared to those who received atropine + morphine.

<u>Increase in serum lactate levels > 2.2 mmol/L</u>

Propofol versus morphine + atropine + suxamethonium (babies 25-31 weeks)

- Low quality evidence from 1 RCT (n=63) showed no clinically significant difference in the relative change in serum lactate levels > 2.2 mmol/L among preterm babies with a gestational age of 25-31 weeks who received propofol compared to those who received morphine + atropine + suxamethonium.

Important outcomes

Neurodevelopmental outcomes ≥ 18 months

- No studies reported on this important outcome

Days on invasive ventilation

- No studies reported on this important outcome

Adverse drug reactions

Viscid respiratory secretions

Propofol versus morphine + atropine + suxamethonium (babies 25-31 weeks)

- Low quality evidence from 1 RCT (n=63) showed no clinically significant difference in viscid respiratory secretions among preterm babies with a gestational age of 25-31 weeks who received propofol compared to those who received morphine + atropine + suxamethonium.

Mortality prior to discharge

- No studies reported on this important outcome

Economic evidence statements

- No economic evidence on the cost effectiveness of premedication regimens for intubation in preterm babies was available.

Recommendations

E2.1 Consider premedication before elective non-urgent intubation in preterm babies.

E2.2 If giving premedication, consider either:

- an opioid analgesic (for example, morphine[b] or fentanyl[c]), combined with a neuromuscular blocking agent (for example, suxamethonium) **or**
- propofol[d] alone.

Research recommendations

What is the most effective combination of an analgesic with a neuromuscular blocker, or an analgesic with an anaesthetic agent for premedication in preterm babies requiring elective/semi-elective intubation?

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[b] Although this is common in UK clinical practice, at the time of consultation (October 2018), morphine did not have a UK marketing authorisation for children under 12 years (intravenous administration) or under 1 year (oral administration). The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

c Although this is common in UK clinical practice, at the time of consultation (October 2018), fentanyl did not have a UK marketing authorisation for children under 2 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

d Although this is common in UK clinical practice, at the time of consultation (October 2018), propofol did not have a UK marketing authorisation for children under 1 month. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines

Rationale and impact

Why the committee made the recommendations

There was some evidence from small, single studies that using an analgesic with a neuromuscular blocker, or an anaesthetic such as propofol used alone, is an effective regimen to achieve successful intubation in preterm babies, while avoiding adverse effects.

However, there was a lack of evidence to show exactly which medicines or classes of medicines form the best combination, so the committee recommended that healthcare professionals should consider premedication before elective intubation and recommended that further research be done in this area.

Impact of the recommendations on practice

Current practice of using premedication for elective intubation in preterm babies varies among units. Units that currently use single medicines (such as morphine or fentanyl) may need to change practice to follow the recommendation. The recommendation will make practice more consistent across the NHS.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As one of the aims of premedication is to facilitate an easier intubation the committee agreed that the ease of intubation, specifically the number of intubation attempts and time to successful intubation, was a critical outcome. Adverse physiological events during intubation were also critical, as preterm babies' physiological responses to painful stimuli, such as endotracheal intubation, can have short-term detrimental cardiac and neurological effects, as well as leading to poor pain control and perception later on in infancy and childhood (Choong 2010). Adverse physiological events were therefore used as a surrogate outcome for the effect of premedications on neurodevelopmental delay, as there was no evidence for this outcome.

Premedication is also used to reduce pain and discomfort during intubation, so pain and comfort scores were critical outcomes, however, there was no evidence for these.

Days on ventilation and adverse drug reactions were considered important outcomes for interpreting the evidence due to their roles in indicating whether the drugs have any iatrogenic effects and how well preterm babies respond to intubation.

The quality of the evidence

Evidence was available from 2 RCTs that compared any premedication versus a placebo; 2 RCTs that compared any premedication including neuromuscular blockers (single agent or combination of agents) versus any premedication; and 3 RCTs that compared neuromuscular blocker and atropine combinations. No studies were found comparing any premedication including atropine (single agent or combination of agents) versus any premedication. The quality of the evidence in this review ranged from moderate to very low although the majority for all comparisons and outcomes was of low and very low quality.

There was no evidence for pain and comfort scores during intubation, neurodevelopmental outcomes ≥ 18 months, days on ventilation, adverse drug reactions, or mortality prior to discharge. While some outcomes, such as changes in mean arterial blood pressure could have been interpreted as adverse drug reactions, the presentation of many of the drugs in combination with others meant that it was not possible to isolate which drug was causing the effect. Thus, such outcomes were grouped as adverse physiological responses during intubation.

The quality of evidence was most often downgraded because of the uncertainty around the risk estimate and methodological limitations affecting the risk of bias.

Uncertainty around the risk estimate was generally attributable to low event rates and small sample sizes. Furthermore, approximately half of the studies did not report the number of days on ventilation as means, but rather as medians so imprecision could not be assessed for these studies.

Methodological limitations affecting the risk of bias were generally attributed to several studies not reporting the method for randomisation, treatment allocation, or blinding, not reporting all outcomes that were stated in the protocol and one trial containing less than 15 participants in both arms.

The low quality of the evidence impacted the decision-making and the strength of the recommendations, as the small sample sizes examining multiple agents made it difficult to isolate individual drug effects. Due to the insufficient evidence to make strong recommendations the committee made a ‘consider’ recommendation and prioritised making a research recommendation.

Benefits and harms

The committee agreed that there was little evidence of benefit for morphine used alone and that morphine alone had been shown to lead to harms such as an increased duration and severity of hypoxaemia. Combinations that included morphine as an analgesic took longer to achieve successful intubation and led to larger changes from baseline in mean arterial blood pressure during intubation compared to other combinations.

Some combinations of drugs led to some benefits such as a decreased number of intubation attempts, a decreased time to achieve intubation and an increase in the number of intubations successful on first attempt. This was achieved without any evidence of adverse physiological effects. However, as such a varied number of combinations had been used in the studies included in the review, it was difficult to ascertain exactly which drugs provided the best combination. Although there was no apparent difference between dual and triple combinations, there were no comparisons that assessed combinations to “no treatment.” This means that there may have been no difference between dual and triple combinations because they were equally effective (compared to no treatment) or equally ineffective.

When propofol (an anaesthetic agent) alone was compared to a combination of agents that included a neuromuscular blocker, propofol was faster in achieving successful intubation and led to smaller changes from baseline in mean arterial blood pressure during intubation.

The committee were aware that analgesics with a slower onset of action (such as morphine) were not usually useful in intubation as they did not act fast enough to provide any benefit and that analgesics with a faster onset of action (such as fentanyl or remifentanil) were preferable, and hence suggested fentanyl as an example of an analgesic that could be used..

The committee agreed that using a combination of agents for intubation or propofol alone was likely to lead to easier intubation, reduce pain and discomfort for the baby and would not lead to adverse physiological effects.

Cost effectiveness and resource use

There was no economic evidence on the cost effectiveness of premedications for elective intubation in preterm babies.

The strategy utilising an analgesic and either a neuromuscular blocking or anaesthetic agent is associated with a potential reduction in the number of attempts and the time to achieve intubation. The committee noted the low acquisition costs associated with premedications and the lack of any associated harms. Failure to intubate or prolonged time to intubation is associated with delays in providing an airway and/or assisted invasive ventilation and surfactant administration. This can have severe consequences for a baby and require costly care.

The committee also noted that the use of propofol in preterm babies is associated with a high amount of wastage due to it being dispensed in adult-sized, single-use vials. Drug wastage results in incremental costs without incremental value to patients. However, the NHS indicative price for propofol is relatively low (i.e. £2.16 per vial) (BNF, 2018) and the incorporation of wastage is unlikely to impact significantly the incremental cost-effectiveness.

Given the above, the committee were of a view that a strategy utilising an analgesic and a neuromuscular blocking agent, or an anaesthetic agent is expected to represent the most cost-effective use of NHS resources.

Other factors the committee took into account

The committee noted that there is currently a wide variety of practice between units: some units used a combination premedication already, some used morphine, fentanyl, midazolam or propofol alone and some did not use premedication. The recommendations might therefore lead to a change in practice in some units.

While morphine as a single or combination of agents may be associated with more harms than benefits, the committee noted that intubation is a painful procedure and that the one-time use of morphine during this procedure would provide pain relief.

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1 Appendices

2 Appendix A – Review protocols

3 Review protocol for question 5.1 What is the effectiveness of morphine during respiratory support?

Field (based on PRISMA-P	Content
Review question in SCOPE	Is morphine effective and safe to use during assisted ventilation?
Review question in guideline	What is the effectiveness of morphine during respiratory support?
Type of review question	Intervention
Objective of the review	To determine if morphine improve outcomes in babies requiring respiratory support
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies receiving respiratory support Exclusions: • Preterm babies with any congenital abnormalities except patent ductus arteriosus • Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, necrotising enterocolitis, neurological disorders. RCTs with <15 participants in each arm will not routinely be included. Consideration will be given to their inclusion if the evidence from larger RCTs is judged not to be sufficient – in quality or quantity. Studies where >2/3 of preterm babies receive respiratory support will be included in the review
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Morphine
Eligibility criteria – comparator(s)/control or reference (gold) standard	Control • Placebo/no intervention

Field (based on PRISMA-P	Content
	Other non-opioid analgesics: • Paracetamol Other opioids: • Fentanyl • Sedatives: • Midazolam Non-pharmacological interventions: • Sucrose (EBM, non-nutritive sucking) • Postural support • Positioning aids • Swaddling • Containment holding • Skin to skin contact Comparisons: • Morphine versus each comparator listed, inter-group comparisons will not be considered.
Outcomes and prioritisation	Critical outcomes: • Mortality prior to discharge • Severe intraventricular haemorrhage (IVH) (grade 3 or 4) • Pain and comfort scores Important outcomes: • Unplanned or accidental extubation • Days to achieve full enteral feeding • Hypotension which requires intervention

Field (based on PRISMA-P	Content
	• Parental satisfaction
Eligibility criteria – study design	Systematic reviews of RCTs RCTs If insufficient RCTs: prospective cohort studies If insufficient prospective cohort studies: retrospective cohort studies
Other inclusion exclusion criteria	Inclusion: • English-language • Developed countries with a neonatal care system similar to the UK (e.g. OECD countries) • Studies conducted post 1990 Exclusion: • Analgesics or sedatives used as pre-medication
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of ventilated preterm babies: Gestational age: • <26+6 weeks • 27-31+6 weeks • 32-36+6 weeks Ventilation techniques: • Non-invasive • Invasive
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting and data extraction will not be undertaken for this question.

Field (based on PRISMA-P	Content
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance but download all results Dates: from 1990 Studies conducted post 1990 will be considered for this review question, as the GC felt that significant advances have occurred in ante-natal and post-natal respiratory management since this time period and outcomes for preterm babies prior to 1990 are not the same as post 1990.
Identify if an update	Not an update
Author contacts	Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual

Field (based on PRISMA-P	Content
	The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • AMSTAR for systematic reviews • Cochrane risk of bias tool for RCTs • Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Pairwise meta-analysis will be conducted where appropriate When meta-analysing continuous data, final and change scores will be pooled and if any studies reports both, the method used in the majority of studies will be analysed. Minimally important differences: Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Mortality – any change (statistically significant)
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway

Field (based on PRISMA-P	Content
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Dr Janet Rennie in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	Not registered

Review protocol for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

Field (based on PRISMA-P	Content
Review question in SCOPE	New question
Review question in guideline	What is the effectiveness of using premedication for intubation in preterm babies?
Type of review question	Intervention
Objective of the review	To determine the optimal premedication regimen (if any) for intubation in preterm babies
Eligibility criteria – population/disease/condition/issue/domain	Preterm babies undergoing intubation Exclusions: • Preterm babies with congenital abnormalities excluding patent ductus arteriosus • Preterm babies who are ventilated solely due to a specific non-respiratory comorbidity, such as sepsis, necrotising enterocolitis, neurological disorders, congenital heart disease • RCTs with <15 participants in each arm will not routinely be included. Consideration will be given to their inclusion if the evidence from larger RCTs is judged not to be sufficient – in quality or quantity.
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Anticholinergics • Atropine Analgesics • Fentanyl • Remifentanyl • Morphine • Alfentanyl Sedatives • Midazolam

Field (based on PRISMA-P	Content
	Anaesthetics • Propofol Neuromuscular blockers • Suxamethonium • Atracurium • Rocuronium
Eligibility criteria – comparator(s)/control or reference (gold) standard	Comparisons: • Any premedication versus placebo/ nothing • Any premedication including neuromuscular blockers (single agent or combination of agents) versus any premedication • Any premedication including atropine (single agent or combination of agents) versus any premedication Comparisons will be limited to intra-class and not include inter-class comparisons.
Outcomes and prioritisation	Critical outcomes: • Ease of intubation (e.g. number of intubation attempts, time to successful intubation, failed intubation) • Pain and comfort scores during intubation • Adverse Physiological response during intubation (e.g. Hypoxia, heart rate and blood pressure changes, cortisol, catecholamines) Important outcomes: • Neurodevelopmental outcome ≥18 months: ○ Cerebral palsy (reported as presence or absence of condition, not severity of condition)

Field (based on PRISMA-P	Content
	○ Neurodevelopmental delay (reported as dichotomous outcomes, not continuous outcomes such as mean change in score) ▪ Severe (sore of >2 SD below normal on validated assessment scales, or on Bayley's assessment scale of mental developmental index (MDI) or psychomotor developmental index (PDI) <70 or complete inability to assign score due to CP or severe cognitive delay) ▪ Moderate (score of 1-2 SD below normal on validated assessment scales, or on Bayley's assessment scale of MDI or PDI 70-84) ○ Neurosensory impairment (reported as presence or absence of condition, not severity of condition) ▪ Severe hearing impairment (e.g deaf) ▪ Severe visual impairment (e.g blind) • Days on invasive ventilation • Adverse Drug reactions (e.g. Atropine induced tachycardia and viscid respiratory and gastrointestinal secretions, neuroblocker induced hyperkalaemia and respiratory depression) • Mortality prior to discharge
Eligibility criteria – study design	• Systematic reviews of RCTs • RCTs • If insufficient RCTs: prospective cohort studies • If insufficient prospective cohort studies: retrospective cohort studies
Other inclusion exclusion criteria	Inclusion: • English-language

Field (based on PRISMA-P	Content
	• Developed countries with a neonatal care system similar to the UK (e.g. OECD countries) • Studies conducted post 1990
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of preterm babies: Gestational age: • <26+6 weeks • 27-31+6 weeks • 32-36+6 weeks
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting and data extraction will not be undertaken for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): • Apply standard animal/non-English language exclusion • Limit to RCTs and systematic reviews in first instance but download all results • Dates: from 1990 Studies conducted post 1990 will be considered for this review question, as the GC felt that significant advances have occurred in ante-natal and post-

Field (based on PRISMA-P	Content
	natal respiratory management since this time period and outcomes for preterm babies prior to 1990 are not the same as post 1990.
Identify if an update	Not an update
Author contacts	Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • AMSTAR for systematic reviews • Cochrane risk of bias tool for RCTs • Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual

Field (based on PRISMA-P	Content
Methods for analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis will be conducted where appropriate When meta-analysing continuous data, final and change scores will be pooled and if any studies reports both, the method used in the majority of studies will be analysed. Minimally important differences: Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Mortality – any change (statistically significant)
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Dr Janet Rennie in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.

Field (based on PRISMA-P	Content
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	Not registered to PROSPERO

Appendix B – Literature search strategies

Literature search strategies for question 5.1 What is the effectiveness of morphine during respiratory support?

Systematic reviews and RCTs

Date of initial search: 13/06/2017

Database: Embase 1980 to 2017 Week 24, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 26/06/2018

Database(s): Embase 1980 to 2018 Week 26, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh*).tw.
8	(LBW or VLBW).tw.
9	exp Intensive Care, Neonatal/ use ppez
10	newborn intensive care/ use emez
11	exp Intensive Care Units, Neonatal/ use ppez
12	neonatal intensive care unit/ use emez
13	(special and care and baby and unit*).tw.
14	((newborn or neonatal) adj ICU*1).tw.
15	(SCBU or NICU).tw.
16	exp Respiratory Distress Syndrome, Newborn/ use ppez
17	neonatal respiratory distress syndrome/ use emez
18	or/1-17
19	exp Respiration, Artificial/ use ppez
20	exp Intubation, Intratracheal/ use ppez
21	exp artificial ventilation/ use emez
22	exp assisted ventilation/ use emez
23	exp Ventilators, Mechanical/ use ppez
24	exp ventilator/ use emez
25	(ventilat* or respirator or respirators or intubat*).tw.
26	((respirat* or breath* or airway* or oxygen*) adj3 (support* or assist* or artificial or control* or oscillat* or pressure)).tw.
27	nasal cannula.tw.
28	or/19-27
29	18 and 28
30	Morphine/ use ppez
31	morphine/ use emez
32	morphine.tw.
33	or/30-32
34	29 and 33
35	exp Fentanyl/ use ppez
36	fentanyl/ use emez
37	(fentan?l or phentan?).tw.
38	exp Midazolam/ use ppez
39	midazolam/ use emez or midazolam maleate/ use emez
40	midazolam.tw.
41	Acetaminophen/ use ppez
42	paracetamol/ use emez
43	(paracetamol or acet?minophen or acetamidophenol).tw.

#	Searches
44	exp Sucrose/ use ppez
45	exp Sweetening Agents/ use ppez
46	exp sweetening agent/ use emez
47	(sucrose* or aspartame* or dextrose* or fructose* or glycerine* or glucose* or honey or lactose* or lycerine* or polycose* or sacchar* or sugar* or syrup* or ((sweet* or pleasant or nice) adj3 (solution* or agent* or taste* or tasting))).tw.
48	Breast Feeding/ use ppez
49	exp breast feeding/ use emez
50	Milk, Human/ use ppez
51	breast milk/ use emez
52	(breastfeed* or (breast adj2 milk) or breastmilk or breastfed or (breast adj2 feed*) or (breast adj2 fed)).tw.
53	sucking/ use emez
54	suck*.tw.
55	Posture/ use ppez
56	body posture/ use emez
57	((posture* or postural) adj2 (support* or help* or stabili* or stable)).tw.
58	exp Patient Positioning/ use ppez
59	positioning/ use emez
60	kangaroo care/ use emez
61	(position* or hammock* or swaddl* or containment or hold or holding).tw.
62	((skin adj2 skin) or (kangaroo adj2 care)).tw.
63	or/35-62
64	29 and 63
65	34 or 64
66	limit 65 to english language
67	limit 66 to yr="1990 -Current"
68	Letter/ use ppez
69	letter.pt. or letter/ use emez
70	note.pt.
71	editorial.pt.
72	Editorial/ use ppez
73	News/ use ppez
74	exp Historical Article/ use ppez
75	Anecdotes as Topic/ use ppez
76	Comment/ use ppez
77	Case Report/ use ppez
78	case report/ or case study/ use emez
79	(letter or comment*).ti.
80	or/68-79
81	randomized controlled trial/ use ppez
82	randomized controlled trial/ use emez
83	random*.ti,ab.
84	or/81-83
85	80 not 84
86	animals/ not humans/ use ppez
87	animal/ not human/ use emez
88	nonhuman/ use emez
89	exp Animals, Laboratory/ use ppez
90	exp Animal Experimentation/ use ppez
91	exp Animal Experiment/ use emez
92	exp Experimental Animal/ use emez
93	exp Models, Animal/ use ppez
94	animal model/ use emez
95	exp Rodentia/ use ppez
96	exp Rodent/ use emez
97	(rat or rats or mouse or mice).ti.
98	or/85-97
99	67 not 98
100	Meta-Analysis/
101	Meta-Analysis as Topic/
102	systematic review/
103	meta-analysis/
104	(meta analy* or metanaly* or metaanaly*).ti,ab.
105	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
106	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
107	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
108	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

#	Searches
109	(search* adj4 literature).ab.
110	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
111	cochrane.jw.
112	((pool* or combined) adj2 (data or trials or studies or results)).ab.
113	or/100-101,104,106-111 use ppez
114	or/102-105,107-112 use emez
115	or/113-114
116	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
117	116 use ppez
118	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
119	118 use ppez
120	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
121	120 use emez
122	117 or 119
123	121 or 122
124	115 or 123
125	99 and 124
126	remove duplicates from 125

Observational studies

Date of initial search: 13/06/2017

Database: Embase 1980 to 2017 Week 24, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 26/06/2018

Database(s): Embase 1980 to 2018 Week 26, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh*).tw.
8	(LBW or VLBW).tw.
9	exp Intensive Care, Neonatal/ use ppez
10	newborn intensive care/ use emez
11	exp Intensive Care Units, Neonatal/ use ppez
12	neonatal intensive care unit/ use emez
13	(special and care and baby and unit*).tw.
14	((newborn or neonatal) adj ICU*1).tw.
15	(SCBU or NICU).tw.
16	exp Respiratory Distress Syndrome, Newborn/ use ppez
17	neonatal respiratory distress syndrome/ use emez
18	or/1-17
19	exp Respiration, Artificial/ use ppez
20	exp Intubation, Intratracheal/ use ppez
21	exp artificial ventilation/ use emez
22	exp assisted ventilation/ use emez
23	exp Ventilators, Mechanical/ use ppez
24	exp ventilator/ use emez
25	(ventilat* or respirator or respirators or intubat*).tw.
26	((respirat* or breath* or airway* or oxygen*) adj3 (support* or assist* or artificial or control* or oscillat* or pressure)).tw.

#	Searches
27	nasal cannula.tw.
28	or/19-27
29	18 and 28
30	Morphine/ use ppez
31	morphine/ use emez
32	morphine.tw.
33	or/30-32
34	29 and 33
35	exp Fentanyl/ use ppez
36	fentanyl/ use emez
37	(fentan?l or phentan?).tw.
38	exp Midazolam/ use ppez
39	midazolam/ use emez or midazolam maleate/ use emez
40	midazolam.tw.
41	Acetaminophen/ use ppez
42	paracetamol/ use emez
43	(paracetamol or acet?minophen or acetamidophenol).tw.
44	exp Sucrose/ use ppez
45	exp Sweetening Agents/ use ppez
46	exp sweetening agent/ use emez
47	(sucrose* or aspartame* or dextrose* or fructose* or glycerine* or glucose* or honey or lactose* or lycerine* or polycose* or sacchar* or sugar* or syrup* or ((sweet* or pleasant or nice) adj3 (solution* or agent* or taste* or tasting))).tw.
48	Breast Feeding/ use ppez
49	exp breast feeding/ use emez
50	Milk, Human/ use ppez
51	breast milk/ use emez
52	(breastfeed* or (breast adj2 milk) or breastmilk or breastfed or (breast adj2 feed*) or (breast adj2 fed)).tw.
53	sucking/ use emez
54	suck*.tw.
55	Posture/ use ppez
56	body posture/ use emez
57	((posture* or postural) adj2 (support* or help* or stabili* or stable)).tw.
58	exp Patient Positioning/ use ppez
59	positioning/ use emez
60	kangaroo care/ use emez
61	(position* or hammock* or swaddl* or containment or hold or holding).tw.
62	((skin adj2 skin) or (kangaroo adj2 care)).tw.
63	or/35-62
64	29 and 63
65	34 or 64
66	limit 65 to english language
67	limit 66 to yr="1990 -Current"
68	Letter/ use ppez
69	letter.pt. or letter/ use emez
70	note.pt.
71	editorial.pt.
72	Editorial/ use ppez
73	News/ use ppez
74	exp Historical Article/ use ppez
75	Anecdotes as Topic/ use ppez
76	Comment/ use ppez
77	Case Report/ use ppez
78	case report/ or case study/ use emez
79	(letter or comment*).ti.
80	or/68-79
81	randomized controlled trial/ use ppez
82	randomized controlled trial/ use emez
83	random*.ti,ab.
84	or/81-83
85	80 not 84
86	animals/ not humans/ use ppez
87	animal/ not human/ use emez
88	nonhuman/ use emez
89	exp Animals, Laboratory/ use ppez
90	exp Animal Experimentation/ use ppez
91	exp Animal Experiment/ use emez

#	Searches
92	exp Experimental Animal/ use emez
93	exp Models, Animal/ use ppez
94	animal model/ use emez
95	exp Rodentia/ use ppez
96	exp Rodent/ use emez
97	(rat or rats or mouse or mice).ti.
98	or/85-97
99	67 not 98
100	Epidemiologic Studies/
101	Case Control Studies/
102	Retrospective Studies/
103	Cohort Studies/
104	Longitudinal Studies/
105	Follow-Up Studies/
106	Prospective Studies/
107	Cross-Sectional Studies/
108	or/100-107 use ppez
109	clinical study/
110	case control study/
111	family study/
112	longitudinal study/
113	retrospective study/
114	prospective study/
115	cohort analysis/
116	or/109-115 use emez
117	((retrospective* or cohort* or longitudinal or follow?up or prospective or cross section*) adj3 (stud* or research or analys*)).ti.
118	108 or 116 or 117
119	99 and 118
120	remove duplicates from 119

Health Economics

Date of initial search: 13/06/2017

Database: Embase 1980 to 2017 Week 24, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 26/06/2018

Database(s): Embase 1980 to 2018 Week 26, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh*).tw.
8	(LBW or VLBW).tw.
9	exp Intensive Care, Neonatal/ use ppez
10	newborn intensive care/ use emez
11	exp Intensive Care Units, Neonatal/ use ppez
12	neonatal intensive care unit/ use emez
13	(special and care and baby and unit*).tw.
14	((newborn or neonatal) adj ICU*1).tw.
15	(SCBU or NICU).tw.
16	exp Respiratory Distress Syndrome, Newborn/ use ppez
17	neonatal respiratory distress syndrome/ use emez
18	or/1-17
19	exp Respiration, Artificial/ use ppez
20	exp Intubation, Intratracheal/ use ppez

#	Searches
21	exp artificial ventilation/ use emez
22	exp assisted ventilation/ use emez
23	exp Ventilators, Mechanical/ use ppez
24	exp ventilator/ use emez
25	(ventilat* or respirator or respirators or intubat*).tw.
26	((respirat* or breath* or airway* or oxygen*) adj3 (support* or assist* or artificial or control* or oscillat* or pressure)).tw.
27	nasal cannula.tw.
28	or/19-27
29	18 and 28
30	Morphine/ use ppez
31	morphine/ use emez
32	morphine.tw.
33	or/30-32
34	29 and 33
35	exp Fentanyl/ use ppez
36	fentanyl/ use emez
37	(fentan?l or phentan?).tw.
38	exp Midazolam/ use ppez
39	midazolam/ use emez or midazolam maleate/ use emez
40	midazolam.tw.
41	Acetaminophen/ use ppez
42	paracetamol/ use emez
43	(paracetamol or acet?minophen or acetamidophenol).tw.
44	exp Sucrose/ use ppez
45	exp Sweetening Agents/ use ppez
46	exp sweetening agent/ use emez
47	(sucrose* or aspartame* or dextrose* or fructose* or glycerine* or glucose* or honey or lactose* or lycerine* or polycose* or sacchar* or sugar* or syrup* or ((sweet* or pleasant or nice) adj3 (solution* or agent* or taste* or tasting))).tw.
48	Breast Feeding/ use ppez
49	exp breast feeding/ use emez
50	Milk, Human/ use ppez
51	breast milk/ use emez
52	(breastfeed* or (breast adj2 milk) or breastmilk or breastfed or (breast adj2 feed*) or (breast adj2 fed)).tw.
53	sucking/ use emez
54	suck*.tw.
55	Posture/ use ppez
56	body posture/ use emez
57	((posture* or postural) adj2 (support* or help* or stabili* or stable)).tw.
58	exp Patient Positioning/ use ppez
59	positioning/ use emez
60	kangaroo care/ use emez
61	(position* or hammock* or swaddl* or containment or hold or holding).tw.
62	((skin adj2 skin) or (kangaroo adj2 care)).tw.
63	or/35-62
64	29 and 63
65	34 or 64
66	limit 65 to english language
67	limit 66 to yr="1990 -Current"
68	Letter/ use ppez
69	letter.pt. or letter/ use emez
70	note.pt.
71	editorial.pt.
72	Editorial/ use ppez
73	News/ use ppez
74	exp Historical Article/ use ppez
75	Anecdotes as Topic/ use ppez
76	Comment/ use ppez
77	Case Report/ use ppez
78	case report/ or case study/ use emez
79	(letter or comment*).ti.
80	or/68-79
81	randomized controlled trial/ use ppez
82	randomized controlled trial/ use emez
83	random*.ti,ab.
84	or/81-83

#	Searches
85	80 not 84
86	animals/ not humans/ use ppez
87	animal/ not human/ use emez
88	nonhuman/ use emez
89	exp Animals, Laboratory/ use ppez
90	exp Animal Experimentation/ use ppez
91	exp Animal Experiment/ use emez
92	exp Experimental Animal/ use emez
93	exp Models, Animal/ use ppez
94	animal model/ use emez
95	exp Rodentia/ use ppez
96	exp Rodent/ use emez
97	(rat or rats or mouse or mice).ti.
98	or/85-97
99	67 not 98
100	Economics/
101	Value of life/
102	exp "Costs and Cost Analysis"/
103	exp Economics, Hospital/
104	exp Economics, Medical/
105	Economics, Nursing/
106	Economics, Pharmaceutical/
107	exp "Fees and Charges"/
108	exp Budgets/
109	or/100-108 use ppez
110	health economics/
111	exp economic evaluation/
112	exp health care cost/
113	exp fee/
114	budget/
115	funding/
116	or/110-115 use emez
117	budget*.ti,ab.
118	cost*.ti.
119	(economic* or pharmaco?economic*).ti.
120	(price* or pricing*).ti,ab.
121	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
122	(financ* or fee or fees).ti,ab.
123	(value adj2 (money or monetary)).ti,ab.
124	or/117-122
125	109 or 116 or 124
126	99 and 125
127	Remove duplicates from 126

Systematic reviews, RCTs, health economics

Date of initial search: 13/06/2017

Database: The Cochrane Library, issue 6 of 12, June 2017

Date of updated search: 27/06/2018

Database: The Cochrane Library, issue 6 of 12, June 2018

ID	Search
#1	MeSH descriptor: [Infant, Newborn] explode all trees
#2	(infan* or neonat* or neo-nat* or newborn* or new-born* or baby or babies or preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie or premies)
#3	((low adj3 birth near/3 weigh*) or (LBW or VLBW))
#4	MeSH descriptor: [Respiratory Distress Syndrome, Newborn] explode all trees
#5	MeSH descriptor: [Intensive Care, Neonatal] explode all trees
#6	MeSH descriptor: [Intensive Care Units, Neonatal] explode all trees
#7	(special care baby unit* or ((newborn or neonatal) near ICU*1) or (SCBU or NICU))
#8	{or #1-#7}
#9	MeSH descriptor: [Respiration, Artificial] explode all trees
#10	MeSH descriptor: [Intubation, Intratracheal] explode all trees
#11	MeSH descriptor: [Ventilators, Mechanical] explode all trees

ID	Search
#12	(ventilat* or respirator or respirators or intubat*)
#13	((respirat* or breath* or airway* or oxygen*) near/3 (support* or assist* or artificial or control* or oscillat* or pressure))
#14	nasal cannula
#15	{or #9-#14}
#16	#8 and #15
#17	MeSH descriptor: [Morphine] explode all trees
#18	morphine
#19	#17 or #18
#20	#16 and #19
#21	MeSH descriptor: [Fentanyl] explode all trees
#22	(fentan?l or phentan?)
#23	MeSH descriptor: [Midazolam] explode all trees
#24	midazolam
#25	MeSH descriptor: [Acetaminophen] explode all trees
#26	(paracetamol or acet?minophen or acetamidophenol)
#27	MeSH descriptor: [Sucrose] explode all trees
#28	MeSH descriptor: [Sweetening Agents] explode all trees
#29	(sucrose* or aspartame* or dextrose* or fructose* or glycerine* or glucose* or honey or lactose* or lycerine* or polycose* or sacchar* or sugar* or syrup* or ((sweet* or pleasant or nice) near/3 (solution* or agent* or taste* or tasting)))
#30	MeSH descriptor: [Breast Feeding] explode all trees
#31	MeSH descriptor: [Milk, Human] explode all trees
#32	(breastfeed* or (breast near/2 milk) or breastmilk or breastfed or (breast near/2 feed*) or (breast near/2 fed))
#33	suck*
#34	MeSH descriptor: [Posture] explode all trees
#35	MeSH descriptor: [Patient Positioning] explode all trees
#36	((posture* or postural) near/2 (support* or help* or stabili* or stable))
#37	(position* or hammock* or swaddl* or containment or hold or holding)
#38	((skin adj2 skin) or (kangaroo near/2 care))
#39	{or #21-#38}
#40	#16 and #39
#41	#20 or #40 Publication Year from 1990 to 2017

Literature search strategies for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

Systematic reviews and RCTs

Date of initial search: 08/11/17

Database(s): Embase 1980 to 2017 Week 45, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh$).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez

#	Searches
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emez
17	newborn care/ use emez
18	(special and care and baby and unit*).tw.
19	((newborn or neonatal or neo-natal) adj ICU*1).tw.
20	((newborn or neonat* or neo-nat*) adj2 (unit or care or department* or facilit* or hospital*)).tw.
21	(SCBU or NICU).tw.
22	((infan* or baby or babies or preterm or pre-term or prematur* or pre?mie* or premie*1) adj2 (unit* or care or department* or facilit* or hospital*)).tw.
23	or/1-22
24	exp Intubation, Intratracheal/ use ppez
25	exp respiratory tract intubation/ use emez
26	intubat*.tw.
27	or/24-26
28	23 and 27
29	Premedication/
30	"Hypnotics and Sedatives"/
31	"Anaesthesia and Analgesia"/ or Analgesia/ or Anaesthesia/
32	Cholinergic Antagonists/ or Muscarinic Antagonists/
33	exp Analgesics, Opioid/
34	exp Neuromuscular Nondepolarizing Agents/ or exp Neuromuscular Blockade/ or exp Neuromuscular Depolarizing Agents/ or exp Neuromuscular Blocking Agents/
35	Alfentanil/ or Atropine/ or Atracurium/ or Fentanyl/ or Midazolam/ or Morphine/ or Propofol/
36	or/29-35 use ppez
37	exp premedication/
38	hypnotic sedative agent/
39	anesthesiological procedure/ or analgesia/ or anaesthesia/ or anesthetic agent/
40	cholinergic receptor blocking agent/ or muscarinic receptor blocking agent/
41	narcotic analgesic agent/
42	muscle relaxant agent/ or neuromuscular blocking agent/ or neuromuscular blocking/ or neuromuscular depolarizing agent/ or neuromuscular depolarizing agent/
43	alfentanil/ or atracurium besilate/ or atropine/ or fentanyl/ or midazolam/ or propofol/ or remifentanil/ or rocuronium/ or suxamethonium/
44	or/37-43 use emez
45	(alfentan?l or atracurium or atropine or fentan?l or midazolam or morphine or propofol or remifentan?l or rocuronium or suxamethonium).tw.
46	(premedication or pre-medication or premed* or pre-med*).tw.
47	(sedat* or hypnotics or anaesth* or analges* or narcotic* or opioid* or cholinergic antagonist* or muscarinic antagonist* or neuromuscular block* or neuromuscular nondepolarizing agent* or neuromuscular depolarizing agent* or muscle relax*).tw.
48	or/45-47
49	36 or 44 or 48
50	28 and 49
51	limit 50 to english language
52	limit 51 to yr="1990 -Current"
53	Letter/ use ppez
54	letter.pt. or letter/ use emez
55	note.pt.
56	editorial.pt.
57	Editorial/ use ppez
58	News/ use ppez
59	exp Historical Article/ use ppez
60	Anecdotes as Topic/ use ppez
61	Comment/ use ppez
62	Case Report/ use ppez
63	case report/ or case study/ use emez
64	(letter or comment*).ti.
65	or/53-64
66	randomized controlled trial/ use ppez
67	randomized controlled trial/ use emez
68	random*.ti,ab.
69	or/66-68
70	65 not 69
71	animals/ not humans/ use ppez

#	Searches
72	animal/ not human/ use emez
73	nonhuman/ use emez
74	exp Animals, Laboratory/ use ppez
75	exp Animal Experimentation/ use ppez
76	exp Animal Experiment/ use emez
77	exp Experimental Animal/ use emez
78	exp Models, Animal/ use ppez
79	animal model/ use emez
80	exp Rodentia/ use ppez
81	exp Rodent/ use emez
82	(rat or rats or mouse or mice).ti.
83	or/70-82
84	52 not 83
85	Meta-Analysis/
86	Meta-Analysis as Topic/
87	systematic review/
88	meta-analysis/
89	(meta analy* or metanaly* or metaanaly*).ti,ab.
90	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
91	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
92	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
93	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
94	(search* adj4 literature).ab.
95	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
96	cochrane.jw.
97	((pool* or combined) adj2 (data or trials or studies or results)).ab.
98	or/85-86,89,91-96 use ppez
99	or/87-90,92-97 use emez
100	or/98-99
101	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
102	101 use ppez
103	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
104	103 use ppez
105	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
106	105 use emez
107	102 or 104
108	106 or 107
109	100 or 108
110	84 and 109
111	remove duplicates from 110

Observational studies

Date of initial search: 08/11/17

Database(s): Embase 1980 to 2017 Week 45, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.

#	Searches
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh$).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emez
17	newborn care/ use emez
18	(special and care and baby and unit*).tw.
19	((newborn or neonatal or neo-natal) adj ICU*1).tw.
20	((newborn or neonat* or neo-nat*) adj2 (unit or care or department* or facilit* or hospital*)).tw.
21	(SCBU or NICU).tw.
22	((infan* or baby or babies or preterm or pre-term or prematur* or pre?mie* or premie*1) adj2 (unit* or care or department* or facilit* or hospital*)).tw.
23	or/1-22
24	exp Intubation, Intratracheal/ use ppez
25	exp respiratory tract intubation/ use emez
26	intubat*.tw.
27	or/24-26
28	23 and 27
29	Premedication/
30	"Hypnotics and Sedatives"/
31	"Anaesthesia and Analgesia"/ or Analgesia/ or Anaesthesia/
32	Cholinergic Antagonists/ or Muscarinic Antagonists/
33	exp Analgesics, Opioid/
34	exp Neuromuscular Nondepolarizing Agents/ or exp Neuromuscular Blockade/ or exp Neuromuscular Depolarizing Agents/ or exp Neuromuscular Blocking Agents/
35	Alfentanil/ or Atropine/ or Atracurium/ or Fentanyl/ or Midazolam/ or Morphine/ or Propofol/
36	or/29-35 use ppez
37	exp premedication/
38	hypnotic sedative agent/
39	anesthesiological procedure/ or analgesia/ or anaesthesia/ or anesthetic agent/
40	cholinergic receptor blocking agent/ or muscarinic receptor blocking agent/
41	narcotic analgesic agent/
42	muscle relaxant agent/ or neuromuscular blocking agent/ or neuromuscular blocking/ or neuromuscular depolarizing agent/ or neuromuscular depolarizing agent/
43	alfentanil/ or atracurium besilate/ or atropine/ or fentanyl/ or midazolam/ or propofol/ or remifentanil/ or rocuronium/ or suxamethonium/
44	or/37-43 use emez
45	(alfentan?l or atracurium or atropine or fentan?l or midazolam or morphine or propofol or remifentan?l or rocuronium or suxamethonium).tw.
46	(premedication or pre-medication or premed* or pre-med*).tw.
47	(sedat* or hypnotics or anaesth* or analges* or narcotic* or opioid* or cholinergic antagonist* or muscarinic antagonist* or neuromuscular block* or neuromuscular nondepolarizing agent* or neuromuscular depolarizing agent* or muscle relax*).tw.
48	or/45-47
49	36 or 44 or 48
50	28 and 49
51	limit 50 to english language
52	limit 51 to yr="1990 -Current"
53	Letter/ use ppez
54	letter.pt. or letter/ use emez
55	note.pt.
56	editorial.pt.
57	Editorial/ use ppez
58	News/ use ppez
59	exp Historical Article/ use ppez
60	Anecdotes as Topic/ use ppez
61	Comment/ use ppez
62	Case Report/ use ppez
63	case report/ or case study/ use emez
64	(letter or comment*).ti.
65	or/53-64
66	randomized controlled trial/ use ppez

#	Searches
67	randomized controlled trial/ use emez
68	random*.ti,ab.
69	or/66-68
70	65 not 69
71	animals/ not humans/ use ppez
72	animal/ not human/ use emez
73	nonhuman/ use emez
74	exp Animals, Laboratory/ use ppez
75	exp Animal Experimentation/ use ppez
76	exp Animal Experiment/ use emez
77	exp Experimental Animal/ use emez
78	exp Models, Animal/ use ppez
79	animal model/ use emez
80	exp Rodentia/ use ppez
81	exp Rodent/ use emez
82	(rat or rats or mouse or mice).ti.
83	or/70-82
84	52 not 83
85	Epidemiologic Studies/
86	Case Control Studies/
87	Retrospective Studies/
88	Cohort Studies/
89	Longitudinal Studies/
90	Follow-Up Studies/
91	Prospective Studies/
92	Cross-Sectional Studies/
93	or/85-92 use ppez
94	clinical study/
95	case control study/
96	family study/
97	longitudinal study/
98	retrospective study/
99	prospective study/
100	cohort analysis/
101	or/94-100 use emez
102	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
103	93 or 101 or 102
104	84 and 103
105	remove duplicates from 104

Health economics

Date of initial search: 08/11/17

Database(s): Embase 1980 to 2017 Week 45, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 03/07/2018

Database(s): Embase 1980 to 2018 Week 27, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Infant, Newborn/ use ppez
2	newborn/ use emez
3	prematurity/ use emez
4	(infan* or neonat* or neo-nat* or newborn* or baby or babies).ti,ab,jw,nw.
5	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1).tw.
6	exp low birth weight/ use emez
7	(low adj3 birth adj3 weigh$).tw.
8	(LBW or VLBW).tw.
9	exp Respiratory Distress Syndrome, Newborn/ use ppez
10	neonatal respiratory distress syndrome/ use emez

#	Searches
11	exp Intensive Care, Neonatal/ use ppez
12	newborn intensive care/ use emez
13	exp Intensive Care Units, Neonatal/ use ppez
14	neonatal intensive care unit/ use emez
15	Neonatal Nursing/ use ppez
16	exp newborn nursing/ use emez
17	newborn care/ use emez
18	(special and care and baby and unit*).tw.
19	((newborn or neonatal or neo-natal) adj ICU*1).tw.
20	((newborn or neonat* or neo-nat*) adj2 (unit or care or department* or facilit* or hospital*)).tw.
21	(SCBU or NICU).tw.
22	((infan* or baby or babies or preterm or pre-term or prematur* or pre?mie* or premie*1) adj2 (unit* or care or department* or facilit* or hospital*)).tw.
23	or/1-22
24	exp Intubation, Intratracheal/ use ppez
25	exp respiratory tract intubation/ use emez
26	intubat*.tw.
27	or/24-26
28	23 and 27
29	Premedication/
30	"Hypnotics and Sedatives"/
31	"Anaesthesia and Analgesia"/ or Analgesia/ or Anaesthesia/
32	Cholinergic Antagonists/ or Muscarinic Antagonists/
33	exp Analgesics, Opioid/
34	exp Neuromuscular Nondepolarizing Agents/ or exp Neuromuscular Blockade/ or exp Neuromuscular Depolarizing Agents/ or exp Neuromuscular Blocking Agents/
35	Alfentanil/ or Atropine/ or Atracurium/ or Fentanyl/ or Midazolam/ or Morphine/ or Propofol/
36	or/29-35 use ppez
37	exp premedication/
38	hypnotic sedative agent/
39	anesthesiological procedure/ or analgesia/ or anaesthesia/ or anesthetic agent/
40	cholinergic receptor blocking agent/ or muscarinic receptor blocking agent/
41	narcotic analgesic agent/
42	muscle relaxant agent/ or neuromuscular blocking agent/ or neuromuscular blocking/ or neuromuscular depolarizing agent/ or neuromuscular depolarizing agent/
43	alfentanil/ or atracurium besilate/ or atropine/ or fentanyl/ or midazolam/ or propofol/ or remifentanil/ or rocuronium/ or suxamethonium/
44	or/37-43 use emez
45	(alfentan?l or atracurium or atropine or fentan?l or midazolam or morphine or propofol or remifentan?l or rocuronium or suxamethonium).tw.
46	(premedication or pre-medication or premed* or pre-med*).tw.
47	(sedat* or hypnotics or anaesth* or analges* or narcotic* or opioid* or cholinergic antagonist* or muscarinic antagonist* or neuromuscular block* or neuromuscular nondepolarizing agent* or neuromuscular depolarizing agent* or muscle relax*).tw.
48	or/45-47
49	36 or 44 or 48
50	28 and 49
51	limit 50 to english language
52	limit 51 to yr="1990 -Current"
53	Letter/ use ppez
54	letter.pt. or letter/ use emez
55	note.pt.
56	editorial.pt.
57	Editorial/ use ppez
58	News/ use ppez
59	exp Historical Article/ use ppez
60	Anecdotes as Topic/ use ppez
61	Comment/ use ppez
62	Case Report/ use ppez
63	case report/ or case study/ use emez
64	(letter or comment*).ti.
65	or/53-64
66	randomized controlled trial/ use ppez
67	randomized controlled trial/ use emez
68	random*.ti,ab.
69	or/66-68
70	65 not 69
71	animals/ not humans/ use ppez

#	Searches
72	animal/ not human/ use emez
73	nonhuman/ use emez
74	exp Animals, Laboratory/ use ppez
75	exp Animal Experimentation/ use ppez
76	exp Animal Experiment/ use emez
77	exp Experimental Animal/ use emez
78	exp Models, Animal/ use ppez
79	animal model/ use emez
80	exp Rodentia/ use ppez
81	exp Rodent/ use emez
82	(rat or rats or mouse or mice).ti.
83	or/70-82
84	52 not 83
85	Economics/
86	Value of life/
87	exp "Costs and Cost Analysis"/
88	exp Economics, Hospital/
89	exp Economics, Medical/
90	Economics, Nursing/
91	Economics, Pharmaceutical/
92	exp "Fees and Charges"/
93	exp Budgets/
94	or/85-93 use ppez
95	health economics/
96	exp economic evaluation/
97	exp health care cost/
98	exp fee/
99	budget/
100	funding/
101	or/95-100 use emez
102	budget*.ti,ab.
103	cost*.ti.
104	(economic* or pharmaco?economic*).ti.
105	(price* or pricing*).ti,ab.
106	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
107	(financ* or fee or fees).ti,ab.
108	(value adj2 (money or monetary)).ti,ab.
109	or/102-107
110	94 or 101 or 109
111	84 and 110
112	remove duplicates from 111

Systematic reviews, RCTs and Health economics

Date of initial search: 08/11/2017

Databases: The Cochrane Library, issue 11 of 12, November 2017

Date of updated search: 02/07/2018

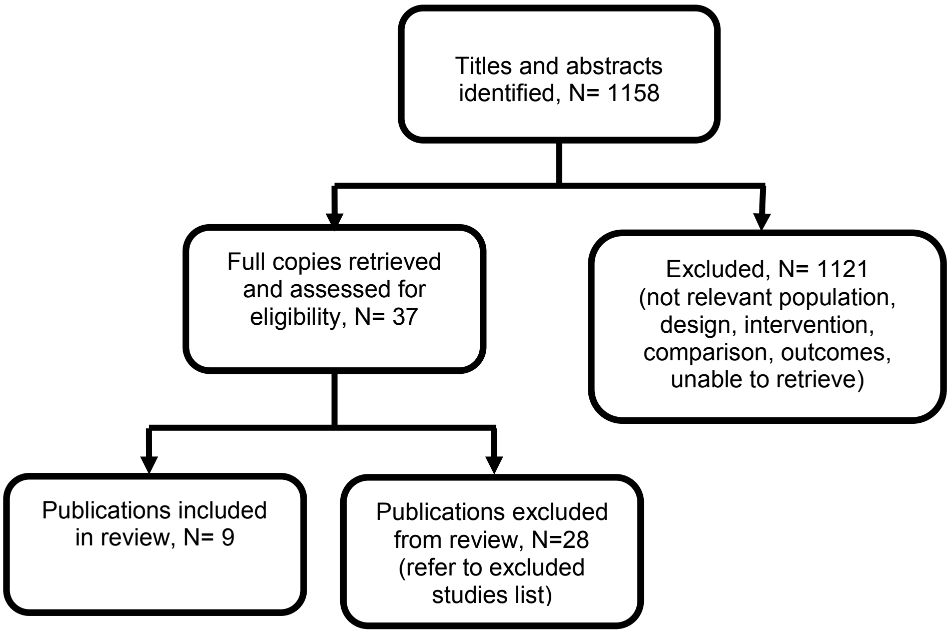
Databases: The Cochrane Library, issue 7 of 12, July 2018

ID	Search
#1	MeSH descriptor: [Infant, Newborn] explode all trees
#2	(infan* or neonat* or neo-nat* or newborn* or baby or babies)
#3	(preterm or pre-term or prematur* or pre-matur* or pre?mie* or premie*1)
#4	(low near birth near weigh*)
#5	MeSH descriptor: [Intensive Care, Neonatal] this term only
#6	MeSH descriptor: [Intensive Care Units, Neonatal] this term only
#7	(special and care and baby and unit*)
#8	((newborn or neonatal or neo-natal) near (ICU*1 or unit*))
#9	(SCBU or NICU)
#10	{or #1-#9}
#11	MeSH descriptor: [Intubation, Intratracheal] explode all trees

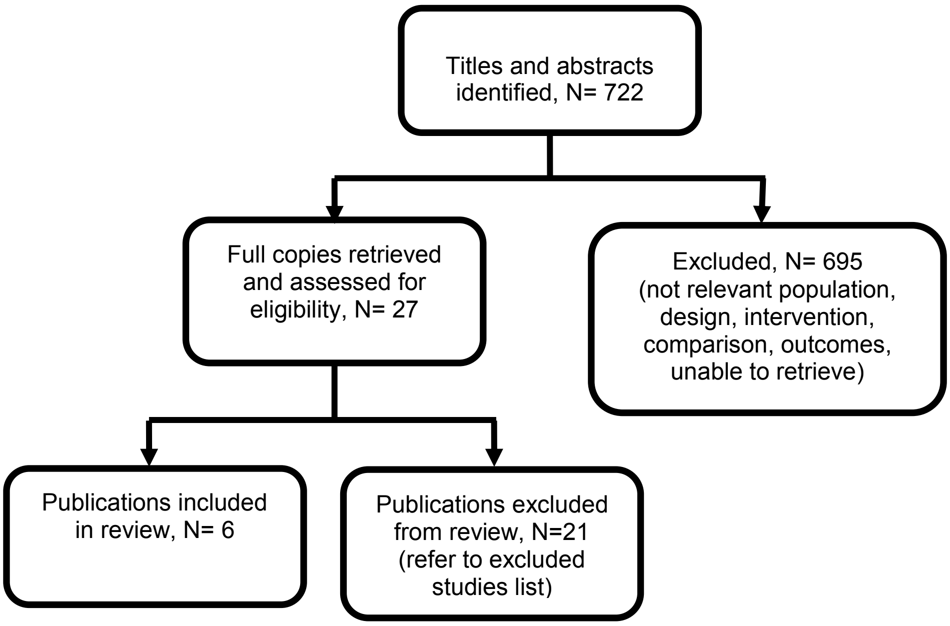
ID	Search
#12	intubat*
#13	#11 or #12
#14	#10 and #13
#15	MeSH descriptor: [Premedication] this term only
#16	MeSH descriptor: [Hypnotics and Sedatives] this term only
#17	MeSH descriptor: [Anesthesia and Analgesia] this term only
#18	MeSH descriptor: [Analgesia] this term only
#19	MeSH descriptor: [Anesthesia] this term only
#20	MeSH descriptor: [Cholinergic Antagonists] this term only
#21	MeSH descriptor: [Muscarinic Antagonists] this term only
#22	MeSH descriptor: [Analgesics, Opioid] explode all trees
#23	MeSH descriptor: [Neuromuscular Nondepolarizing Agents] explode all trees
#24	MeSH descriptor: [Neuromuscular Blockade] explode all trees
#25	MeSH descriptor: [Neuromuscular Depolarizing Agents] explode all trees
#26	MeSH descriptor: [Neuromuscular Blocking Agents] explode all trees
#27	MeSH descriptor: [Alfentanil] this term only
#28	MeSH descriptor: [Atropine] this term only
#29	MeSH descriptor: [Atracurium] this term only
#30	MeSH descriptor: [Fentanyl] this term only
#31	MeSH descriptor: [Midazolam] this term only
#32	MeSH descriptor: [Morphine] this term only
#33	MeSH descriptor: [Propofol] this term only
#34	(alfentan?l or atracurium or atropine or fentan?l or midazolam or morphine or propofol or remifentan?l or rocuronium or suxamethonium)
#35	(sedat* or hypnotics or anaesth* or analges* or narcotic* or opioid* or cholinergic antagonist* or muscarinic antagonist* or neuromuscular block* or neuromuscular nondepolarizing agent* or neuromuscular depolarizing agent* or muscle relax* or premedication or pre-medication or premed* or pre-med*)
#36	{or #15-#35}
#37	#14 and #36 Publication Year from 1990 to 2017

Appendix C – Clinical evidence study selection

Clinical evidence study selection for question 5.1 What is the effectiveness of morphine during respiratory support?



Clinical evidence study selection for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?



Appendix D – Clinical evidence tables

Clinical evidence tables for question 5.1 What is the effectiveness of morphine during respiratory support?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Anand, Kj, Hall, Rw, Desai, N, Shephard, B, Bergqvist, Ll, Young, Te, Boyle, Em, Carbajal, R, Bhutani, Vk, Moore, Mb, Kronsberg, Ss, Barton, Ba, Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial, Lancet (London, England), 363, 1673-1682, 2004 **Ref Id** 642981 **Country/ies where the study was carried out** France, Sweden, United Kingdom, United States **Study type**	**Sample size** N= 898 n intervention= 449 n control= 449 **Characteristics** Morphine group, n=449 Gestational age, 23-26 weeks, n (%)= 176 (39.2%) Gestational age, 27-29 weeks, n (%)= 190 (42.3%) Gestational age, 30-32 weeks, n (%)= 83 (18.5%) Birthweight, mean (SD)= 1037 (340) Apgar score at 5 min, median (IQR)= 7 (6-8) CRIB score, median (IQR)= 4 (1-8) Placebo group, n=449	**Interventions** Neonates in the intervention group received a loading dose of morphine (100 g/kg infused over 1 h), followed by continuous infusions of 10 g kg^{-1} h^{-1} for those of gestational age 23–26 weeks, 20 g kg^{-1} h^{-1} for those of 27–29 weeks' gestation, or 30 g kg^{-1} h^{-1} for those of 30–32 weeks' gestation. Doses were based on morphine pharmacokinetic data available at the time of protocol development. Analgesia with bolus doses of the study drug or increases in the infusion rate were not permitted, but the infusion rate was increased if the baby grew to a higher gestational stratum.	**Details** Randomisation Ventilated preterm neonates from 16 participating centres were randomly assigned to blinded placebo or intervention groups. Randomisation was done by an automated telephone response system with faxed confirmation of treatment codes to the participating neonatal intensive-care unit, the hospital pharmacy, or both. Randomisation was stratified by the participating neonatal intensive-care unit and by gestational age at birth (23–26 weeks, 27–29 weeks, and 30–32 weeks) to ensure equal numbers in each group. To eliminate clinical bias, neonates were assigned a study drug code (with four unit-specific codes for each randomised group) and drugs	**Results** Severe IVH (Grade 3 or 4) Morphine group -Overall= 55/411 (13%) -23-26 weeks= 31/152 (20%) -27-29 weeks= 22/181 (12%) -30-32 weeks= 2/78 (10%) Placebo group -Overall= 46/429 (11%) -23-26 weeks= 33/164 (20%) -27-29 weeks= 11/182 (6%) -30-32 weeks= 2/83 (2%) Mortality prior to discharge Morphine group -Overall= 58/449 (13%)	**Limitations** **Cochrane risk of bias tool** Selection bias -Random sequence generation: low risk -Allocation concealment: low risk Performance bias -Blinding: low risk Detection bias -Blinding: low risk Attrition bias -Incomplete outcome data: low risk Reporting bias -Selective reporting: low risk Other bias -Other sources of bias: high risk - patients in both arms received open-label morphine after the start of the study if the attending nurse or physician deemed it necessary

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** To determine whether preemptive morphine analgesia would decrease the rate of neonatal death, severe intraventricular haemorrhage (IVH), and periventricular leucomalacia (PVL) in preterm neonates **Study dates** 1998 **Source of funding** National Institute for Child Health and Human Development; Office of the Scottish Executive; Swedish Research Council; Vardal Foundation; Free Masons, Sweden; Fondation pour la Sante CNP; Orebro University	Gestational age, 23-26 weeks, n (%)= 174 (38.8%) Gestational age, 27-29 weeks, n (%)= 190 (42.3%) Gestational age, 30-32 weeks, n (%)= 85 (18.9%) Birthweight, mean (SD)= 1054 (354) Apgar score at 5 min, median (IQR)= 7 (6-8) CRIB score, median (IQR)= (1-8) **Inclusion criteria** Infants born at 23-32 weeks gestation who were intubated within 72hr of birth and had been ventilated < 8hr at enrolment **Exclusion criteria** Infants with major congenital anomalies, birth asphyxia, intrauterine growth		were dispensed by pharmacists not involved in their clinical care. Unmasking of treatment code was limited by specific criteria, and the unmasked code at that institution was discontinued. Data collection Data was collected by trained staff; discrepancies between interpretations of data were adjudicated and a consensus interpretation was used. Responses to tracheal suctioning were assessed by means of the premature infant pain profile (PIPP) before the start of study drug infusion, at 24 hr and 72 hr during infusion, and 12 hr after the end of the infusion. At each time point, heart rate, respiratory rate, and oxygen saturation were recorded before and 2 minutes after tracheal suctioning. Statistical analyses Intention-to-treat analyses were used. Group outcomes were compared by X-squared tests or Fisher's exact tests, and homogeneity of the odds ratios across gestational ages was	-23-26 weeks= 46/176 (26%) -27-29 weeks= 10/190 (5%) -30-32 weeks= 2/83 (2%) Placebo group -Overall= 47/449 (11%) -23-26 weeks= 41/174 (24%) -27-29 weeks= 6/190 (3%) -30-32 weeks= 0/85	**Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Hospital Research Foundation	retardation; mothers with maternal opioid addiction or were participating in other clinical trials		tested by the Breslow-Day test. For only the data from observed clinical outcomes, treatment group and gestational age were forced into logistic regression models to predict each outcome. The fit of the logistic model was assessed by the Hosmer-Lemeshow goodness-of-fit test; the global test, that all regression parameters are zero, was tested with the –2 log likelihood statistic. All analyses were done with SAS software (version 8.1) and the critical p value was set at 0·05. Results of logistic regression analyses are presented as point estimate odds ratios with two-sided 95% CI. Pain assessments (scores on the premature infant pain profile) and vital signs (heart rate, respiratory rate, oxygen saturation) were compared between the randomised groups by use of t tests at each time point.		
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Anand, K. J. S., McIntosh, N., Lagercrantz, H., Pelausa, E., Young, T. E., Vasa, R., Analgesia and sedation in preterm neonates who require ventilatory support: Results from the NOPAIN trial, Archives of Pediatrics and Adolescent Medicine, 153, 331-338, 1999 **Ref Id** 642987 **Country/ies where the study was carried out** Canada, Germany, United Kingdom, and United States **Study type** Pilot RCT **Aim of the study** The aim of the study was too determine the	N= 67 n intervention group 1= 22 n intervention group 2= 24 n control group= 21 **Characteristics** Midazolam group Gestational age, mean (SD), wk= 28.6 (2.5) Birth weight, mean (SD), g= 1245 (445) Duration of study drug, mean (SD), hours of infusion= 122.2 (122.1) CRIB score, mean (SD)= 5.7 (3.5) Morphine sulfate group Gestational age, mean (SD), wk= 29.2 (2.2) Birth weight, mean (SD), g= 1230 (475) Duration of study drug, mean (SD), hours of infusion= 81.0 (94.1) CRIB score, mean (SD)= 4.5 (3.1) Dextrose group Gestational age, mean (SD), wk= 28.1 (2.2)	Intervention group 1 - Midazolam hydrochloride (0.1/mg/mL in 10% dextrose) infusions Intervention group 2 - Morphine sulfate (0.05 mg/mL in 10% dextrose) infusions Control - Placebo (10% dextrose) infusions Bolus doses or increases in the rate of infusion of the study drug were not allowed. Study drug infusions were continued for as long as clinically necessary or for a maximum of 14 days. At the discretion of the clinical team, additional analgesia was provided with intravenous morphine doses, and the amount and frequency of analgesia were recorded as outcome measures	Randomisation Randomisation was performed in blocks and stratified by each centre. Randomised group allocation was faxed to the participating NICUs and hospital pharmacies. Data Collection Severity of illness was measured by the Clinical Risk Index for Babes (CRIB) and the Neonatal Medical Index (NMI). Level of sedation assessed by COMFORT score. Responses to pain measured by the Premature Infant Pain Profile (PIPP) score Data analysis Intention-to-treat analyses were used. Binary and categorical outcomes were compared among treatment groups using a likelihood ration X-squared procedure. Logistic regressions were used to investigate the the effects of treatment group allocation and other clinical variables on binary outcomes (placebo used as the reference group). Linear regression analyses were used for	Mortality prior to discharge, n (%) Midazolam= 1 (4.6%) Morphine sulfate= 0 Dextrose= 2 (9.5%) Severe IVH (Grade 3 or 4), n (%) Midazolam= 5 (22.7%) Morphine sulfate= 0 Dextrose= 3 (14.3%) COMFORT scores before drug infusion, mean (SD) Midazolam= 15.9 (3.8) Morphine sulfate= 17.3 (4.6) Dextrose=15.6 (3.2) COMFORT scores during	**Cochrane risk of bias tool** Selection bias -Random sequence generation: low risk -Allocation concealment: low risk Performance bias -Blinding: low risk Detection bias -Blinding: low risk Attrition bias -Incomplete outcome data: low risk Reporting bias -Selective reporting: low risk Other bias -Other sources of bias: high risk - patients in both arms received open-label morphine after the start of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
incidence of clinical outcomes in the study population; estimate the effect size and adverse effects associated with analgesia and sedation and to calculate the sample size for a definite test of study hypothesis **Study dates** Not reported **Source of funding** International Association for the Study of Pain; Sprint, Inc.; Astra Pain Control; Twigs at Egleston Children's Hospital	Birth weight, mean (SD), g= 1049 (419) Duration of study drug, mean (SD), hours of infusion= 121.1 (120.8) CRIB score, mean (SD)= 6.6 (4.0) **Inclusion criteria** Infants born between 24-32 weeks gestation, intubated and required ventilatory support for less than 8 hours at the time of enrollment **Exclusion criteria** Infants with a postnatal age > 72 hr, had positive pressure ventilation for 8+ hr, had major congenital anomies or severe intrapartum asphyxia or were participating in other research studies		comparisons of mean outcome levels and differences in baseline characteristics. p<0.05 were used for primary outcomes and p<0.01 were used for secondary outcomes	drug infusion, mean (SD) Midazolam= 14.9 (4.6) Morphine sulfate= 14.7 (3.2) Dextrose= 17.5 (4.2) COMFORT scores after drug infusion, mean (SD) Midazolam= 15.8 (4.7) Morphine sulfate= 18.9 (4.0) Dextrose= 16.2 (4.1) PIPP scores before drug infusion, mean (SD) Midazolam= 10.5 (4.1) Morphine sulfate= 11.5 (4.0) Dextrose=11.4 (3.8)	the study if the attending nurse or physician deemed it necessary **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				PIPP scores during drug infusion, mean (SD) Midazolam= 8.9 (3.3) Morphine sulfate= 7.9 (2.3) Dextrose=12.7 (3.8) PIPP scores after drug infusion, mean (SD) Midazolam= 8.9 (4.4) Morphine sulfate= 10.2 (2.9) Dextrose= 9.9 (3.7) Days to enteral feeding, mean (SD) Midazolam= 11.0 (7.1) Morphine sulfate= 10.9 (7.8) Dextrose= 12.8 (17.4)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Carbajal, R., Lenclen, R., Jugie, M., Paupe, A., Barton, B. A., Anand, K. J., Morphine does not provide adequate analgesia for acute procedural pain among preterm neonates, Pediatrics, 115, 1494-500, 2005 **Ref Id** 410024 **Country/ies where the study was carried out** **Study type** Please see Anand 2004 for study details **Aim of the study** **Study dates**	**Sample size** N= 42 Intervention= 21 Control= 21 **Characteristics** Morphine group Gestational age, wk, mean (SD)= 27.3 (1.8) Birth weight, g, mean (SD)= 947 (269) Apgar score, 1 min, mean (SD)= 6 (2-7) Apgar score, 5 min, mean (SD)= 8 (7-10) CRIB score, median (IQR)= 4 (1-6) Placebo group Gestational age, wk, mean (SD)= 27.2 (1.7) Birth weight, g, mean (SD)= 972 (270) Apgar score, 1 min, mean (SD)= 5 (3-7) Apgar score, 5 min, mean (SD)= 8 (7-10) CRIB score, median (IQR)= 4 (1-5)	**Interventions**	**Details**	**Results** Pain score, DAN scale, mean (SD) Morphine group T1= 4.5 (3.8) T2= 4.4 (3.7) T3= 3.1 (3.4) Placebo group T1= 4.8 (4.0) T2= 4.6 (2.9) T3= 4.7 (3.6) Pain score, PIPP scale, mean (SD) Morphine group T1= 10.0 (3.6) T2= 8.8 (4.9) T3= 7.8 (3.6) Placebo group T1= 11.5 (4.8) T2= 11.1 (3.7) T3= 9.1 (4.0)	**Limitations** **Cochrane risk of bias tool** Selection bias -Random sequence generation: low risk -Allocation concealment: low risk Performance bias -Blinding: low risk Detection bias -Blinding: low risk Attrition bias -Incomplete outcome data: high risk; study did not report how incomplete data was managed i.e. with intention-to-treat analysis Reporting bias -Selective reporting: low risk Other bias -Other sources of bias: low risk **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding	**Inclusion criteria** **Exclusion criteria**				
Full citation Cignacco, E, Hamers, Jp, Lingen, Ra, Zimmermann, Lj, Müller, R, Gessler, P, Nelle, M, Pain relief in ventilated preterms during endotracheal suctioning: a randomized controlled trial, Swiss Medical WeeklySwiss Med Wkly, 138, 635-645, 2008 **Ref Id** 643119 **Country/ies where the study was carried out** Switzerland **Study type**	**Sample size** N= 30 Intervention= 16 Placebo= 14 **Characteristics** Morphine group Gestational age, weeks, n (%) 24-28= 9 (56.3) 28-32= 5 (31.3) 32-37= 2 (12.5) Gestational age, mean (SD)= 28.17 (3.00) Birth weight, g, mean (SD)= 1113.44 (562.46) Apgar score, 1 min, mean (SD)= 4.38 (1.996) Apgar score, 5 min, mean (SD)= 6.63 (2.15) Placebo group	**Interventions** Intervention Morphine group -Each time a child needed to be suctioned the nurse on duty for this child administrated the allocated medication. The interval between treatments depended on the need for suctioning in the individual infant and was decided by the nurse in charge. In view of the long half-life of morphine in preterm infants, an interval of six hours was set for repeating medication during ETS. If suctioning the infant became necessary sooner, the medication was either modified accordingly (0.05 mg/kg) or not given at	**Details** Randomisation -Randomisation was completed using a computer list regarding medication (morphine or a placebo) as well as comforting technique after suctioning (MSS or standard technique). Allocation concealment was made by the study investigator for both interventions and for each infant, and the allocation was included in the same sequentially numbered and sealed opaque envelope. The medication itself was pre-prepared, labelled and numbered according to the computer generated list in the correct dose by the hospital pharmacy. The two medications were of identical	**Results** Pain scores, BPSN, mean (SD) Morphine group -T0 (baseline)= 3.54 (2.69) -T1 (after administering an analgesic, 5 min before ETS)= 3.64 (2.80) -T2 (during ETS)= 6.67 (2.54) Placebo group -T0 (baseline)= 4.45 (2.22) -T1 (after administering an analgesic, 5	**Limitations** **Cochrane risk of bias tool** Selection bias -Random sequence generation: low risk -Allocation concealment: low risk Performance bias -Blinding: low risk Detection bias -Blinding: low risk Attrition bias -Incomplete outcome data: low risk Reporting bias -Selective reporting: low risk Other bias -Other sources of bias: high risk; patients in both arms received open-label

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Factorial RCT **Aim of the study** To assess whether an intermittent dose of morphine reduces pain during endotracheal suctioning (ETS) and that subsequent multisensorial stimulation (MSS), as a non pharmacological comforting intervention helps infants to recover from experienced pain **Study dates** May 2004-April 2006 **Source of funding** Executive Directory of Nursing, University Hospital in Bern; 'Reach Out' project of the 'Eleonoren Foundation,' Children's University Hospital, Zurich; 'Ettore and Valeria Rossi	Gestational age, weeks, n (%) 24-28= 8 (57.1) 28-32= 3 (21.4) 32-37= 3 (21.4) Gestational age, mean (SD)= 28.08 (3.93) Birth weight, g, mean (SD)= 1110.21 (703.50) Apgar score, 1 min, mean (SD)= 4.5 (2.53) Apgar score, 5 min, mean (SD)= 6.7 (2.15) **Inclusion criteria** Preterm babies born 24-37 weeks postmenstrual age, intubated and mechanically ventilated **Exclusion criteria** Babies with IVH grade 3 or 4, their condition involved partial or total loss of sensitivity, received morphine intravenously up to 10 hr before study	all. Additional open-label morphine was allowed if infants were considered to be in pain, as verified by a pain score. -Routine ETS was carried out by qualified and trained nurses, who administered the iv medication five minutes before the ETS. After suctioning, the infant was comforted either by randomized MSS or by using a standard method (holding the child in the incubator) by the same nurse for two to three minutes. Through MSS, the preterm is calmed after a painful procedure by massaging the back and face. A few drops of a vanillin-oil are spread onto the nurse’s hand used for massaging (orogustatory level) and the child is also spoken to gently (auditory level). Furthermore, the infant is provided with a cotton wool stick sprinkled with sucrose so that he/she can suck on it (olfactory level).	appearance. An attending neonatologist in the participating NICUs identified potential neonatal subjects and communicated this information to a member of the research team. A member of the research team approached the parents of potentially eligible neonates and explained the study to the parents. After receiving informed consent the primary investigator or the study nurse opened the envelope and assigned the child according to its number to one of the treatment groups. Data collection The "Bernese Pain Scale for Neonates" (BPSN), "Premature Infant Pain Profile" (PIPP) and "Visual Analogue Scale" (VAS) were used to measure pain scores Data analysis Hypotheses were examined using variance analysis (univariate analysis and the general linear model). Mauchly’s test of sphericity was verified before interpretation of results. Nominal variables were	min before ETS)= 3.05 (1.57) -T2 (during ETS)= 7.62 (2.94) Pain scores, PIPP, mean (SD) Morphine group -T0 (baseline)= 5.49 (1.82) -T1 (after administering an analgesic, 5 min before ETS)= 5.43 (0.98) -T2 (during ETS)= 6.84 (1.54) Placebo group -T0 (baseline)= 5.01 (1.53) -T1 (after administering an analgesic, 5 min before ETS)= 4.84 (1.28)	morphine after the start of the study if the attending nurse or physician deemed it necessary; both trial arms did not have > 15 participants **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Foundation,' Berne, Switzerland	commencement, APGAR score <3 after 5 min or with a cord blood pH of <7.00, mother was addicted to drugs	-In the case of assignment to the morphine groups, a dose of 0.1 mg/kg was set Control Placebo group	compared with Fischer's exact tests (for contingency tables with small cell frequency). In case data were not distributed normally, nonparametric procedures were used. Comparing MSS and standard comforting, we expected that infants in the placebo group would be comforted more quickly through MSS. Measurement of MSS was at T4, a point in time at which the design was a factorial one, we fit a rank transformed ANOVA including the variables morphine, MSS and their interaction. No power analysis was done in this respect. The assumptions for parametric tests were verified by Q-Q-Plots.	-T2 (during ETS)= 6.61 (2.08) Mortality prior to discharge, n (%) Morphine group= 2 (12.5) PLacebo group= 3 (21.4) Severe IVH (Grade 3 or 4), n (%) Morphine group= 1 (6.25) Placebo group= 0 (0.00)	
Full citation Dyke, M. P., Kohan, R., Evans, S., Morphine increases synchronous ventilation in preterm infants, Journal of	**Sample size** N= 26 Intervention= 12 Control= 14 **Characteristics**	**Interventions** Loading dose of morphine 100 pg/kg over 30 min followed by a continuous intravenous infusion at 10 pg/kg per hour was given.	**Details** Randomisation Randomisation was completed with a computer-generated random number sequence conducted by the pharmacy staff. Infants were block-	**Results** Mortality prior to discharge, n Morphine group= 0 Placebo group= 0	**Limitations** **Cochrane risk of bias tool** Selection bias -Random sequence generation: low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
paediatrics and child health, 31, 176-179, 1995 **Ref Id** 643180 **Country/ies where the study was carried out** Australia **Study type** RCT **Aim of the study** The aim of the study was to assess the short-term cardiorespiratory effects of intravenous morphine infusion preterm babies who are ventilated **Study dates** April-November 1992 **Source of funding** Not reported	Gestational age, wk, median (IQR) Morphine group= 31 (29.25-33) Placebo group= 32 (29.75-34) Birth weight, g, median (IQR) Morphine group= 1703 (1513-1956) Placebo group= 1863 (1532-2456) Exogenous surfactant administered, n Morphine group= 9/12 Placebo group= 12/14 **Inclusion criteria** Babies born between 29-36 weeks gestation and required intermittent mandatory ventilation **Exclusion criteria** Babies with major congenital malformations		randomised in groups of 4 and stratified by gestation into 2 strata (29-32 weeks and 33-36 weeks) Data collection Nursing staff were issued with a 1 mL syringe from pharmacy containing morphine (1 mg/mL in 5% dextrose) or 5% dextrose as a placebo. A standard series of dilutions with 5% dextrose were then performed to yield one solution of morphine (100ug/mL) for use as a bolus dose and a further solution containing morphine (10ug/mL) for use as a continuous IV infusion (or placebo diluted in identical fashion). The bolus solution was administered in a dose of 1 mL/kg body weight (equivalent to 100ug/kg morphine) over 30 min to be followed immediately by the infusion at a dose of 1 mL/kg per hour (10ug/kg per hour morphine). The infusion was continued until the infant was successfully weaned from intermittent mandatory ventilation or for a maximum of 48 h therapy. Clinical staff		-Allocation concealment: low risk Performance bias -Blinding: low risk Detection bias -Blinding: low risk Attrition bias -Incomplete outcome data: low risk Reporting bias -Selective reporting: low risk Other bias -Other sources of bias: high risk; both trial arms did not have > 15 participants **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			remained blinded to treatment allocation throughout the study period. Data analysis Non-parametric data are presented as median values with 25-75th percentiles (IQR) and were analysed using a Wilcoxon rank sum test or Fisher's exact test as appropriate. The proportions of synchronous respiration for the two groups were compared using a time adjusted Kruskal-Wallis test. Repeated measures analysis of variance was used to compare values of heart rate, mean arterial pressure, respiratory rate and ventilator rate over time.		
Full citation Menon, G., Boyle, E. M., Bergqvist, L. L., McIntosh, N., Barton, B. A., Anand, K. J. S., Morphine analgesia and gastrointestinal morbidity in preterm infants:	**Sample size** Please see Anand 2004 for Participant and Intervention information **Characteristics**	**Interventions**	**Details**	**Results** Days to enteral feeding, median (IQR) -Morphine= 5 (3–8) -Placebo= 4 (2–7)	**Limitations** **Cochrane risk of bias tool** Selection bias -Random sequence generation: low risk -Allocation concealment: low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Secondary results from the NEOPAIN trial, Archives of Disease in Childhood: Fetal and Neonatal Edition, 93, f362-f367, 2008 **Ref Id** 619771 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Inclusion criteria** **Exclusion criteria**			Days to enteral feeding, mean (SD) -Morphine= 5.3 (1.3) -Placebo= 4.3 (1.3)	Performance bias -Blinding: low risk Detection bias -Blinding: low risk Attrition bias -Incomplete outcome data: low risk Reporting bias - Selective reporting: high risk; p-values and CIs not reported Other bias -Other sources of bias: high risk; patients in both arms received open-label morphine after the start of the study if the attending nurse or physician deemed it necessary **Other information**
Full citation Quinn, Mw, Wild, J, Dean, Hg, Hartley, R, Rushforth, Ja, Puntis, Jw,	**Sample size** N= 41 n intervention= 21 n control= 20	**Interventions** The dose regimen of the trial solution (25mg morphine in 30 mL 5% dextrose) was 2 mL per h for each kg	**Details** Randomisation Randomisation with stratified tables was carried out in the pharmacy department. Babies	**Results** Sury et al. (1990) pain scores at 0 hr, median (IQR)	**Limitations** **Cochrane risk of bias tool** Selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Levene, Mi, Randomised double-blind controlled trial of effect of morphine on catecholamine concentrations in ventilated pre-term babies, Lancet (London, England), 342, 324-327, 1993 **Ref Id** 643604 **Country/ies where the study was carried out** United Kingdom **Study type** RCT **Aim of the study** The aim of the study was to investigate the use of morphine to provide analgesia and sedation for ventilated preterm babies	**Characteristics** Morphine group -Birthweight, g, median (IQR)= 1200 (860-1490) -Gestational age, wk, median (IQR)= 28 (27-31) -Apgar score 1 min, median (IQR)= 4 (3-6) -Apgar score 5 min, median (IQR)= 7 (6-8) -Postnatal age on entry, hr, median (IQR)= 5 (4-11) -Arterial pO2, kPa, median (IQR)= 78 (61-97) -Arterial pCO2, kPa, median (IQR)= 51 (36-59) Placebo group -Birthweight, g, median (IQR)= 1200 (925-1670) -Gestational age, wk, median (IQR)= 29 (27-31) -Apgar score 1 min, median (IQR)= 4 (3-7) -Apgar score 5 min, median (IQR)= 8 (6-9)	birthweight for 2 h as a loading infusion, then 0-5 mL per h for each kg birthweight as a continuous infusion. The baby therefore received a loading infusion of 100)ig/kg per h for 2 h followed by 25 /lg/kg per h as a continuous infusion. Treatment with trial solution was continued until the baby had recovered sufficiently to be weaned from ventilation. Babies in the control group received infusions of 5% dextrose. The infusion was started 1 hr after the first dose of Curosurf had been given; this was taken as the entry point to the trial (0 h). The syringes were labelled "trial solution" and the duty pharmacist held the code to the contents	were randomly assigned to receive either morphine in 5% dextrose solution or 5% dextrose solution (placebo group) Data collection Blood samples were taken immediately before Curosurf was given (-1 1 h), on entry to the study (0 h), and at 24 h, for catecholamine assay. Blood gas analysis was done and adrenaline and noradrenaline were assayed by a radioenzymic method.9,10 1 mL whole blood was drawn from the baby. The coefficients of variation within and between assays were 7% and 12%, respectively. All samples from a baby were analysed in the same assay. Plasma morphine concentration was measured in the 24 h sample by high-performance liquid chromatography in 12 cases. A previously validated pain score (Sury, Mcluckie, & Booker, 1990) was assigned to each baby by the attending nurse at the same time as blood sampling. A score of 1-4 was	-Morphine group= 4 (4-11) -Placebo group= 4 (4-15) Sury et al., (1990) pain scores at 24 hr, median (IQR) -Morphine group= 5 (4-16) -Placebo group= 5 (4-11) Sury et al. (1990) pain scores at 0 hr, mean (SD) -Morphine group= 5.8 (2.1) -Placebo group= 6.9 (3.3) Sury et al., (1990) pain scores at 24 hr, mean (SD) -Morphine group= 7.6 (3.6) -Placebo group= 6.3 (2.1) IVH (Grade not specified), n -Morphine group= 6	-Random sequence generation: low risk -Allocation concealment: low risk Performance bias -Blinding: low risk Detection bias -Blinding: low risk Attrition bias -Incomplete outcome data: low risk Reporting bias -Selective reporting: high risk; p-values and CIs not reported Other bias -Other sources of bias: high risk; grade of IVH was not specified **Other information** -No babies received dopamine before study entry, but 4 morphine-treated and 3 placebo-treated babies received dopamine during the first 24 h. 2 babies (1 in each group) had received pancuronium before entry to the trial, 3 (1 morphine,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates October 1991-May 1992 **Source of funding** Sir Halley Stewart Trust	-Postnatal age on entry (hr), median (IQR)= 6 (4-10) -Arterial pO2, kPa, median (IQR)= 71 (58-82) -Arterial pCO2, kPa, median (IQR)= 49 (40-61) **Inclusion criteria** Babies born at gestational age of < 34 weeks, required mechanical ventilation, received Curosurf for respiratory distress syndrome. Both inborn and outborn babies were included. **Exclusion criteria** Babies did not have arterial line in situ, clinician felt the baby was experiencing pain and needed morphine or had previous treatment with any opioid		given for level of consciousness, crying, posture, and facial expression. A high pain score indicated a high perceived degree of pain. The incidence of factors, other than pain, that may affect catecholamine concentrations (partial pressure of oxygen < 7 kPa, dopamine and pancuronium administration) was recorded at 0 h and 24 h. The clinical outcome of the infants was noted, especially as regards periventricular haemorrhage diagnosed by daily realtime ultrasound, pneumothorax diagnosed on chest radiograph, patent ductus arteriosus diagnosed clinically, duration of intubation in completed days, and death of the infant during the first 6 months of life Data analysis Statistical analyses (Minitab, Wtest, and Winterval procedures) were done with the Wilcoxon signed rank test for paired data, the Mann Whitney U test for unpaired data, and	-Placebo group= 6 Deaths before 28 days, n -Morphine group= 6 -Placebo group= 4	2 placebo) received this drug in the 24 h after entry, and 2 (both placebo) received it after 24 h. 7 babies in the morphine group and 10 in the placebo group had p02 below 7 kPa before entry into the study; 8 and 4, respectively, had the same degree of hypoxia within 24 h of trial solution infusion.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			the chi-square test for categorical data		
Full citation Saarenmaa, E., Huttunen, P., Leppaluoto, J., Meretoja, O., Fellman, V., Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: A randomized trial, Journal of PediatricsJ Pediatr, 134, 144-150, 1999 **Ref Id** 643649 **Country/ies where the study was carried out** Finland **Study type** RCT	**Sample size** N= 163 n intervention group= 80 n comparison group= 83 **Characteristics** Fentanyl group -Antenatal steroids, n (%)= 23 (40%) -Birth weight, g, median (IQR)= 1720 (1100-2795) -Gestational age, wk, median (IQR)= 31.7 (29.4-37.0) -Apgar score 1 minute, median (IQR)= 7 (5-9) -Apgar score 5 minute, median (IQR)= 8 (6-8) -Arterial pH at birth, median (IQR)= 7.24 (7.19-7.31) -Postnatal age at start of infusion, hr, median (IQR)= 11 (6-21)	**Interventions** Randomised infants received a loading dose of 10.5 mg/kg fentanyl or 140 mg/kg morphine in 1 hour. Maintenance dose was continued at a rate of 1.5 mg/kg/hr fentanyl or 20 mg/kg/hr morphine for at least 24 hours	**Details** Randomisation Babies were randomised in 5 blocks with closed envelopes and stratified for birth weight of less and equal or more than 1500g Data collection An arterial blood sample (1.5 mL blood in ethylenediamine tetra acetic acid vials containing 15 mL of 1% sodium metabisulphite) was obtained for determination of plasma adrenaline, noradrenaline, and b-endorphin concentrations on entry to the study (0 hours) and at 2 and 24 hours after the infusion was begun. The samples were centrifuged and stored at –70°C until analysed. If the nurse evaluated the response to procedures to be painful on the basis of the infant's behaviour, additional boluses were administered.	**Results** Mortality prior to discharge, n (%) Morphine group= 7 (9%) Fentanyl group= 6 (7%) Severe IVH (Grade 3 or 4), n (%) Morphine group= 4 (5%) Fentanyl group= 7 (8%) Days to enteral feeding <= 1500g, median (IQR) (d) Morphine group= 11 (6-12) Fentanyl group= 7 (6-11) Days to enteral feeding >	**Limitations** **Cochrane risk of bias tool** Selection bias -Random sequence generation: low risk -Allocation concealment: low risk Performance bias -Blinding: low risk Detection bias -Blinding: low risk Attrition bias -Incomplete outcome data: low risk Reporting bias -Selective reporting: low risk Other bias -Other sources of bias: low risk **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To compare the efficacy and adverse effects of fentanyl or morphine analgesia during the first 2 days of life in newborn who underwent mechanical ventilation **Study dates** January 1994-March 1996 **Source of funding** Not reported	Morphine group -Antenatal steroids, n (%)= 26 (42%) -Birth weight, g, median (IQR)= 1580 (1100-2790) -Gestational age, wk, median (IQR)= 31.0 (28.9-35.3) -Apgar score 1 minute, median (IQR)= 6 (5-8) -Apgar score 5 minute, median (IQR)= 7 (6-9) -Arterial pH at birth, median (IQR)= 7.28 (7.16-7.34) -Postnatal age at start of infusion, hr, median (IQR)= 9 (6-18) **Inclusion criteria** Babies with a gestational age > 24 weeks, spent at least 1 day on mechanical ventilation, had an indwelling arterial line, and no chromosomal aberations or major anomalies		The bolus, equal to a 1-hour maintenance infusion dose, could be given 4 times a day at the most. Weaning from the opioid infusion occurred gradually during 0.5 to 2 days depending on the duration of the infusion Data analysis Comparison of the fentanyl and morphine baseline data was performed with the two-tailed Student t test or chi-squared test. Hormone concentrations were analysed with Student t test, and in case of skewed distribution a logarithmic transformation or the Mann Whitney U test was used. A P value <.05 was regarded as significant. Data are presented as median and interquartile range. Urinary retention and decreased gastrointestinal motility were observed in two thirds of cases when morphine was used in our hospital before the trial. To show a 40% reduction in these side effects in the fentanyl group compared with morphine with a power of	1500g, median (IQR) (d) Morphine group= 4 (3-6) Fentanyl group= 4 (3-5) Days to enteral feeding <= 1500g, mean (SD) (d) Morphine group= 10.0 (1.6) Fentanyl group= 7.8 (1.3) Days to enteral feeding > 1500g, mean (SD) (d) Morphine group= 4.3 (0.78) Fentanyl group= 4.0 (0.52)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Not reported		80% (a = 0.05), a total sample size of 160 was needed		
Full citation Simons, Sh, Dijk, M, Lingen, Ra, Roofthooft, D, Duivenvoorden, Hj, Jongeneel, N, Bunkers, C, Smink, E, Anand, Kj, Anker, Jn, Tibboel, D, Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial, JAMAJama, 290, 2419-27, 2003 **Ref Id** 643704 **Country/ies where the study was carried out** -the Netherlands **Study type**	**Sample size** -N= 150 -n intervention group= 73 -n control group= 77 **Characteristics** Morphine group -Gestational age, median (IQR), wk= 29.1 (27.4-31.6) -Birth weight, median (IQR), g= 1130 (850-1680) -Postnatal age at start of trial, median (IQR), hr= 9 (5-13) -Apgar score, 1 min, median (IQR)= 6 (4-8) -Apgar score, 5 min, median (IQR)= 8 (7-9) -CRIB score, median (IQR)= 2 (1-6)	**Interventions** Intervention group Morphine hydrochloride -Received a loading dose (100ug/kg) followed by a continuous infusion (10ug/kg per hour) Control group Placebo (sodium chloride) -Received a loading dose (100ug/kg) followed by a continuous infusion (10ug/kg per hour) -To prevent possible overdosing, the study medication loading dose was not given if a preintubation morphine loading dose had been given < 3 hr before the start of the study -The use of masked study medication was continued for 7 days or less, as required by the patient's clinical condition	**Details** Randomisation -Neonates had an equal probability of being assigned to either condition. The randomisation code was developed using a computer random-number generator to select random permuted blocks. These blocks of 10 were stratified into 5 groups of gestational age ranges to obtain a balanced number of infants within each stratum -Using the computer-generated randomisation list, independent pharmacists placed ampules of either 1mL of morphine hydrochloride or 1mL of placebo into boxes. These boxes were numbered with the study numbers and stored with increasing numbers for the different gestational age groups in a locked closet accessible	**Results** NIPS pain scores at baseline, median (IQR) -Morphine group= 0.0 (0.0-0.0) -Placebo group= 0.0 (0.0-0.8) NIPS pain scores 30 min after start of infusion, median (IQR) -Morphine group= 0.0 (0.0-0.0) -Placebo group= 0.0 (0.0-1.0) NIPS pain scores before	**Limitations** **Cochrane risk of bias tool** Selection bias -Random sequence generation: low risk -Allocation concealment: low risk Performance bias -Blinding: low risk Detection bias -Blinding: low risk Attrition bias -Incomplete outcome data: low risk Reporting bias -Selective reporting: low risk Other bias -Other sources of bias: high risk; patients in both arms received open-label morphine after the start of the study if the attending

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
-RCT **Aim of the study** -To assess the effects of continuous intravenous morphine infusion on pain responses, rates of intraventricular hemorrhage (IVH), and poor neurological outcomes (severe IVH, periventricular leukomalacia, or death) **Study dates** -December 2000-October 2002 **Source of funding** -the Netherlands Organization for Scientific Research	Placebo group -Gestational age, median (IQR), wk= 29.2 (27.3-31.4) -Birth weight, median (IQR), g= 1230 (915-1560) -Postnatal age at start of trial, median (IQR), hr= 8 (5-12) -Apgar score, 1 min, median (IQR)= 6 (4-8) -Apgar score, 5 min, median (IQR)= 8 (7-9) -CRIB score, median (IQR)= 3 (1-7) **Inclusion criteria** -Neonates admitted to the NICU who required mechanical ventilation -Postnatal age < 3 days -Artificial ventilation < 8 hours -Indwelling arterial catheter **Exclusion criteria** -Severe asphyxia	-If patients from either group were judged to be in pain or distress during masked study medication use, they were given additional morphine based on decisions of the attending physician (independent of the study). Allowed additional doses were 50ug/kg followed by 5 to 10ug/kg per hour of continuous open-label morphine	only to the researchers. At a patient's enrollment, the next box in line for the specific group was taken out by one of the researchers -All research and clinical staff and parents of the infants were blinded to treatment Statistical analyses -SPSS was used to analyse data -Nonparametric tests were used and results were shown as medians and interquartile ranges when variables deviated from the normal distribution -Background characteristics compared using nonparametric Mann-Whitney U tests or Fisher exact tests -Pain scores were compared using multiple regression analyses with VAS-bedside and NIPS -Summary statistics were used to increase reliability and to take repeated measures into account during analyses -Logistic regression analyses were used for clinical outcomes	suctioning, median (IQR) -Morphine group= 0.5 (0.0-1.0) -Placebo group= 1.0 (0.0-1.0) NIPS pain scores during suctioning, median (IQR) -Morphine group= 4.8 (3.7-6.0) -Placebo group= 4.8 (3.2-6.0) NIPS pain scores 30 min after suctioning, median (IQR) -Morphine group= 0.0 (0.0-1.0) -Placebo group= 0.0 (0.0-1.0) Severe IVH (Grade 3 or 4), n (%)	nurse or physician deemed it necessary **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	-Severe IVH -Major congenital malformations -Facial malformations -Neurologic disorders -Receiving continuous or intermittent neuromuscular blockers			-Morphine group= 3 (4%) -Placebo group= 7 (9%) 28-day mortality, n (%) -Morphine group= 4 (5%) -Placebo group= 7 (9%)	

Clinical evidence tables for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Choong,K., Alfaleh,K., Doucette,J., Gray,S., Rich,B., Verhey,L., Paes,B., Remifentanil for endotracheal intubation in neonates: A randomised controlled trial, Archives of Disease in Childhood: Fetal and Neonatal	**Sample size** n= 30 Intervention= 15 Control= 15 **Characteristics** Intervention, n=15 Gestational age, weeks, median	**Interventions** Each study drug was identical, colourless and odourless in appearance and was reconstituted to similar volumes. They were prepared and administered sequentially in identical clear syringes marked as drug 1, 2 and 3 for each study patient. Control arm assigned as follows: drug 1, atropine (20 µg/kg); drug 2, fentanyl (2 µg/kg	**Details** Randomisation: random numbers table Allocation concealment: Study drugs were identical Blinding: Everyone in the trial was blinded to group allocation Attrition: Intention to treat analysis Outcomes: primary outcome was time to successful	**Results** Ease of intubation Time to successful intubation, seconds, median (IQR) Intervention= 247 (48-349) Control= 156 (46-395) p-value= 0.88	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- High risk ("Patients were randomised to one of two treatment groups in a 1:1 allocation ratio

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Edition, 95, F80-F84, 2010 **Ref Id** 259441 **Country/ies where the study was carried out** Canada **Study type** Single-centre, double-blinded, randomised trial **Aim of the study** The aim of the study was to assess the efficacy and safety of remifentanil as a premedication for preterm infants undergoing elective endotracheal intubation. **Study dates** January 2006 to February 2008	(IQR)= 27.1 (25.6-28.7) Birth weight, grams, median (IQR)= 940 (735-1342.5) Male sex, n= 10 RDS, n= 8 Chronic lung disease, n= 0 Apnoea of prematurity, n= 1 Control, n=15 Gestational age, weeks, median (IQR)= 28.0 (25.0-30.0) Birth weight, grams, median (IQR)= 995 (750-1190) Male sex, n= 7 RDS, n= 6 Chronic lung disease, n= 2 Apnoea of prematurity, n= 0 **Inclusion criteria** Haemodynamically stable, had existing IV access, were admitted to NICU at McMaster	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. Participants were prepared for intubation according to standard of practice. 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.	intubation (total time in seconds from the first insertion of the laryngoscope blade into the mouth until final confirmation of ETT placemeny by clinical examination). Secondary outcomes: SPO2, heart rate, blood pressure changes, adverse events (chest wall rigidity, viscid airway secretions) Statistical analysis: "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. χ2 and Fisher's exact tests, where appropriate, were applied for binary outcomes. We reported two-sided 95% confi dence intervals and p-values"	Number of intubation attempts, mean (SD) Intervention= 1.7 (0.9) Control= 1.8 (0.8) Intubated on first attempt, n Intervention= 9/15 Control= 6/15 Change in SPO2, %, mean (SD) Intervention= -55 (27) Control= -47 (25) Change in blood pressure, mm Hg, mean (SD) Intervention= 4.3 (15.9) Control= 4.3 (7.5) Trauma Intervention= 2/15 Control= 2/15 Chest wall rigidity Intervention= 2/15 Control= 0/15	using a random numbers table.") Allocation concealment- Low risk ("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.") Blinding of participants and personnel- Low risk "All patients, caregivers, medical and nursing staff, outcome assessors and investigators were masked to the study group assignment." Blinding of outcome assessment- Low risk Incomplete outcome data- Low risk ("None of the patients were withdrawn after randomisation, and there were no protocol violations.")

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Abbott Laboratories	Children's Hospital, and elective endotracheal intubation anticipated **Exclusion criteria** Emergent intubations, cyanotic congenital heart lesions, anticipated difficult airway, concurrent or recent intravenous opioid infusions administered within 3 h of the procedure, pre-existing hyperkalemia, family history of malignant hyperthermia and previous enrollment in the trial				Selective reporting- Low risk (All of the outcomes were reported with respective IQRs and SDs) Other sources of bias- Low risk **Other information**
Full citation Feltman,D.M., Weiss,M.G., Nicoski,P., Sinacore,J., Rocuronium for nonemergent intubation of term and	**Sample size** n= 44 Intervention= 20 Control= 24	**Interventions** When intubation was required (as determined by the clinical team), an infant randomized to the intervention group received atropine 0.02 mg kg1 followed by	**Details** Randomisation: Method of randomisation was not described Allocation concealment: Method of	**Results** Success rate of intubation on first attempt, n (%) Intervention= 7 (35) Control= 2 (8)	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
preterm infants, Journal of Perinatology, 31, 38-43, 2011 **Ref Id** 259647 **Country/ies where the study was carried out** US **Study type** Single-centre, double-blinded RCT **Aim of the study** The aim of the study was to assess the clinical characteristics of rocuronium as premedication for nonemergent intubation in preterm babies. **Study dates** Not reported	**Characteristics** Intervention (rocuronium), n=20 Corrected gestational age, weeks, mean (SD)= 30.6 (2.9) Birth weight, grams, mean (SD)= 1358 (624) Male sex, n (%)= 8 (40) Control, n=24 Corrected gestational age, weeks, mean (SD)= 28.5 (2.9) Birth weight, grams, mean (SD)= 1167 (580) Male sex, n (%)= 17 (71) **Inclusion criteria** All infants < 36 weeks corrected gestational age **Exclusion criteria** Infants > 36 weeks corrected gestational	fentanyl 2 mg kg1 followed by rocuronium 0.5mg kg1. An infant in the control group received only atropine 0.02 mg kg1 followed by fentanyl 2 mg kg1 for premedication. An infant who was tachycardic (heart rate >180 beats per minute) did not receive atropine. All medications were given through intravenous route with normal saline flushes after each medication. Intubations of all infants >36 weeks CGA who received rocuronium by NICU protocol were enrolled in an observational study. Infants received the atropine/fentanyl/rocuronium regimen previously described before intubation. Atropine was held if the infant was tachycardic.	allocation concealment was not described Blinding: Did not state whether parents, researchers, or staff were blinded Attrition: Reasons for patient drop out were described; did not describe whether a method like intention-to-treat analysis was used to manage attrition Outcomes: Intubation complications Statistical analysis: Logistic regression analysis to examine relationship between intubation on first attempt and variables. Adverse effects presented in descriptive format.		generation- Unclear risk (Method of randomisation was not described) Allocation concealment- Unclear risk (Method of allocation concealment was not described) Blinding of participants and personnel- Unclear risk (Did not state whether parents, researchers, or staff were blinded) Blinding of outcome assessment- Unclear risk (Did not state whether outcome assessment was blinded) Incomplete outcome data- High risk (Reasons for patient drop out were described; did not describe whether a method like intention-to-treat analysis was used to manage attrition) Selective reporting-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	age, already received rocuronium as part of premedication for intubation, airway abnormalities, contraindications for rocuronium				High risk (Data for many of the outcomes for the control group were not reported) Other sources of bias- Unclear risk (Did not state funding source) **Other information**
Full citation Ghanta, S., Abdel-Latif, M. E., 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, PediatricsPediatrics, 119, e1248-e1255, 2007 **Ref Id** 643245	**Sample size** n= 66 Intervention= 33 Control= 30 **Characteristics** Intervention group, n=33 Gestational age, weeks, median (IQR)= 28 (25-31) Birth weight, grams, median (IQR)= 1095 (759-1612) Male sex, n (%)= 11 (36.7) Control, n=30	**Interventions** Propofol was administered as a single 2.5 mg/kg IV dose. A maximum of 2 doses of propofol (2.5 mg/kg each) was allowed. The infant would then default to the control with suxamethonium if sleep had not been achieved in the desired time frame of 3 minutes or after the second dose of propofol. The doses of drugs are as follows (all intravenous): morphine, 100 g/kg; atropine, 10 g/kg; and suxamethonium, 2 mg/kg. Two repeat doses of suxamethonium at 1 mg/kg each (maximum total dose of 4 mg/kg per intubation attempt) were administered if muscle relaxation	**Details** Randomisation: random numbers table Allocation concealment: staff were unaware of treatment allocation Blinding: Blinding not possible due to different appearances of study drugs Attrition: Intention to treat analysis was used Outcomes: Number of intubation attempts, additional doses of induction agents required, presence of intubation trauma (presence of blood in the nasal or orophyryngeal areas during or after intubation)	**Results** Time to successful intubation, seconds, median (iQR) Intervention= 120 (60-180) Control= 260 (60=435) p < 0.001 Multiple attempts to achieve successful intubation, n (%) Intervention= 13 (39) Control= 17 (57) p= 0.263	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- Unclear risk ("sampling numbers, based on a random number table, were used to assign each infant to blocks of 10 to receive either propofol or MASux after stratification by body weight (1250 g and 1250 g) at the time of intubation.")

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia **Study type** Single-centre, RCT **Aim of the study** The aim of the study was to compare the effectiveness of propofol to a regimen of morphine, atropine, and suxamethonium, as premedication for nonemergency neonatal endotracheal intubation. **Study dates** March 2004 to December 2005 **Source of funding** No funding received	Gestational age, weeks, median (IQR)= 27 (25-30) Birth weight, grams, median (IQR)= 1020 (770-1455) Male sex, n (%)=18 (54.5) **Inclusion criteria** Newborn infants requiring elective or semielective intubation, sufficient time to obtain informed parental consent, subsequent need for semielective intubation **Exclusion criteria** Major congenital abnormalities, parents with insufficient English-language skills	was not achieved in the space of 3 to 5 minutes. Repeat applications of suxamethonium up to a maximum total of 4 mg/kg were allowed (if required) for each intubation attempt. Each doctor was allowed a maximum of 2 intubation attempts, and each attempt was curtailed if the heart rate decreased below 60 beats per minute and/or the oxygen saturations decreased below 60%.	Statistical analysis: "Results are presented as percentages and medians with interquartile ranges (25th to 75th percentile). The Fisher's exact and Mann-Whitney U tests were used where appropriate."	Intubation-related trauma (oropharyngeal trauma), n (%) Intervention= 2 (6) Control= 2 (23) p= 0.117 Increase in serum lactate levels >2.2 mmol/L before and after intubation, n (%) Intervention= 0/18 (0) Control= 1/15 (7) Masseter spasm after suxamethonium, n (%) Control only= 1/30 (3) Apnea after propofol, n (%) Intervention only= 0/33 (0)	Allocation concealment- Low risk ("Group assignments were drawn from consecutively numbered, sealed, opaque envelopes that were opened by the trial team on the infant's admission into the study immediately before intubation. Random sequences and envelopes were prepared by a senior nurse who was entirely uninvolved in the trial.") Blinding of participants and personnel- High risk ("Blinding was not possible, because the drugs were very different in appearance: propofol is opaque and white, whereas MASux is a combination of 3 different ampoules of clear liquid.") Blinding of outcome assessment- Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					risk (unclear if outcome assessment was blinded) Incomplete outcome data- Low risk ("Statistical analysis was undertaken on an intention-to-treat basis according to a preestablished analysis plan. This was to allow for possible crossovers to MASux from propofol, should the latter fail to achieve hypnosis.") Selective reporting- High risk (Not all medians and IQRs reported for outcomes) Other sources of bias- Low risk **Other information**
Full citation Lemyre, Brigitte, Doucette, Joanne, Kalyn,	**Sample size** n= 34 Intervention= 17 Control= 17	**Interventions** Infants requiring an elective intubation were randomly	**Details** Randomisation: computer-generated random number	**Results** Number of intubation	**Limitations** The quality assessment was performed using the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Angela, Gray, Shari, Marrin, Michael L., Morphine for elective endotracheal intubation in neonates: a randomized trial [ISRCTN43546373], BMC Pediatrics, 4, 20-20, 2004 **Ref Id** 713289 **Country/ies where the study was carried out** Canada **Study type** Single-centre, double-blinded, placebo-controlled trial **Aim of the study** The aim of the study was to assess the efficacy of morphine as premedication for achieving better intubation conditions and success while maintaining vital signs stability.	**Characteristics** Intervention (morphine), n=17 Gestational age, weeks, median (IQR)= 28 (26-33) Birth weight, grams, median (IQR)= 1065 (731.5-2043) Male sex, n (%)= 11 (65) Control, n=17 Gestational age, weeks, median (IQR)= 27 (26-30) Birth weight, grams, median (IQR)= 904 (689-1535.5) Male sex, n (%)= 9 (53) **Inclusion criteria** Admitted to McMaster University Medical Center Level III NICU, likely to need an elective oral or nasotracheal	assigned to receive either morphine 0.2 mg/kg IV or placebo (0.9% NaCl), given over 1 minute, followed 5 minutes later by the intubation. Morphine and placebo were supplied in identical unidose vials, labeled PIN Rx. All team members performed the intubations. After 2 unsuccessful attempts by a junior team member, a more experienced intubator was called.	table Allocation concealment: one pharmacist prepared the drugs according to the randomization sequence and placed them in sealed, consecutively numbered envelopes, which were opened just before intubation Blinding: Study drugs were identical Attrition: Not reported Outcomes: Primary outcome: duration of severe hypoxemia (Sp02 < 85% with a HR< 90/min). Secondary outcomes: duration of the procedure, duration of hypoxemia (Sp02 < 85%), number of attempts, maximum change in blood pressure from baseline, occurrence of bradycardia (HR<90/min) Statistical analysis: "Continuous variables were compared using the Mann-Whitney U test. Dichotomous variables were compared using Fisher's exact test or Chisquare test. A p value < 0.05 (2-sided) was	attempts, n, median (IQR) Morphine= 2 (1-3.5) Control= 1 (1, 2.5) p value= 0.34 Intubation achieved at first attempt, n Morphine= 7 Control= 9 p value= 0.49 Intubation needing rescue intubator, n Morphine= 7 Control= 4 p value= 0.27 Duration of procedure, seconds, median (IQR) Morphine= 271 (57.5-418.5) Control= 94 (62-215.5) p value= 0.27	Cochrane risk of bias tool for RCTs Random sequence generation- Low risk ("Infants were randomized according to a computer-generated random number table with random block sizes.") Allocation concealment- Low risk ("Morphine and placebo were supplied in identical unidose vials, labeled PIN Rx, which were prepared by one pharmacist according to the randomization sequence and placed in sealed, consecutively numbered envelopes, which were opened just before intubation.") Blinding of participants and personnel- Low risk ("One of three investigators, not involved in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates December 1999 to September 2000 **Source of funding** Not reported	intubation, infant was less than 30 weeks gestation, already ventilated, on NCPAP for respiratory distress **Exclusion criteria** Absence of IV access, upper airway anomaly potentially leading to a difficult intubation, cyanotic heart disease, upper gastrointestinal obstruction, concurrent opioid administration		considered significant for the primary outcome; p < 0.01 was considered significant for secondary outcomes to account for multiple analyses in a small sample. Level of experience of the intubator, birth weight and gestational age were separately explored as potential confounders of the primary outcome using ANOVA or linear regression."	n who experienced some degree of severe hypoxemia Morphine= 8/17 Control= 7/17 n who experienced hypoxemia Morphine= 17/17 Control= 14/17 Duration of severe hypoxemia, seconds, median (IQR) Morphine= 10 (0-62.5) Control= 5 (0-45) p value= 0.45 Duration of hypoxemia, seconds, median (IQR) Morphine= 235 (82.5-340) Control= 90 (20-187.5) p value=0.04	procedure collected the following data manually: duration of the procedure (defined as the time between insertion of the laryngoscope in the mouth to confirmation of endotracheal tube placement by auscultation) and the number of intubation attempts (defined as number of times the laryngoscope was inserted in the mouth).") Blinding of outcome assessment- Low risk Incomplete outcome data- Unclear risk (Study did not report a method, such as ITT, to manage attrition) Selective reporting- Low risk (All outcomes were reported with respective SDs and IQRs and p values) Other sources of bias- Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Maximum increase in mean BP from baseline, mm Hg, median (IQR) Morphine= 18 (9-24.25) Control= 20 (11.75-28) p value= 0.65 Bracycardia during procedure, n Morphine= 16 Control= 12 p value= 0.175	**Other information**
Full citation Norman,E., Wikstrom,S., Hellstrom-Westas,L., Turpeinen,U., Hamalainen,E., Fellman,V., Rapid sequence induction is superior to morphine for intubation of preterm infants: A randomized controlled trial, Journal of	**Sample size** n= 34 Intervention= 17 Control= 17 **Characteristics** Intervention, n=17 Gestational age, weeks, median (IQR)= 27 (25.6-28.5)	**Interventions** The infants were randomized to receive intravenously atropine and morphine, or the combination of glycopyrrolate, thiopental, suxamethonium and remifentanil. To counteract a blood pressure drop following drug administration, a saline infusion of 5 ml/kg was given to infants who had never received a transfusion. The dosage of the	**Details** Randomisation: Block randomisation Allocation concealment: Group allocation performed with sealed envelopes Blinding: All investigators, medical and nursing staff and parents were blinded to group assignment Attrition: Not reported Outcomes: Total intubation	**Results** Total duration of intubation procedure, seconds, median (IQR) Intervention= 45 (35-154) Control= 97 (49-365) p value= 0.031	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- Low risk ("The randomization (Figure 1A) was performed using blocks of 4 (2:2

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pediatrics, 159, 893-899, 2011 **Ref Id** 260366 **Country/ies where the study was carried out** Sweden **Study type** Single-centre, randomsied controlled trial **Aim of the study** The aim of the study was to assess the efficacy of two regimens of premedication for intubation. **Study dates** July 2005 to October 2009 **Source of funding**	Birth weight, grams, median (IQR)= 925 (743-1220) Male sex, n= 11 Indication for intubation, n RDS= 9 Apnoea= 7 Hemodynamically significant PDA= 1 Control= 17 Gestational age, weeks, median (IQR)= 26.6 (25.1-28.7) Birth weight, grams, median (IQR)= 924 (721-1240) Male sex, n= 9 Indication for intubation, n RDS= 8 Apnoea= 6 Hemodynamically significant PDA= 3 **Inclusion criteria** Gestational age less than 37 weeks, no administration of analgesics or sedative	drugs was calculated in relation to body weight and listed in precalculated tables with weight increment steps of 50 g. All intubations were performed nasally by experienced neonatologists. Nonpharmacological and pharmacological pain treatment (morphine bolus, 0.15 mg/kg) was offered according to an algorithm based on pain scoring	score, duration of intubation. Secondary outcomes: changes in plasma cortisol, mean arterial blood pressure, heart rate, rSCO2, behaviour and neurophysiology Statistical analysis: Mann-Whitney, Fisher´s exact test, t-test and ANOVA were used, as appropriate. P-value <.05 was considered significant.	Number of intubation attempts needed, n, median (IQR) Intervention= 1 (1-1.5) Control= 1 (1-2) p value not statistically significant Plasma cortisol concentrations, nmol/L, median (IQR) Baseline Intervention= 168 (37-324) Control= 183 (93-286) 20 min after intubation Intervention= 185 (114-380) Control= 275 (152-357) 6 hours after intubation Intervention= 172 (79-299) Control= 240 (60-283)	allocation ratio), with stratification for gestational age (GA) and postnatal age (PNA).") Allocation concealment- Low risk ("Group allocation with drug dilution and administration regimen was provided in sealed envelopes. All investigators, medical and nursing staff, and the parents were masked as to the study group assignment.") Blinding of participants and personnel- Low risk ("Only two nurses who prepared and administered the drugs, were aware of group allocation. To maintain blinding, similar amount of solutions (using saline as placebo) were administered with identical clear syringes numbered 1-5 in both

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Region Skane; Lund University funds; Royal Physiographic Society; Jerring, Crafoord, Ekdahl and Elsa Lungberg and Greta Fleron Foundations. One author was supported by the County Council of Varmland and another was supported by the Axelsson-Johnsson foundation	drugs during the previous 24 hours **Exclusion criteria** Asphyxia, serum potassium > 6 mmol/L, major malformations, postoperative care			24 hours after intubation Intervention= 142 (26-223) Control= 72 (46-187) No statistically significant differences MABP relative change during intubation from baseline, %, mean (SD) Intervention= 2 (22) Control= 21 (23)	groups.") Blinding of outcome assessment- Low risk ("Only two nurses who prepared and administered the drugs, were aware of group allocation. To maintain blinding, similar amount of solutions (using saline as placebo) were administered with identical clear syringes numbered 1-5 in both groups.") Incomplete outcome data- Unclear risk (Did not state whether a method such as ITT was used to manage drop outs) Selective reporting- Unclear (Not all of the outcomes were adequately reported i.e. ranges were presented without medians) Other sources of bias- Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information
Full citation Durrmeyer, X., Breinig, S., Claris, O., Tourneux, P., Alexandre, C., Saliba, E., Beuchee, A., Jung, C., Levy, C., Marchand-Martin, L., Marcoux, M. O., Dechartres, A., Danan, C., Effect of atropine with Propofol vs Atropine with atracurium and sufentanil on oxygen desaturation in neonates requiring nonemergency intubation a randomized clinical trial, JAMA - Journal of the American Medical Association, 319, 1790-1801, 2018 **Ref Id** 864244 **Country/ies where the study was carried out** France	**Sample size** n= 171 Atropine-atracurium-sufentanil= 82 Atropine-propofol= 89 **Characteristics** Atropine-atracurium-sufentanil, n= 82 Gestational age, weeks, median (IQR)= 29 (26-32) Birth weight, grams, median (IQR)= 1130 (850-1685) Reason for intubation, n (%) RDS= 50 (61.0) Apnoea= 9 (11.0) Surgery= 16 (19.5) Other= 7 (8.5) Ventilatory mode before intubation, n (%) Invasive ventilation=11 (13.4)	**Interventions** "6 syringes were prepared for all participants. The first 4 syringes contained a series of active drugs and placebo according to the treatment group: atropine, then placebo, then placebo, and then propofol in the atropine-propofol group or atropine, then atracurium, then sufentanil, and then placebo in the atropine-atracurium-sufentanil group. These 4 syringes had to be injected successively. If anesthesia was not adequate 2 minutes after the last injection, the 2 additional syringes were injected: placebo then propofol in the atropinepropofol group or atracurium then placebo in the atropineatracurium-sufentanil group. If adequate anesthesia was still not obtained 2 minutes after the sixth syringe injection, open-label drugs could be used at the operator's request, and the participant remained in the study. Adequate anesthesia was defined	**Details** Randomisation: Computer generated randomisation sequence with a 1:1 allocation ratio and stratification by centre and weight Allocation concealment: Randomisation was centralised through a dedicated website and only the pharmacists from the manufacturing organisations had access to the randomisation list. Staff involved in the trial were not aware of the block size throughout the trial Blinding: Double dummy approach with intralipids used to mask the appearance of the different drugs Attrition: Intention to treat analysis was used Outcomes: Primary outcomes: prolonged desaturation (SPO_2) < 80%	**Results** Ease of intubation No. of intubation attempts, median (IQR) Treatment= 1 (1-2) Control= 2 (1-2) p= 0.10 Duration of intubation, minutes, mean (SD) Treatment, n=80= 4.9 (5.7) Control, n=84= 6.6 (5.3) Intubated on first attempt, n/N Treatment= 47/81 Control= 41/87 Adverse physiological response during intubation Prolonged hypoxia, n/N Treatment= 5/80	**Limitations** The quality assessment was performed using the Cochrane risk of bias tool for RCTs Random sequence generation- Low risk (Computer generated randomisation sequence with a 1:1 allocation ratio and stratification by centre and weight.) Allocation concealment- Low risk (Randomisation was centralised through a dedicated website and only the pharmacists from the manufacturing organisations had access to the randomisation list. Staff involved in the trial were not aware of the block size

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** The aim of the study was to assess prolonged desaturation during neonatal nasotracheal intubation after 2 different regimens of premedication **Study dates** 2012-2016 **Source of funding** Grants AOM09 096 in 2009 and grant Prettineo 00-96 from the French Health Ministry (Programme Hospitalier de Recherche Clinique, PHRC).	Noninvasive ventilation= 61 (74.4) Nasal O_2= 0 Room air spontaneous ventilation= 8 (9.8) Unknown= 2 (2.4) Atropine-propofol, n= 89 Gestational age, weeks, median (IQR)= 30 (28-34) Birth weight, grams, median (IQR)= 1310 (815-2285) Reason for intubation, n (%) RDS= 60 (67.4) Apnoea= 3 (3.4) Surgery= 20 (22.5) Other= 6 (6.7) Ventilatory mode before intubation, n (%) Invasive ventilation= 10 (11.2) Noninvasive ventilation= 59 (66.3) Nasal O_2= 1 (1.1) Room air spontaneous ventilation= 15 (16.9) Unknown= 4 (4.5)	as no facial expression, spontaneous movement, or reaction to light tactile stimulation before attempting laryngoscopy. Atropine was administered at 15 µg/kg in both groups. In the atropine-propofol group, the first propofol dose was 2.5 mg/kg in infants more than 1000 g, as previously reported. Because of concerns about this dose in the smallest infants, we used 1 mg/kg as a first dose in infants 1000 g or less. The additional propofol dose was 1 mg/kg for all infants. In the atropine-atracurium-sufentanil group, the first atracurium dose was 0.3 mg/kg and the additional dose 0.1 mg/kg.5,12 Results from the pilot study led us to use a lower sufentanil dose of 0.1 µg/kg in infants 1000 g or less to prevent thoracic rigidity. We used 0.2 µg/kg of sufentanil for those more than 1000 g, as previously reported."	for 60 consecutive seconds between the first drug injection and completion of intubation. Secondary outcomes: intubation conditions (number of intubation attempts, duration of procedure, times to recovery of spontaneous respiratory and limb movements), vital signs (heart rate SPO_2, mean arterial blood pressure, transcutaneous partial CO_2 pressure), worsening of head ultrasound scans, adverse events (predefined list) Statistical analysis: Primary outcome analysed with a generalised mixed model adjusted for weight at inclusion and treatment centre as a random effect. Secondary outcomes: "Median number of intubation attempts, median duration of intubation, quality of sedation, and the times to recovery of respiratory and limb movements were compared with the Kruskal-Wallis test. Differences	Control= 2/83 Change from baseline before and after injection and during intubation, mean (SD) Heart rate, beats/min, 1 min before to 6 min after Treatment, n=80= 11.5 (25.3) control, n=86= 3.3 (19.5) Heart rate, beats/min, 1 min before to 9 min after Treatment, n=80= 11.7 (25.3) control, n=86= 1.6 (25.2) Mean arterial blood pressure, mm Hg, 1 min before to 15 min after Treatment, n=77= 0.2 (12.7) Control, n=80= -6.8 (12.7)	throughout the trial) Blinding of participants and personnel- Low risk (Double dummy approach with intralipids used to mask the appearance of the different drugs) Blinding of outcome assessment- Low risk ("Parents, physicians, nurses, and external statisticians were unaware of treatment allocation.") Incomplete outcome data- High risk (drop outs not accounted for) Selective reporting- Low risk (All of the outcomes were reported with respective IQRs and SDs) Other sources of bias- Low risk **Other information** 8/82 (9.8%) in atropine-atracurium-

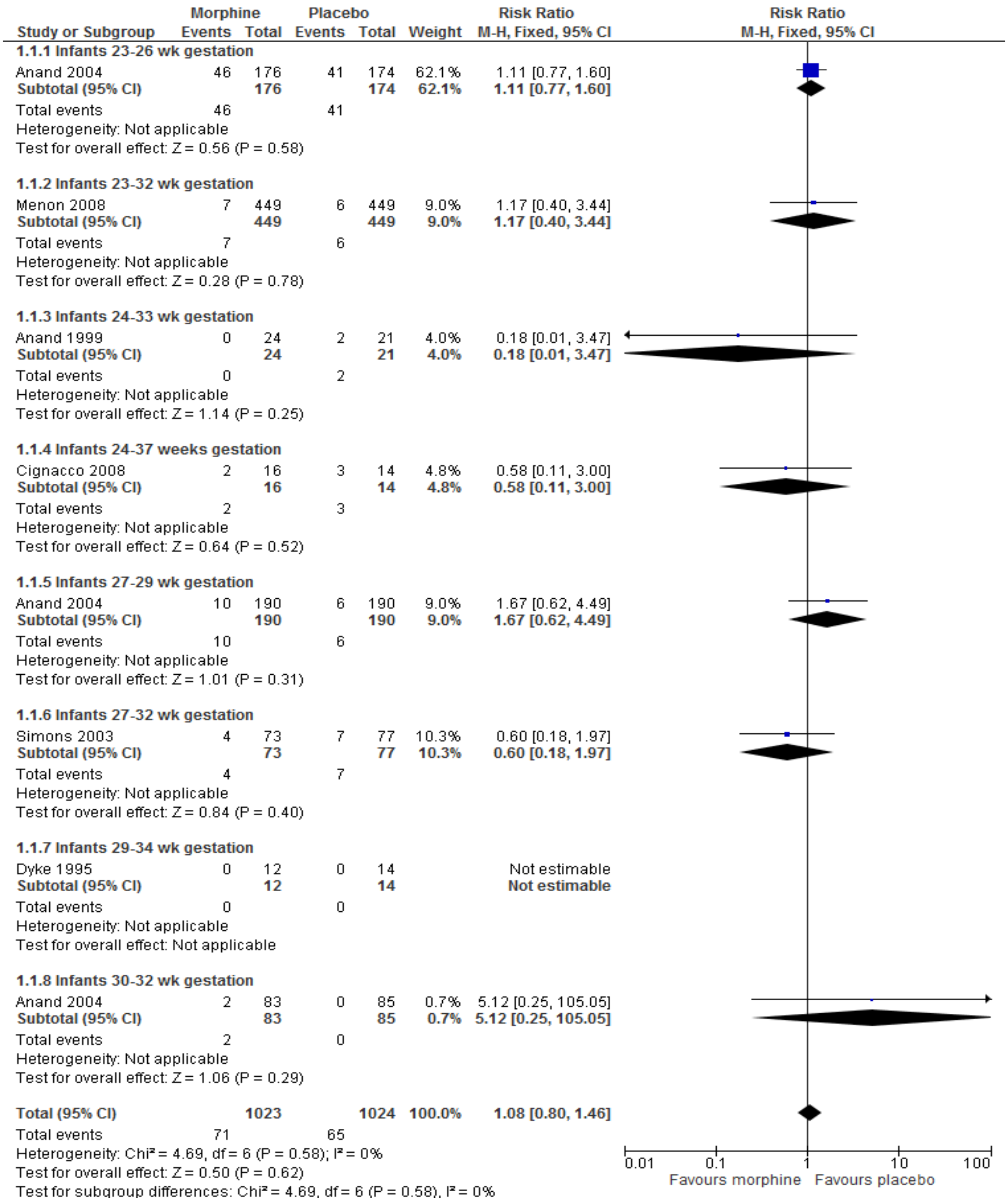
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Hospitalised in the NICU, corrected postmenstrual age younger than 45 weeks and IV access and required nonemergency or planned intubation. **Exclusion criteria** Sedative or anaesthetic administration in the previous 24 hours, hemodynamic failure, upper airway malformation, life threatening situation requiring immediate intubation, inclusion in another trial, any contraindication to any study drug and previous inclusion in the trial.		between groups for the median number of intubation attempts, the median duration of intubation, and the median time to recovery of respiratory and limb movements were calculated using the Hodges-Lehmann estimation of location shift with associated 95% CIs."	Mean arterial blood pressure, mm Hg, 1 min before to 30min after Treatment, n=74= -3.3 (9.4) Control, n=76= -9.1 (9.3) SPO_2, %, 1 min before to 6 min after Treatment, n=80= -12.0 (20.1) Control, n=85= -6.0 (20.1) SPO_2, %, 1 min before to 9 min after Treatment, n=80= -15.9 (22.2) Control, n=84= -8.7 (22.3) Transcutaneous partial carbon dioxide pressure, mm Hg, 1 min before to 15 min after Treatment, n=29= 14.1 (14.4)	sufentanil group and 48/89 (53.9%) in atropine-propofol group received 6 syringes or more open-label drugs ($p < 0.01$)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Control, n=30= 8.0 (14.4) Transcutaneous partial carbon dioxide pressure, mm Hg, 1 min before to 30 min after Treatment, n=29= 16.2 (19.3) Control, n=30= 5.0 (19.1) Adverse drug reactions, n/N Supraventricular tachycardia Treatment= 0/80 Control= 1/83 Chest wall rigidity Treatment= 11/80 Control= 3/83 Mortality prior to discharge, n/N Treatment= 3/80 Control= 2/83 (deaths not attributed to the study drugs)	

Appendix E – Forest plots

Forest plots for question 5.1 What is the effectiveness of morphine during respiratory support?

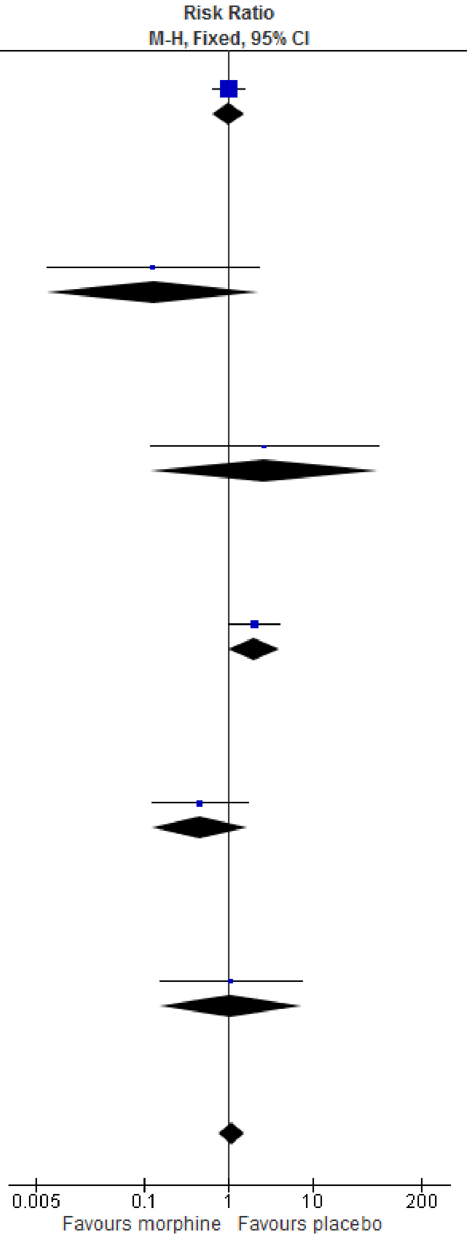
Figure 1: Comparison 1: Morphine versus placebo – Mortality prior to discharge



CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Figure 2: Comparison 1: Morphine versus placebo – Severe IVH (Grade 3 or 4)

Study or Subgroup	Morphine Events	Morphine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Infants 23-26 wk gestation						
Anand 2004	31	152	33	164	57.0%	1.01 [0.65, 1.57]
Subtotal (95% CI)		**152**		**164**	**57.0%**	**1.01 [0.65, 1.57]**
Total events	31		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.2.2 Infants 24-33 wk gestation						
Anand 1999	0	24	3	21	6.7%	0.13 [0.01, 2.30]
Subtotal (95% CI)		**24**		**21**	**6.7%**	**0.13 [0.01, 2.30]**
Total events	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
1.2.3 Infants 24-37 weeks gestation						
Cignacco 2008	1	16	0	14	1.0%	2.65 [0.12, 60.21]
Subtotal (95% CI)		**16**		**14**	**1.0%**	**2.65 [0.12, 60.21]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
1.2.4 Infants 27-29 wk gestation						
Anand 2004	22	181	11	182	19.7%	2.01 [1.00, 4.03]
Subtotal (95% CI)		**181**		**182**	**19.7%**	**2.01 [1.00, 4.03]**
Total events	22		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.97 (P = 0.05)						
1.2.5 Infants 27-32 wk gestation						
Simons 2003	3	73	7	77	12.2%	0.45 [0.12, 1.68]
Subtotal (95% CI)		**73**		**77**	**12.2%**	**0.45 [0.12, 1.68]**
Total events	3		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
1.2.6 Infants 30-32 wk gestation						
Anand 2004	2	78	2	83	3.5%	1.06 [0.15, 7.37]
Subtotal (95% CI)		**78**		**83**	**3.5%**	**1.06 [0.15, 7.37]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)		**524**		**541**	**100.0%**	**1.10 [0.79, 1.54]**
Total events	59		56			
Heterogeneity: Chi² = 7.24, df = 5 (P = 0.20); I² = 31%						
Test for overall effect: Z = 0.55 (P = 0.58)						
Test for subgroup differences: Chi² = 7.23, df = 5 (P = 0.20), I² = 30.9%						



CI: confidence interval; MD: mean difference; M-H: Mantel-Haenszel; RR: risk ratio

Forest plots for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

No meta-analyses were conducted for this review question, because there was not more than one study of the same intervention reporting on the same outcome.

Appendix F – GRADE tables

GRADE tables for question 5.1 What is the effectiveness of morphine during respiratory support?

Table 5: Clinical evidence profile: Comparison 1. Morphine versus placebo

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Mortality prior to discharge												
6	randomised trials	very serious[1,2]	no serious inconsistency[10]	no serious indirectness	very serious[3]	none	71/1023 (6.9%)	65/1024 (6.3%)	RR 1.08 (0.8 to 1.46)	5 more per 1000 (from 13 fewer to 29 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Infants 23-26 wk												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	46/176 (26.1%)	41/174 (23.6%)	RR 1.11 (0.77 to 1.6)	26 more per 1000 (from 54 fewer to 141 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Infants 23-32 wk												
1	randomised trials	very serious[1,4]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/449 (1.6%)	6/449 (1.3%)	RR 1.17 (0.4 to 3.44)	2 more per 1000 (from 8 fewer to 33 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Infants 24-33 wk												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/24 (0%)	2/21 (9.5%)	RR 0.18 (0.01 to 3.47)	78 fewer per 1000 (from 94 fewer to 235 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Infants 24-37 wk												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/16 (12.5%)	3/14 (21.4%)	RR 0.58 (0.11 to 3)	90 fewer per 1000 (from 191 fewer to 429 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Infants 27-29 wk												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/190 (5.3%)	6/190 (3.2%)	RR 1.67 (0.62 to 4.49)	21 more per 1000 (from 12 fewer to 110 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Infants 27-32 wk												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/73 (5.5%)	7/77 (9.1%)	RR 0.6 (0.18 to 1.97)	36 fewer per 1000 (from 75 fewer to 88 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Infants 29-34 wk												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/12 (0%)	0/14 (0%)	RD 0.00 (--0.14 to 0.14)	0 more per 1000 (from 140 fewer to 140 more)	VERY LOW	CRITICAL
Mortality prior to discharge - Infants 30-32 wk												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/83 (2.4%)	0/85 (0%)	RR 5.12 (0.25 to 105.05)	20 more per 1000 (from 20 fewer to 60 more)	VERY LOW	CRITICAL
Severe IVH (Grade 3 or 4)												
4	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	very serious[3]	none	59/524 (11.3%)	56/541 (10.4%)	RR 1.1 (0.79 to 1.54)	10 more per 1000 (from 22	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine	Placebo	Relative (95% CI)	Absolute		
										fewer to 56 more)		
Severe IVH (Grade 3 or 4) - Infants 23-26 wk												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	31/152 (20.4%)	33/164 (20.1%)	RR 1.01 (0.65 to 1.57)	2 more per 1000 (from 70 fewer to 115 more)	VERY LOW	CRITICAL
Severe IVH (Grade 3 or 4) - Infants 24-33 wk												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/24 (0%)	3/21 (14.3%)	RR 0.13 (0.01 to 2.3)	124 fewer per 1000 (from 141 fewer to 186 more)	VERY LOW	CRITICAL
Severe IVH (Grade 3 or 4) - Infants 24-37 wk												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/16 (6.3%)	0/14 (0%)	RR 2.65 (0.12 to 60.21)	60 more per 1000 (from 10 fewer to 230 more)	Not assessed	CRITICAL
Severe IVH (Grade 3 or 4) - Infants 27-29 wk												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	22/181 (12.2%)	11/182 (6%)	RR 2.01 (1 to 4.03)	61 more per 1000 (from 0 more to 183 more)	LOW	CRITICAL
Severe IVH (Grade 3 or 4) - Infants 27-32 wk												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/73 (4.1%)	7/77 (9.1%)	RR 0.45 (0.12 to 1.68)	50 fewer per 1000 (from 80 fewer to 62 more)	VERY LOW	CRITICAL
Severe IVH (Grade 3 or 4) - Infants 30-32 wk												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/78 (2.6%)	2/83 (2.4%)	RR 1.06 (0.15 to 7.37)	1 more per 1000 (from 20 fewer to 153 more)	VERY LOW	CRITICAL
Change in level of sedation during ETS (COMFORT scale, from 5-35) - During drug infusion (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	24	21	-	MD 4.5 lower (6.12 to 2.88 lower)	VERY LOW	CRITICAL
Change in level of sedation during ETS (COMFORT scale from 5-35) - After drug infusion (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	24	21	-	MD 1 higher (0.62 lower to 2.62 higher)	LOW	CRITICAL
Change in pain scores during ETS (PIPP scale from 0-18) - During drug infusion (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24	21	-	MD 4.9 lower (6.51 to 3.29 lower)	MODERATE	CRITICAL
Change in pain scores during ETS (PIPP scale from 0-18) - After drug infusion (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	24	21	-	MD 0.2 higher (1.41 lower to 1.81 higher)	VERY LOW	CRITICAL
Pain scores as a result of ETS (NIPS scale from 0-7) - 30 min after start of drug infusion (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	n=73 Median (range) 0.0 (0.0 to 0.0)	n=77 Median (range) 0.0 (0.0 to 1.0)	-	Median 0.0 difference (p not reported)	MODERATE	CRITICAL
Pain scores as a result of ETS (NIPS scale from 0-7) - Before endotracheal suctioning (Better indicated by lower values)												

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	n=73 Median (range) 0.5 (0.0 to 1.0)	n=77 Median (range) 1.0 (0.0 to 1.0)	-	Median 0.5 less (p not reported)	MODERATE	CRITICAL
Pain scores as a result of ETS (NIPS scale from 0-7) - During endotracheal suctioning (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	n=73 Median (range) 4.8 (3.7 to 6.0)	n=77 Median (range) 4.8 (3.2 to 6.0)	-	Median 0.0 difference (p= 0.58)	MODERATE	CRITICAL
Pain scores as a result of ETS (NIPS scale from 0-7) - 30 min after endotracheal suctioning (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	n=73 Median (range) 0.0 (0.0 to 1.0)	n=77 Median (range) 0.0 (0.0 to 1.0)	-	Median 0.0 difference (p not reported)	MODERATE	CRITICAL
Change in pain scores from baseline during ETS (BPSN scale from 0-27) - After administering analgesia, 5 min before ETS (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	16	14	-	MD 1.5 higher (0.25 to 2.75 higher)	LOW	CRITICAL
Change in pain scores from baseline during ETS (BPSN scale from 0-27) - During ETS (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	16	14	-	MD 0.04 lower (1.29 lower to 1.21 higher)	VERY LOW	CRITICAL
Change in pain scores from baseline during heel stick (DAN scale from 0-10) - Pain score from heel stick 2-3 hr after loading dose (Better indicated by lower values)												
1	randomised trials	very serious[1,7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	21	-	MD 0.1 higher (1.53 lower to 1.73 higher)	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Change in pain scores from baseline during heel stick (DAN scale from 0-10) - Pain score from heel stick after 20-28hr of drug infusion (Better indicated by lower values)												
1	randomised trials	very serious[1,7]	no serious inconsistency	no serious indirectness	serious[7]	none	21	21	-	MD 1.3 lower (2.93 lower to 0.33 higher)	VERY LOW	CRITICAL
Change in pain scores from baseline during heel stick (PIPP scale from 0-18) - Pain score from heel stick 2-3 hr after loading dose (Better indicated by lower values)												
1	randomised trials	very serious[1,7]	no serious inconsistency	no serious indirectness	serious[7]	none	21	21	-	MD 0.8 lower (2.6 lower to 1 higher)	VERY LOW	CRITICAL
Change in pain scores from baseline during heel stick (PIPP scale from 0-18) - Pain score from stick after 20-28 hr of drug infusion (Better indicated by lower values)												
1	randomised trials	very serious[1,7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	21	-	MD 0.2 higher (1.6 lower to 2 higher)	LOW	CRITICAL
Days to full enteral feeding - Infants 24-33 wk gestation (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	24	21	-	MD 1.9 lower (9.97 lower to 6.17 higher)	LOW	IMPORTANT
Days to full enteral feeding - Infants 23-32 wk (Better indicated by lower values)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[9]	none	n=449 Median (range) 20 days (13 to 29)	n=449 Median (range) 17 days (12 to 26)	-	Median 3 fewer days (p=0.003)	LOW	IMPORTANT

CI: confidence interval; RD: risk difference; RR: risk ratio; MD: mean difference

[1] The quality of evidence was downgraded by 1 as a result of patients in both arms receiving open-label morphine after the start of the study if the attending nurse or physician deemed it necessary (Anand 1999; Anand 2004; Cignacco 2008; Menon 2008; Simons 2003)

[2] The quality of evidence was downgraded by 1 because 1 or both arms of the trial had < 15 participants (Cignacco 2008; Dyke 1995)

[3] The quality of the evidence was downgraded by 2 because the 95% CI crosses 2 MIDs
[4] The quality of the evidence was downgraded by 1 because of suspected reporting bias as not all CIs and p-values were reported (Menon 2008)
[5] Not calculable because there were no events
[6] Not calculable because there were no events in the control arm
[7] The quality of evidence was downgraded by 1 because the 95% CI crosses one MID
[8] The quality of the evidence was downgraded by 1 because of suspected attrition bias where the study did not report how incomplete data was managed (Carbajal 2005)
[9] The quality of the evidence was downgraded by 1 - imprecision was not calculable because the results were reported as medians
[10] The 6 studies each used slightly different age range inclusion criteria – however there was no statistical heterogeneity in the meta-analysis. Results for each age range are also presented separately below

Table 6: Clinical evidence profile: Comparison 3. Morphine versus fentanyl

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Morphine**	**Fentanyl**	**Relative (95% CI)**	**Absolute**		
Severe IVH (Grade 3 or 4)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/80 (5%)	7/83 (8.4%)	0.59 (0.18 to 1.95)	35 fewer per 1000 (from 69 fewer to 80 more)	LOW	CRITICAL

RR: risk ratio; CI: confidence interval; MD: mean difference
[1] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs

Table 7: Clinical evidence profile: Comparison 4. Morphine versus midazolam

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Morphine**	**Midazolam**	**Relative (95% CI)**	**Absolute**		
Mortality prior to discharge												
1	randomised trials	serious[1]	no serious inconsistency	none	very serious[2]	none	0/24 (0%)	1/22 (4.5%)	RR 0.31 (0.01 to 7.16)	31 fewer per 1000 (from 45 fewer to 280 more)	VERY LOW	CRITICAL
Severe IVH (Grade 3 or 4)												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine	Midazolam	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	none	very serious[2]	none	0/24 (0%)	5/22 (22.7%)	RR 0.08 (0.01 to 0.91)[3]	209 fewer per 1000 (from 227 fewer to 98 more)	VERY LOW	CRITICAL
Change in level of sedation during ETS (COMFORT scale from 5-35) – Level of sedation during drug infusion (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	none	serious[4]	none	24	22	-	MD 1 lower (2.72 lower to 0.72 higher)	LOW	CRITICAL
Change in level of sedation during ETS (COMFORT scale from 5-35) – Level of sedation after drug infusion (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	none	serious[4]	none	24	22	-	MD 1.7 higher (0.26 to 3.14 higher)[3]	LOW	CRITICAL
Change in pain scores during ETS (PIPP scale) – Level of sedation during drug infusion (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	none	serious[4]	none	24	22	-	MD 2 lower (3.66 to 0.34 lower)	LOW	CRITICAL
Change in pain scores during ETS (PIPP scale) – Level of sedation after drug infusion (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	none	serious[4]	none	24	22	-	MD 0.3 higher (1.36 lower to 1.96 higher)	LOW	CRITICAL
Days to enteral feeding – Infants 24-33 wk gestation (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	none	very serious[2]	none	24	22	-	MD 0.1 lower (4.41 lower to 4.21 higher)	VERY LOW	IMPORTANT

RR: risk ratio; CI: confidence interval; MD: mean difference
[1]The quality of the evidence was downgraded by 1 as a result of both arms receiving open-label analgesic (Anand 2004)
[2]The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs
[3] Results calculated at the 90% CI
[4]The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID

GRADE tables for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

Table 8: Clinical evidence profile: Comparison 1. Any premedication versus placebo/nothing

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any premedication	Placebo/nothing	Relative (95% CI)	Absolute		
No. of intubation attempts - Morphine vs placebo												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	n=17 Median (IQR) 2 attempts (1 to 3.5)	n=17 Median (IQR) 1 attempt (1 to 2.5)	-	Median 1 more attempt (p= 0.34)	MODERATE	CRITICAL
Time to intubation, seconds - Morphine vs placebo												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	n=34 Median (IQR) 271 seconds (57.5 to 418.5)	n=34 Median (IQR) 94 seconds (62 to 215.5)	-	Median 177 seconds more (p= 0.27)	MODERATE	CRITICAL
Intubation needing rescue intubator - Morphine vs placebo												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	7/17 (41.2%)	4/17 (23.5%)	RR 1.75 (0.63 to 4.89)	176 more per 1000 (from 87 fewer to 915 more)	LOW	CRITICAL
Intubation achieved at first attempt - Morphine vs placebo												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	7/17 (41.2%)	9/17 (52.9%)	RR 0.78 (0.38 to 1.6)	116 fewer per 1000 (from 328	LOW	CRITICAL

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any premedication	Placebo/nothing	Relative (95% CI)	Absolute		
										fewer to 318 more)		
Hypoxemia - Morphine vs placebo												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	17/17 (100%)	14/17 (82.4%)	RR 1.21 (0.95 to 1.53)	173 more per 1000 (from 41 fewer to 436 more)	MODERATE	CRITICAL
Duration of hypoxemia, seconds - Morphine vs placebo												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	n=17 Median (IQR) 235 seconds (82.5 to 340)	n=17 Median (IQR) 90 seconds (20 to 187.5)	-	Median145 seconds more (p= 0.04)	MODERATE	CRITICAL
Severe hypoxemia - Morphine vs placebo												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/17 (47.1%)	7/17 (41.2%)	RR 1.14 (0.53 to 2.44)	58 more per 1000 (from 194 fewer to 593 more)	LOW	CRITICAL
Duration of severe hypoxemia, seconds - Morphine vs placebo												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	n=17 Median (IQR) 10 seconds (0 to 62.5)	n=17 Median (IQR) 5 seconds (0 to 45)	-	Median 5 seconds more	MODERATE	CRITICAL

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any premedication	Placebo/nothing	Relative (95% CI)	Absolute		
										(p= 0.45)		
Maximum increase in mean BP from baseline, mm Hg (Better indicated by lower values) - Morphine vs placebo												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	n=17 Median (IQR) 18 mm hg (9 to 24.25)	n=17 Median (IQR) 20 mm Hg (11 to 75.28)	-	Median 2 mm Hg less (p= 0.65)	MODERATE	CRITICAL
No. experiencing bradycardia during procedure - Morphine vs placebo												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	16/17 (94.1%)	12/17 (70.6%)	RR 1.33 (0.96 to 1.85)	233 more per 1000 (from 28 fewer to 600 more)	MODERATE	CRITICAL

BP: blood pressure; bpm: beats per minute; CI: confidence interval; IQR: intra-quartile range; MD: mean difference; RR: risk ratio
[1] The quality of evidence was downgraded by 1 - imprecision was not calculable because results were reported as medians
[2] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs
[3] The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID

1 2 **Table 9: Clinical evidence profile: Comparison 2. Any premedication including neuromuscular blockers (single agent or combination of agents) vs any premedication**

Quality assessment							Number of babies		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Any premedication including neuromuscular blockers**	**Any premedication**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Intubated on first attempt - Fentanyl + atropine + suxamethonium vs remifentanil + placebo + atropine												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/15 (40%)	9/15 (60%)	RR 0.67 (0.32 to 1.4)	198 fewer per 1000 (from 408 fewer to 240 more)	LOW	CRITICAL
Intubated on first attempt - Rocuronium + atropine + fentanyl vs Atropine + fentanyl												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	7/20 (35%)	2/24 (8.3%)	RR 4.2 (0.98 to 18)	267 more per 1000 (from 2 fewer to 1000 more)	VERY LOW	CRITICAL
Intubated on first attempt - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	47/81 (58%)	41/87 (47.1%)	RR 1.23 (0.92 to 1.64)	108 more per 1000 (from 38 fewer to 302 more)	LOW	CRITICAL
Duration of intubation, seconds, median (IQR) - Fentanyl + atropine + suxamethonium vs remifentanil + placebo + atropine												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any premedication including neuromuscular blockers	Any premedication	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	n=15 Median (IQR) 247 seconds (48 to 349)	n=15 Median (IQR) 156 seconds (46 to 395)	-	Median 91 seconds more (p= 0.88)	MODERATE	CRITICAL
Duration of intubation, minutes, mean (SD) - Atropine+atracurium+sufentanil vs atropine+propofol (Better indicated by lower values)												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	80	84	-	MD 1.7 lower (3.39 to 0.01 lower)	LOW	CRITICAL
Number of intubation attempts - Fentanyl + atropine + suxamethonium vs remifentanil + placebo + atropine (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	15	15	-	MD 0.1 higher (0.51 lower to 0.71 higher)	MODERATE	CRITICAL
Number of intubation attempts - Atropine+atracurium+sufentanil vs atropine+propofol (Better indicated by lower values)												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[5]	none	n=82 Median (IQR) 1 attempt (1 to 2)	n=89 Median (IQR) 2 attempts (1 to 2)	-	Median 1 fewer attempts (p=0.10)	LOW	CRITICAL
Prolonged hypoxia - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/80 (6.3%)	2/83 (2.4%)	RR 2.59 (0.52 to 12.99)	38 more per 1000 (from 12 fewer to 289 more)	VERY LOW	CRITICAL

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any premedication including neuromuscular blockers	Any premedication	Relative (95% CI)	Absolute		
Change in SPO2 from baseline during intubation, % - Fentanyl + atropine + suxamethonium vs remifentanil + placebo + atropine (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	15	15	-	MD 8 higher (10.62 lower to 26.62 higher)	MODERATE	CRITICAL
Change in SPO2 from baseline during intubation, % - Atropine+atracurium+sufentanil vs atropine+propofol, 1 min before injection to 6 min after (Better indicated by lower values)												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	80	85	-	MD 6 lower (12.14 lower to 0.14 higher)	LOW	CRITICAL
Change in SPO2 from baseline during intubation, % - Atropine+atracurium+sufentanil vs atropine+propofol, 1 min before injection to 9 min after (Better indicated by lower values)												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	80	84	-	MD 7.2 lower (14.01 to 0.39 lower)	LOW	CRITICAL
Change in blood pressure from baseline during intubation, mm Hg - Fentanyl + atropine + suxamethonium vs remifentanil + placebo + atropine (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	15	15	-	MD 0 higher (8.9 lower to 8.9 higher)	LOW	CRITICAL
Change in blood pressure from baseline during intubation, mm Hg - Atropine+atracurium+sufentanil vs atropine+propofol, 1 min before injection to 15 min after (Better indicated by lower values)												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	77	80	-	MD 7 higher (3.03 to	LOW	CRITICAL

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any premedication including neuromuscular blockers	Any premedication	Relative (95% CI)	Absolute	Quality	Importance
										10.97 higher)		
Change in blood pressure from baseline during intubation, mm Hg - Atropine+atracurium+sufentanil vs atropine+propofol, 1 min before injection to 30 min after (Better indicated by lower values)												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	74	76	-	MD 5.8 higher (2.81 to 8.79 higher)	LOW	CRITICAL
Change in heart rate from baseline during intubation, beats/min - Fentanyl + atropine + suxamethonium vs remifentanil + placebo + atropine (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	15	15	-	MD 0 higher (21.7 lower to 21.7 higher)	LOW	CRITICAL
Change in heart rate from baseline during intubation, beats/min - Atropine+atracurium+sufentanil vs atropine+propofol, 1 min before injection to 6 min after (Better indicated by lower values)												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	80	86	-	MD 8.2 higher (1.29 to 15.11 higher)	LOW	CRITICAL
Change in heart rate from baseline during intubation, beats/min - Atropine+atracurium+sufentanil vs atropine+propofol, 1 min before injection to 9 min after (Better indicated by lower values)												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	80	86	-	MD 10.1 higher (2.41 to 17.79 higher)	LOW	CRITICAL
Change in partial carbon dioxide pressure, mm Hg - Atropine+atracurium+sufentanil vs atropine+propofol, 1 min before injection to 15 min after (Better indicated by lower values)												

Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any premedication including neuromuscular blockers	Any premedication	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	29	30	-	MD 6.1 higher (1.25 lower to 13.45 higher)	LOW	CRITICAL
Change in partial carbon dioxide pressure, mm Hg - Atropine+atracurium+sufentanil vs atropine+propofol, 1 min before injection to 30 min after (Better indicated by lower values)												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	29	30	-	MD 11.2 higher (1.4 to 21 higher)	LOW	CRITICAL
Adverse drug reactions - Chest wall rigidity - Fentanyl + atropine + suxamethonium vs remifentanil + placebo + atropinep												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/15 (0%)	2/15 (13.3%)	RR 0.2 (0.01 to 3.85)	107 fewer per 1000 (from 132 fewer to 380 more)	LOW	IMPORTANT
Adverse drug reactions - Chest wall rigidity - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	serious[3]	none	11/80 (13.8%)	3/83 (3.6%)	RR 3.8 (1.1 to 13.13)	101 more per 1000 (from 4 more to 438 more)	LOW	IMPORTANT
Adverse drug reactions - Viscid respiratory secretions - Fentanyl + atropine + suxamethonium vs remifentanil + placebo + atropine												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any premedication including neuromuscular blockers	Any premedication	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/15 (13.3%)	2/15 (13.3%)	RR 1 (0.16 to 6.2)	0 fewer per 1000 (from 112 fewer to 693 more)	LOW	IMPORTANT
Adverse drug reactions - Pneumothorax - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	4/80 (5%)	2/83 (2.4%)	RR 2.08 (0.39 to 11.02)	26 more per 1000 (from 15 fewer to 241 more)	VERY LOW	IMPORTANT
Adverse drug reactions - Digestive tract perforation - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/80 (1.3%)	3/83 (3.6%)	RR 0.35 (0.04 to 3.26)	23 fewer per 1000 (from 35 fewer to 82 more)	VERY LOW	IMPORTANT
Adverse drug reactions - Pulmonary haemorrhage - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	2/80 (2.5%)	1/80 (1.3%)	RR 2 (0.19 to 21.62)	13 more per 1000 (from 10 fewer to 258 more)	VERY LOW	IMPORTANT
Adverse drug reactions - Cardiac arrest - Atropine+atracurium+sufentanil vs atropine+propofol												

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any premedication including neuromuscular blockers	Any premedication	Relative (95% CI)	Absolute		
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/80 (1.3%)	1/83 (1.2%)	RR 1.04 (0.07 to 16.31)	0 more per 1000 (from 11 fewer to 184 more)	VERY LOW	IMPORTANT
Adverse drug reactions - Supraventricular tachycardia - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	0/80 (0%)	1/83 (1.2%)	RR 0.35 (0.01 to 8.36)	8 fewer per 1000 (from 12 fewer to 89 more)	VERY LOW	IMPORTANT
Adverse drug reactions - Pulmonary hypertension - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	2/80 (2.5%)	1/83 (1.2%)	RR 2.08 (0.19 to 22.44)	13 more per 1000 (from 10 fewer to 258 more)	VERY LOW	IMPORTANT
Adverse drug reactions - Aspiration syndrome - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/80 (1.3%)	0/83 (0%)	RR 3.11 (0.13 to 75.26)	-	VERY LOW	IMPORTANT
Adverse drug reactions - Hyponatremia - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	0/80 (0%)	1/83 (1.2%)	RR 0.35 (0.01 to 8.36)	8 fewer per 1000 (from 12	VERY LOW	IMPORTANT

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Any premedication including neuromuscular blockers	Any premedication	Relative (95% CI)	Absolute		
										fewer to 89 more)		
Mortality prior to discharge - Atropine+atracurium+sufentanil vs atropine+propofol												
1	randomised trials	serious risk of bias[4]	no serious inconsistency	no serious indirectness	very serious[1]	none	3/80 (3.8%)	2/83 (2.4%)	RR 1.56 (0.27 to 9.07)	13 more per 1000 (from 18 fewer to 194 more)	VERY LOW	IMPORTANT

BP: blood pressure; bpm: beats per minute; CI: confidence interval; Hg: mercury; MD: mean difference; IQR: intra-quartile range; RR: risk ratio; SPO2: peripheral capillary oxygen saturation
[1] The quality of the evidence was downgraded by 2 because the CI crosses 2 MIDs
[2] The quality of the evidence was downgraded by 2 because the study did not state the method of allocation concealment, blinding, or randomisation and not all the outcomes were reported (Feltman 2011)
[3] The quality of the evidence was downgraded by 1 because the CI crosses 1 MID
[4] The quality of evidence was downgrade by 1 because of high attrition (Durrmeyer 2018)
[5] The quality of evidence was downgraded by 1 - imprecision was not calculable because results were reported as medians

Table 10: Clinical evidence profile: Comparison 4. Other comparisons containing neuromuscular blocker and atropine combinations

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Other comparisons	Control	Relative (95% CI)	Absolute		
Time to successful intubation, seconds - Propofol vs morphine + atropine + suxamethonium												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	n=33 Median (IQR) 120 seconds (60 to 180)	n=30 Median (IQR) 260 seconds (60 to 435)		Median 140 seconds less (p= 0.007)	MODERATE	CRITICAL

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Other comparisons**	**Control**	**Relative (95% CI)**	**Absolute**		
Time to successful intubation, seconds - Glycopyrrolate + thiopental + suxamethonium + remifentanyl vs Atropine + morphine												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	n=17 Median (IQR) 45 seconds (35 to 154)	n=17 Median (IQR) 97 seconds (49 to 365)	-	Median 52 seconds less (p= 0.031)	LOW	CRITICAL
Successful intubation on first attempt - Propofol vs morphine + atropine + suxamethonium												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	20/33 (60.6%)	13/30 (43.3%)	RR 1.4 (0.85 to 2.29)	173 more per 1000 (from 65 fewer to 559 more)	MODERATE	CRITICAL
No. of intubation attempts needed - Glycopyrrolate + thiopental + suxamethonium + remifentanyl vs Atropine + morphine												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	n=17 Median (IQR) 1 attempt (1 to 1.5)	n=17 Median (IQR) 1 attempt (1 to 2)	-	No difference (p not reported)	LOW	CRITICAL
Intubation-related trauma (oropharyngeal trauma) - Propofol vs morphine + atropine + suxamethonium												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	2/33 (6.1%)	2/30 (6.7%)	RR 0.91 (0.14 to 6.06)	6 fewer per 1000 (from 57 fewer to 337 more)	MODERATE	CRITICAL
Plasma cortisol concentrations during intubation, nmol/L - Baseline - Glycopyrrolate + thiopental + suxamethonium + remifentanyl vs Atropine + morphine												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	n=17 Median (IQR) 168 nmol/L (37 to 324)	n=17 Median (IQR) 183 nmol/L (93 to 286)	-	Median 15 nmol/L less	LOW	CRITICAL

Quality assessment							Number of babies		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Other comparisons	Control	Relative (95% CI)	Absolute		
										(p not reported)		
Plasma cortisol concentrations during intubation, nmol/L - 20 min after intubation - Glycopyrrolate + thiopental + suxamethonium + remifentanyl vs Atropine + morphine												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	n=17 Median (IQR) 185 mol (114 to 380)	n=17 Median (IQR) 275 nmol/L (152 to 357)	-	Median 90 mol/L less (p not reported)	LOW	CRITICAL
Plasma cortisol concentrations during intubation, nmol/L - 6 hours after intubation - Glycopyrrolate + thiopental + suxamethonium + remifentanyl vs Atropine + morphine												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	n=17 Median (IQR) 172 nmol/L (79 to 299)	n=17 Median (IQR) 240 nmol/L (60 to 283)	-	Median 68 mol/L less (p not reported)	LOW	CRITICAL
Plasma cortisol concentrations during intubation, nmol/L - 24 hours after intubation - Glycopyrrolate + thiopental + suxamethonium + remifentanyl vs Atropine + morphine												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	n=17 Median (IQR) 142 mol/L IQR= 26-223	n=17 Median (IQR) 72 nmol/L IQR= 46-187	-	Median 70 mol/L more (p not reported)	LOW	CRITICAL
Mean arterial blood pressure relative change during intubation from baseline, % (Better indicated by lower values) - Glycopyrrolate + thiopental + suxamethonium + remifentanyl vs Atropine + morphine												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17	17	-	MD 19 lower (34.13 to 3.87 lower)	LOW	CRITICAL
Increase in serum lactate levels > 2.2mmol/L - Propofol vs morphine + atropine + suxamethonium												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[3]	none	0/18 (0%)	1/15 (6.7%)	RR 0.28 (0.01 to 6.43)	48 fewer per 1000 (from 66	LOW	CRITICAL

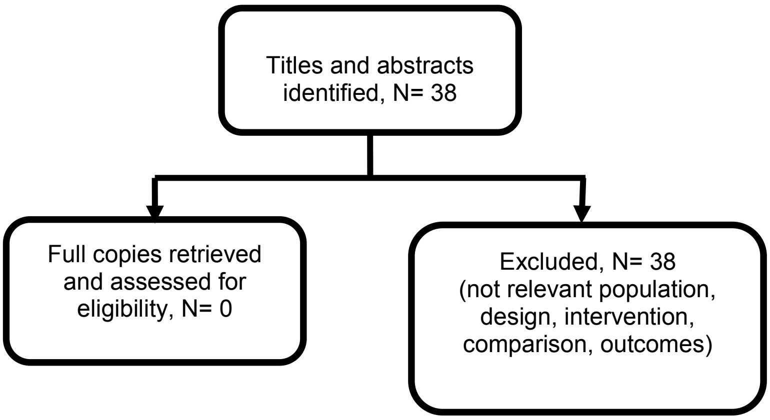
Quality assessment							Number of babies		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Other comparisons	Control	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias								fewer to 362 more)		
Viscid respiratory secretions - Propofol vs morphine + atropine + suxamethonium												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	2/33 (6.1%)	2/30 (6.7%)	RR 0.91 (0.14 to 6.06)	6 fewer per 1000 (from 57 fewer to 337 more)	LOW	CRITICAL

BP: blood pressure; bpm: beats per minute; CI: confidence interval; Hg: mercury; MD: mean difference; IQR: intra-quartile range; RR: risk ratio; SPO2: peripheral capillary oxygen saturation

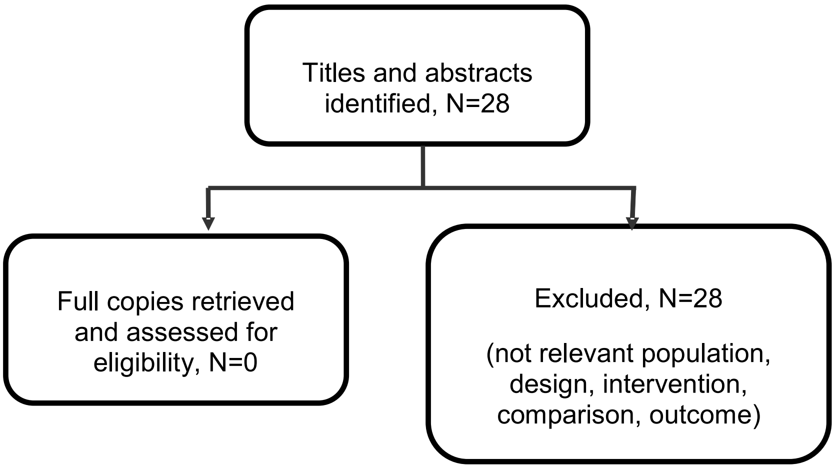
[1] The quality of evidence was downgraded by 1 because a method for managing attrition was not mentioned and not all outcomes were reported
[2] The quality of evidence was downgraded by 1 because the 95% CI crosses 1 MID
[3] The quality of evidence was downgraded by 2 because the 95% CI crosses 2 MIDs
[4] The quality of evidence was downgraded by 1 - imprecision was not calculable because results were reported as medians

Appendix G – Economic evidence study selection

Economic evidence study selection for question 5.1 What is the effectiveness of morphine during respiratory support?



Economic evidence study selection for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?



Appendix H – Economic evidence tables

Economic evidence table for question 5.1 What is the effectiveness of morphine during respiratory support?

No economic evidence was identified for this review.

Economic evidence table for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

No economic evidence was identified for this review.

Appendix I – Economic evidence profiles

Economic evidence profile for question 5.1 What is the effectiveness of morphine during respiratory support?

No economic evidence was identified for this review

Economic evidence profile for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

No economic evidence was identified for this review.

Appendix J – Health economic analysis

Health economic analysis for question 5.1 What is the effectiveness of morphine during respiratory support?

No health economic analysis was undertaken for this review.

Health economics analysis for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

No health economic analysis was undertaken for this review.

Appendix K – Excluded studies

Excluded studied for question 5.1 What is the effectiveness of morphine during respiratory support?

Clinical studies

Study	Reason for Exclusion
Anand, K. J. S. anderson, B. J., Holford, N. H. G., Hall, R. W., Young, T., Shephard, B., Desai, N. S., Barton, B. A., Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: Secondary results from the NEOPAIN trial, British Journal of Anaesthesia, 101, 680-689, 2008	No outcomes relevant to the review
Anand, K. J., Johnston, C. C., Oberlander, T. F., Taddio, A., Lehr, V. T., Walco, G. A., Analgesia and local anesthesia during invasive procedures in the neonate, Clinical Therapeutics, 27, 844-76, 2005	No appropriate study design – literature review was not a systematic review of RCTs
Anand, Kj, McIntosh, N, Lagercrantz, H, Gauthier, T, Pelausa, E, Young, T, Vasa, R, Gortner, L, Desai, Ns, Tuttle, D, Barton, Ba, The pilot NOPAIN trial: morphine and midazolam infusions decrease pain/stress and may alter clinical outcomes in ventilated preterm neonates, Pediatric Research, 41, 136a, 1997	Abstract
Arya, VRamji S, Midazolam Sedation in Mechanically Ventilated Newborns: A Double Blind Randomised Placebo Controlled Trial, Indian Pediatrics, 38, 967-72, 2001	No appropriate intervention – midazolam compared to placebo
Barker, D. P., Simpson, J., Pawula, M., Barrett, D. A., Shaw, P. N., Rutter, N., Randomised, double blind trial of two loading dose regimens of diamorphine in ventilated newborn infants, Archives of Disease in Childhood, 73, F22-F26, 1995	No appropriate intervention – 2 loading doses of diamorphine
Bellu, R., de Waal, K. A., Zanini, R., Opioids for neonates receiving mechanical ventilation, Cochrane database of systematic reviews (online), CD004212, 2005	Data taken from original studies; not all studies appropriate
Bhandari, V., Bergqvist, L. L., Kronsberg, S. S., Barton, B. A., Anand, K. J., Morphine administration and short-term pulmonary outcomes among ventilated preterm infants, Pediatrics, 116, 352-359, 2005	No outcomes relevant to the review
Ceccon, M. E. J., de Oliveira, A. A. S., Analgesia and sedation in mechanical ventilation in neonatology, Current	No relevant study design – literature review, not a systematic review

Study	Reason for Exclusion
Respiratory Medicine Reviews, 8, 53-59, 2012	
Cruz, M. D. D., Fernandes, A. M., De Oliveira, C. R., Factors related to procedural pain management in neonatal intensive care units: A systematic review, Pain Research and Management, 19 (3), e69, 2014	Conference program
De Graaf, J., Van Lingen, R. A., Simons, S. H. P., Anand, K. J. S., Duivenvoorden, H. J., Weisglas-Kuperus, N., Roofthooft, D. W. E., Groot Jebbink, L. J. M., Veenstra, R. R., Tibboel, D., Van Dijk, M., Long-term effects of routine morphine infusion in mechanically ventilated neonates on children's functioning: Five-year follow-up of a randomised controlled trial, Pain, 152, 1391-1397, 2011	No outcomes relevant to the review
De Kort, E. H. M., Reiss, I. K. M., Simons, S. H. P., Sedation of newborn infants for the INSURE procedure, are we sure?, BioMed Research InternationalBiomed Res Int, 2013 (no pagination), 2013	No appropriate intervention – premedication
Deindl, P., Giordano, V., Fuiko, R., Waldhoer, T., Unterasinger, L., Berger, A., Olischar, M., The implementation of systematic pain and sedation management has no impact on outcome in extremely preterm infants, Acta Paediatrica, 105, 798-805, 2016	No outcomes relevant to the review
Ferguson, S. A., Ward, W. L., Paule, M. G., Hall, R. W., Anand, K. J. S., A pilot study of preemptive morphine analgesia in preterm neonates: Effects on head circumference, social behavior and response latencies in early childhood, Neurotoxicology and teratology, 34, 47-55, 2012	No outcomes relevant to the review
Ghanta, S., Abdel-Latif, M. E., 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 randomised, controlled trial, Pediatrics, 119, e1248-e1255, 2007	No appropriate comparator – morphine compared to propofol
Hall, R. W., Kronsberg, S. S., Barton, B. A., Kaiser, J. R., Anand, K. J., Morphine, hypotension and adverse outcomes among preterm neonates: who's to blame? Secondary results from the NEOPAIN trial, Pediatrics, 115, 1351-1359, 2005	No outcomes relevant to the review
Harma, A., Aikio, O., Hallman, M., Saarela, T., Intravenous Paracetamol Decreases Requirements of Morphine in	No relevant intervention – paracetamol compared to control

Study	Reason for Exclusion
Very Preterm Infants, Journal of Pediatrics, 168, 36-40, 2016	
Kaneyasu, M., Pain management, morphine administration and outcomes in preterm infants: a review of the literature, Neonatal Network - Journal of Neonatal Nursing, 31, 21-30, 2012	Not a relevant study design – literature review
MacGregor, R., Evans, D., Sugden, D., Gaussen, T., Levene, M., Outcome at 5-6 years of prematurely born children who received morphine as neonates, Archives of Disease in Childhood: Fetal and Neonatal Edition, 79, F40-F43, 1998	No outcomes relevant to the review
Meyer,S., Gottschling,S., Gortner,L., Propofol compared with the morphine, atropine and suxamethonium regimen as induction agents for neonatal endotracheal intubation: A randomised, controlled trial [15], Pediatrics, 120, 932-933, 2007	No appropriate comparator – morphine compared to propofol
Norman, E, WikstrÃ¶m, S, Rosen, I, Fellman, V, HellstrÃ¶m-Westas, L, Premedication for Intubation with Morphine Causes Prolonged Depression of Electrocortical Background Activity in Preterm Infants, Pediatric Academic Societies Annual Meeting, 2012	No appropriate comparator – morphine compared to rapid sequence intubation
Ranger, M., Synnes, A. R., Vinall, J., Grunau, R. E., Internalizing behaviours in school-age children born very preterm are predicted by neonatal pain and morphine exposure, European Journal of Pain, 18, 844-52, 2014	No outcomes relevant to the review
Saarenmaa, E, Meretoja, O, Fellman, V, Fentanyl or morphine for ventilated newborn infants?, Pediatric Research, 40, 550, 1996	Abstract
Simons, S. H. P., Anand, K. J. S., Pain control: Opioid dosing, population kinetics and side-effects, Seminars in Fetal and Neonatal Medicine, 11, 260-267, 2006	No appropriate study design – literature review
Siwiec, J,, Porzucek, I,, Gadzinowski, J,, Bhat, Rama,, Vidyasagar, Dharmapuri, Effect of Short Term Morphine Infusion on Premature Infant Pain Profile (PIPP)and Hemodynamics, Pediatric Research, 45, 69A	Conference abstract
Stuth, Ea, Berens, Rj, Staudt, Sr, Robertson, Fa, Scott, Jp, Stucke, Ag, Hoffman, Gm, Troshynski, Tj, Tweddell, Js, Zuperku, Ej, The effect of caudal vs intravenous morphine on early extubation and postoperative analgesic requirements for stage 2 and 3 single-ventricle	No relevant comparator – caudal morphine-bupivacaine and post cardiopulmonary bypass (CPB) compared to caudal saline and post-CPB IV morphine

Study	Reason for Exclusion
palliation: a double blind randomised trial, Paediatric Anaesthesia, 21, 441-453, 2011	
Valitalo, P. A., Krekels, E. H. J., Van Dijk, M., Simons, S. H. P., Tibboel, D., Knibbe, C. A. J., Morphine Pharmacodynamics in Mechanically Ventilated Preterm Neonates Undergoing Endotracheal Suctioning, CPT: Pharmacometrics and Systems Pharmacology, 6, 239-248, 2017	No outcomes relevant to the review
Valkenburg, A. J., Van Den Bosch, G. E., De Graaf, J., Van Lingen, R. A., Weisglas-Kuperus, N., Van Rosmalen, J., Groot Jebbink, L. J. M., Tibboel, D., Van Dijk, M., Long-Term Effects of Neonatal Morphine Infusion on Pain Sensitivity: Follow-Up of a Randomised Controlled Trial, Journal of Pain, 16, 926-933, 2015	No outcomes relevant to the review
Wood,C.M., Rushforth,J.A., Hartley,R., Dean,H., Wild,J., Levene,M.I., Randomised double blind trial of morphine versus diamorphine for sedation of preterm neonates, Archives of Disease in Childhood Fetal and Neonatal Edition, 79, F34-F39, 1998	No relevant comparator – morphine compared to diamorphine

Economic studies

All economic studies were excluded at the initial title and abstract screening stage.

Excluded studies for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

Clinical studies

Study	Reason for Exclusion
Al-Faleh, Km, Choong, K, Doucette, J, Rich, B, Gray, S, Verhey, L, Paes, B, Remifentanyl and Atropine for Intubation in Neonates A Randomized Controlled Trial (RAIN), Pediatric academic societies annual meeting; 2009 may 2 5; baltimore MD, united states, 2009	Full text not available
Aranda, J. V., Carlo, W., Hummel, P., Thomas, R., Lehr, V. T., Anand, K. J., Analgesia and sedation during mechanical ventilation in neonates, Clinical TherapeuticsClin Ther, 27, 877-99, 2005	Studies did not meet inclusion criteria
Attardi, D. M., Paul, A. D., Tuttle, D. J., Greenspan, J. S., Premedication for intubation in neonates, Archives of Disease in Childhood: Fetal and Neonatal Edition, 83, F161, 2000	Editorial
Avino, D, Zhang, Wh, Villé, A, Johansson, Ab, Remifentanyl versus morphine-midazolam premedication on the quality of endotracheal intubation in neonates: a noninferiority randomized trial, Journal of PediatricsJ Pediatr, 164, 1032-1037, 2014	Infants were not preterm
Badiee, Z., Vakiliamini, M., Mohammadizadeh, M., Remifentanyl for endotracheal intubation in premature infants: A randomized controlled trial, Journal of Research in Pharmacy Practice, 2, 75-82, 2013	Not an OECD country
Bellù, Roberto, de, Waal Koert A, Zanini, Rinaldo, Opioids for neonates receiving mechanical ventilation, Cochrane Database of Systematic Reviews, 2008	Studies assessed individually
Byrne, E., MacKinnon, R., Should premedication be used for semiâ€• urgent or elective intubation in neonates?, Archives of Disease in Childhood, 91, 79-83, 2006	Studies were assessed individually - did not meet inclusion criteria
de Kort, E. H., Reiss, I. K., Simons, S. H., Sedation of newborn infants for the INSURE procedure, are we sure?, BioMed Research InternationalBiomed Res Int, 2013, 892974, 2013	Studies did not meet inclusion criteria
Fellman, V, Norman, E, Hellstrom-Westas, L, Thiopental/suxamethonium/remifentanyl premedication is superior to morphine for semiurgent intubation in preterm infants - A randomized blinded intervention study, Journal of neonatal-perinatal medicine, 4, 291, 2011	Conference abstract
Guinsburg, R., Kopelman, B. I., Anand, K. J., de Almeida, M. F., Peres Cde, A., Miyoshi, M. H., Physiological, hormonal, and behavioral	Study setting non OECD country- Brazil

Study	Reason for Exclusion
responses to a single fentanyl dose in intubated and ventilated preterm neonates, Journal of PediatricsJ Pediatr, 132, 954-9, 1998	
Meyer,S., Gottschling,S., Gortner,L., Propofol compared with the morphine, atropine, and suxamethonium regimen as induction agents for neonatal endotracheal intubation: A randomized, controlled trial [15], Pediatrics, 120, 932-933, 2007	Editorial
Milesi, C., Baleine, J., Mura, T., Benito-Castro, F., Ferragu, F., Thiriez, G., Thevenot, P., Combes, C., Carbajal, R., Cambonie, G., Nasal midazolam vs ketamine for neonatal intubation in the delivery room: a randomised trial, Archives of Disease in Childhood Fetal & Neonatal EditionArch Dis Child Fetal Neonatal Ed, 103, F221-F226, 2018	Intervention not of interest - ketamine
Naderi, S, Goodarzi, R, Naziri, Grp, Mohammad, Am, Kheiltash, A, Shafaeizadeh, A, Effect of fentanyl and morphine on gallbladder dimensions in newborns admitted to the neonatal intensive care unit: a randomized double-blinded clinical trial, Iranian journal of pediatrics, 27, 2017	Non-OECD country- Iran
Norman, E, WikstrÃ¶m, S, Rosen, I, Fellman, V, HellstrÃ¶m-Westas, L, Premedication for Intubation with Morphine Causes Prolonged Depression of Electrocortical Background Activity in Preterm Infants, Pediatric Academic Societies Annual Meeting, 2012	Outcomes not of interest
Oei, J, Hari, Tr, Lui, K, Suxamethonium, atropine and morphine as induction for neonatal nasotracheal intubation: a randomised controlled trial, Pediatric ResearchPediatr Res, 47, 421a, 2000	Conference abstract
Oei, J, Hari, R, Butha, T, Lui, K, Facilitation of neonatal nasotracheal intubation with premedication: a randomised controlled trial, Journal of Paediatrics and Child Health, 38, 146-150, 2002	< 15 babies in each arm and a proportion of the babies were not preterm
Roberts, K. D., Leone, T. A., Edwards, W. H., Rich, W. D., Finer, N. N., Premedication for nonemergent neonatal intubations: a randomized, controlled trial comparing atropine and fentanyl to atropine, fentanyl, and mivacurium, Pediatrics, 118, 1583-91, 2006	Intervention not of interest (mivacurium)
Shah, V., Ohlsson, A., The effectiveness of premedication for endotracheal intubation in mechanically ventilated neonates. A systematic review, Clinics in Perinatology, 29, 535-54, 2002	Systematic review did not contain any relevant studies
Shah,P.S., Shah,V.S., Propofol for procedural sedation/anaesthesia in neonates, Cochrane	Study reported individually

Study	Reason for Exclusion
database of systematic reviews (Online), 3, CD007248-, 2011	
Tagin, Ma McMillan D, Analgesia and Muscle Paralysis Versus Analgesia for Elective Neonatal Endotracheal Intubation: systematic Review and Meta-Analysis, Pediatric academic societies annual meeting, 2011	Conference abstract
Welzing, L., Roth, B., Experience with remifentanyl in neonates and infants, DrugsDrugs, 66, 1339-1350, 2006	Not a systematic review

OECD: Organisation for Economic Co-operation and Development

Economic studies

All economic studies were excluded at the initial title and abstract screening stage.

Appendix L – Research recommendations

Research recommendations for question 5.1 What is the effectiveness of morphine during respiratory support?

What is the effectiveness of morphine compared with containment holding for preterm babies requiring respiratory support?

Why this is important

Mechanical ventilation is an inherently uncomfortable situation, and preterm babies on respiratory support may also frequently undergo other uncomfortable procedures. Despite advances in neonatology, there is limited research on the use of pharmacological agents or other techniques to reduce pain and discomfort in preterm babies requiring ventilation. Containment holding (holding a baby with one hand on its head and another around its lower back/bottom to provide reassurance and comfort) has been suggested as one technique that may help reduce pain and distress, and may have other benefits. However, no evidence in the NICE evidence review was found to demonstrate its effectiveness, or whether it is more effective than analgesics such as morphine.

Table 11: Research recommendation rationale

Research question	What is the effectiveness of morphine compared with containment holding for preterm babies requiring respiratory support?
Importance to 'patients' or the population	It is important to explore the evidence for non-pharmacological approaches to the management of pain and discomfort in preterm babies requiring invasive ventilation. Investigating whether containment holding is more effective than morphine may potentially reduce complications associated with morphine, improve baby-parent bonding and improve parental experience.
Relevance to NICE guidance	In the NICE evidence review, there is no evidence to recommend the current clinical practice of the routine use of sedative agents for ventilated preterm babies, or evidence to endorse containment holding instead of morphine or other sedatives in ventilated preterm babies and so the committee were unable to make recommendations on these specific areas, but more research might allow this to be done.
Relevance to the NHS	The results of the proposed research could standardise the clinical practice across neonatal units in the NHS. It may also contribute to better parental experience, improved parental-baby bonding and reduced complications that my result from morphine sedation. As containment-holding is 'free' there is a potential cost-saving from reduced use of morphine and its adverse effects. Successful containment holding may also contribute to shorter length of stay.
National priorities	The British Association of Perinatal Medicine has identified this topic as an important clinical area.
Current evidence base	There is currently no evidence comparing morphine versus containment holding in preterm babies requiring respiratory support.
Equality	Preterm babies have an equal right to safe and effective sedation and analgesia. while ventilated, and with the least harmful effects. They also have an equal right to bond with their parents at the earliest available opportunity which may in turn have a positive impact on their health outcomes.

Table 12: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm babies requiring mechanical ventilation
Intervention	Morphine
Comparator	Containment holding
Outcomes	**Critical:** • Mortality • Bronchopulmonary dysplasia • Neurodevelopment outcome at >18 months **Important:** • Severe intraventricular haemorrhage • Pain and comfort scores • Unplanned or accidental extubation • Days to achieve full enteral feeding • Hypotension • Respiratory depression/apnea • Length of hospital stay • Parental experience/satisfaction/happiness •
Study design	Large multicentre randomised controlled trial. Ideally >1000 babies. (i) point-of-care design using electronic patient records for patient identification, randomisation and data acquisition (ii) short two-page information sheet; (iii) explicit mention of possible inclusion benefit; (iv) opt-out consent with enrolment as the default.
Timeframe	2 years follow-up.

Research recommendations for question 5.2 What is the effectiveness of using premedication for intubation in preterm babies?

What is the most effective combination of an analgesic with a neuromuscular blocker or an analgesic with an anaesthetic agent for premedication in preterm babies requiring elective/semi-elective intubation?

Why this is important

Intubation is a potentially painful and distressing procedure which may cause significant physiological disturbances including hypoxia, hypertension and increase neonatal morbidity including intraventricular haemorrhage. Evidence suggests that for routine semi-urgent or non-urgent intubation, the use of premedication is effective: the procedure is quicker, easier and with less physiologic disturbance, pain and discomfort than traditional awake intubation. However, premedication for intubation with potent opiates or anaesthetic agents and muscle relaxants is not a common or routine practice in babies, and little evidence was found in the NICE evidence review to guide the best combination of agents.

Table 13: Research recommendation rationale

Research question	What is the most effective combination of an analgesic with a neuromuscular blocker or an analgesic with an anaesthetic agent for premedication in preterm babies requiring elective/semi-elective intubation?
Importance to 'patients' or the population	Intubation is a common procedure in neonatal intensive care. The aim of a rapid sequence intubation is to minimise the time taken to achieve successful intubation, at the same time decreasing the adverse effects of intubation and improving the patient experience. It is generally accepted that premedication should be used to reduce pain and adverse physiological changes caused by awake intubation of babies wherever possible.
Relevance to NICE guidance	No studies were identified as part of the NICE evidence review that directly examined the safety or effectiveness in a way which allowed determination of the best premedication regime to be made. There is currently no consensus on the need, choice or dose of premedication in the UK and therefore the committee were unale to make recommendations, but more research in this area may allow this to be done.
Relevance to the NHS	The results of the proposed research would standardise the clinical practice across neonatal units across NHS
National priorities	Consensus statement International Evidence Based Group for Neonatal Pain "Tracheal intubation without use of analgesia or sedation should only be performed for resuscitation in delivery suite or life threatening situations with unavailability of IV access"
Current evidence base	There is currently no robust evidence on which combination of an analgesic and either a neuro-muscular blocker or anaesthetics is safe and effective premedication for elective/semi-elective intubation in preterm babies.
Equality	Preterm babies have an equal right to safe and effective premedication as adult patients.

Research question	**What is the most effective combination of an analgesic with a neuromuscular blocker or an analgesic with an anaesthetic agent for premedication in preterm babies requiring elective/semi-elective intubation?**
Feasibility	There are always ethical issues in conducting studies in vulnerable populations, and there are additional considerations relating to premedication interventions. These would require careful consideration, but could be overcome. The numbers of children affected are also (fortunately) small, however a well conducted multicentre study would be likely to be adequately powered.

Table 14: Research recommendation modified PICO table

Criterion	Explanation
Population	Preterm babies requiring elective/semi-elective intubations
Intervention	An analgesic and a neuro-muscular blocker An analgesic and an anaesthetic
Comparator	Different regimens compared with each other.
Outcome	• Success and ease of intubation • Pain and comfort scores during intubation • Adverse physiological response during intubation • Neurodevelopmental outcome at 2 years (corrected age) • Adverse drug reactions • Days on ventilator
Study design	Large, multicentre, randomised controlled trial
Timeframe	2 years follow up.