Pre-medication for intubation and drugs for sedation/analgesia during ventilation.

1. Pre-medication for Intubation.

**Background:**

Traditionally, intubation of newborn infants was done without sedation or muscle relaxation. This practice reflected uncertainty about the effects of these drugs in babies. Over recent years, there has been a growing awareness of the pain and physiological stress that cold intubation places on a baby and so it has become a less common practice. Despite this, there is still much we don't know about the effects of these drugs in babies.

**Does sedation/muscle relaxation help intubation?**

There is little doubt that sedation and muscle relaxation makes intubation easier, quicker and less traumatic. The available trials are small and still mainly in abstract form but they show consistent findings. Oei et al.\(^1\) in a randomised trial of term and preterm babies compared no medication with suxamethonium, atropine and morphine. The pre-medicated babies took fewer attempts (1.3 vs 2.8), were more quickly intubated (60 vs 590 secs) and suffered less trauma (10% vs 50%). Allen et al.\(^2\) in a case control study comparing sedation and neuromuscular blockade with just sedation, had almost identical findings with greater success at first attempt (74% vs 26%) and less trauma (0 vs 15%). Bhutada et al.\(^3\) compared thiopentone with no premedication in term babies and also showed a quicker intubation time (2.7 vs 5.1 mins). Barrington et al.\(^4\) also showed a shorter intubation time with suxamethonium and atropine compared to just atropine.

**Is sedation/muscle relaxation safe in newborns?**

There is no data on the effect of sedation/muscle relaxation premedication on long term outcomes. The available short-term data suggests it enhances physiological stability during the procedure. Barrington et al.\(^4\) showed less increase in intracranial pressure with suxamethonium and atropine vs just atropine. Bhutada et al.\(^3\) showed a greater increase in heart rate but less increase in blood pressure after thiopentone. Oei et al.\(^1\) showed more bradycardia without premedication. The following drugs are used for premedication for intubation. There is almost no data other than the basic pharmacological data on which to base a decision on which is the most appropriate for the newborn.

**Morphine.**

This is the most widely used and probably the best studied premedication sedative in Australia and the UK.\(^5\) An intravenous bolus provides pain relief within one minute that deepens over 5 to 10 mins. The half life is inversely related to gestational age, being between 6 and 12 hours (mean 8.75 hours) in the very preterm infant.\(^6\) Full pain relief in the neonate seems to require a blood level over 120ng/ml.\(^7\) The study of Hartley et al.\(^6\) showed this level was not achieved by 100 microgramsg/kg (mean level 99 ng/ml)\(^7\) but was more reliably achieved by 200 micrograms/kg (mean level 180 ng/ml).\(^8\) Concerns about hypotension have lead some to suggest that Morphine should be given as a slow infusion. However, we were unable to demonstrate any adverse haemodynamic effects of a bolus of 100 ug/kg of Morphine.\(^8\) The main advantage of Morphine is that it is the drug with which we have the most experience in newborn sedation/analgesia and thus, in the absence of evidence to the contrary, this remains the drug of choice.

**Fentanyl:**
Fentanyl Citrate is an opioid analgesic. While reputed as a short acting analgesic, it can have a prolonged elimination time particularly in the newborn. A bolus IV injection produces a rapid effect that diminishes after around 30 minutes as the drug is redistributed in muscle and fat.\textsuperscript{9} The elimination half-life is about 8 hours in term newborns\textsuperscript{10} and probably longer in preterm babies. Fentanyl can cause muscle rigidity which, when it effects the chest wall, can have a profound effect on ventilation. Fahnenstich et al,\textsuperscript{11} observed chest wall rigidity in 8 and laryngospasm in 2 out of 189 term and preterm babies sedated with Fentanyl. When this occurs, IV Naloxone quickly reverses the problem. In babies, 10 micrograms/kg as an IV bolus will depress or abolish respiration and provide analgesia for up to an hour. The advantage of Fentanyl for induction is the rapid onset of action, the disadvantages are the potential side effects.

**Midazolam:**

As a benzodiazapine, midazolam is a useful sedative but does not have an analgesic effect suggesting it may not be appropriate as induction for a painful procedure. In older subjects, it produces a degree of amnesia.\textsuperscript{9} It has a rapid onset of action but in the newborn has a half-life of about 12 hours.\textsuperscript{12} So continuous infusion can easily cause drug accumulation particularly in the preterm infant. Withdrawal encephalopathy, hypotension, respiratory depression, paradoxical agitation and myclonus have all been described.\textsuperscript{9}

**Thiopentone:**

Thiopentone is a barbiturate with hypnotic and anticonvulsant effects but no analgesic effects. It can cause hypotension and the half life is 20-30 hours in the neonate.\textsuperscript{9} Bhutada et al\textsuperscript{3} used it to some advantage in a randomised trial of induction for intubation in term infants. There is no data on its safety in preterm infants.

**Suxamethonium:**

Suxamethonium acts by mimicking acetyl choline and so blocking the nerve terminal. Its rapid onset (30 seconds) but short action (3 to 6 minutes) makes it ideal for intubation. Prolonged paralysis may occur in rare cases with cholinesterase deficiency. Reactive bradycardia can occur with repeated doses and atropine 15 micrograms/kg can be given before to prevent this.\textsuperscript{9} There is very little evidence to guide whether atropine is necessary in newborn intubation. Anecdotally, atropine can produce quite a marked tachycardia that may not be good for haemodynamic stability in the preterm infant.

### What to use on RPA Newborn Care?

While the choice of muscle relaxant is clear, there is little to guide us in the choice of sedative. Morphine should remain our drug of first choice for intubation induction because we have most experience with it and there is no evidence that any of the other drugs are clearly better.

In all situations where there is time to draw up the medications, babies for intubation should be pre-medicated in the following way.

- **Sedation:** 200 micrograms/kg Morphine as an IV bolus. Try to administer 1-5 minutes before commencing the procedure.
- **Muscle relaxation:** 2 mg/kg Suxamethonium as an IV bolus immediately prior to the procedure.
- **Atropine** is probably not indicated routinely but it may be prudent to have some drawn up in case of a reactive bradycardia. In case of reactive bradycardia, give 10 micrograms/kg IV over one minute, repeated if necessary

### 2. Drugs for continued sedation/analgesia in ventilated babies.

Do ventilated babies need sedation/analgesia?
On adult and paediatric intensive care units, sedation and analgesia of patients on ventilation would be routine. This reflects a general acceptance that having a tube in your trachea is not a pleasant experience. That, for many years, this was not routine in preterm newborns probably reflects both their limited ability to fight back and their inability to tell us about their experiences afterwards. As knowledge about newborn pain increased, routine sedation became more widespread but even now there is a lack of data about long-term effects. Most of the study has focused on short-term outcomes such as pain scores or metabolic products of stress.

Three small randomised trials\(^{13-15}\) have compared sedation with Fentanyl against placebo in ventilated preterm infants. All showed better pain or behavioural stress scores and lower stress hormone levels. Orsini et al\(^{15}\) showed no difference in long term outcomes but their Fentanyl group had higher ventilatory requirements early on. Two trials have compared Morphine with placebo\(^{16,17}\). Quinn et al\(^{16}\) showed lower adrenaline levels and slightly lower blood pressures in the morphine group but no differences in any other outcomes. Anand et al\(^{17}\) showed a lower rate of IVH and PVL in a morphine treated cohort (4% vs 24%) and better pain scores but no differences in other mainly short term outcomes. This study also had an arm treated with midazolam who, while having better distress scores than the placebo group, did not benefit in terms of less IVH/PVL (32%). This is of concern because when these findings are combined with the other randomised trial in a systematic review, the midazolam arm shows both a higher rate of IVH and a longer need for ventilation\(^{18}\). This review concludes that there must be concern about the safety of midazolam in the preterm population.

So there is consistent evidence that sedation makes the babies more comfortable and less stressed. On the other hand, sedation may worsen or prolong the respiratory course presumably by suppressing the baby's own respiratory drive and the findings of the NOPAIN trial stress the need for some longer term outcome data.

**Which is the best sedative?**

Fentanyl was compared with morphine as a longer-term sedative in a randomised double blind trial on preterm babies\(^{19}\). There was little difference in outcomes between the two drugs but the Fentanyl group had less problems with GI motility (23% vs 47%) and slightly lower level of stress hormones. However, Arnold et al\(^{20}\) have described development of tolerance to Fentanyl in a cohort of term babies on ECMO and the risk of accumulation and muscle rigidity remain an issue. Wood et al\(^{21}\) compared morphine with diamorphine (Heroin) and showed diamorphine had less effect in lowering blood pressure but there were no differences in other outcomes. Diamorphine is legally not available in Australia.

Probably the best evidence to date comes from the NOPAIN study of Anand et al\(^{17}\). In this study, 67 babies born before 32 weeks were randomised to infusions of morphine, midazolam or placebo. The only difference in outcome was the lower rate of IVH/PVL in the morphine arm. The numbers were limited and the authors conclude this needs confirming in a larger trial.

**What to use on RPA Newborn Care?**

There does not seem to be any reasons we should change from our current first choice drug, morphine. The evidence would point to the need for a loading dose prior to commencing the infusion to ensure analgesic blood levels. The prolonged respiratory course in the sedated arms of some of the trials would also suggest we should be more pro-active with stopping sedation once the baby is actively weaning from ventilation.

**Guideline**

In all babies who are anticipated to need ongoing ventilation, sedation/analgiesia should be considered using:

**Drug of first choice:** Morphine:

- A loading dose of 100 to 200 micrograms/kg of Morphine should be given prior to commencing the infusion with the dose to be judged on the degree of distress shown by the baby.
- Morphine infusion to continue at 20 micrograms/kg/hr but try to wean to 0 micrograms/kg/hr if the baby appears well settled. The infusion rate can be increased to 40 micrograms/kg/hr if the baby remains agitated.
- Stopping the infusion should be considered when the baby is changed to SIMV. There is no need to wean the infusion unless it has been going for over 14 days. Note: preterm half life of morphine about 9 hours. 6

**In babies who remain unsettled on 40 micrograms/kg/hr of Morphine, the following options should be considered:**

1. Make sure there is no other reason for the agitation, the commonest reasons would be inadequate respiratory support and neurological agitation (eg. symptomatic IVH in a preterm baby).
2. Further increasing the dose of Morphine: This could be done either by giving a bolus of 100 to 200 micrograms/kg or by further increasing the infusion rate. Short periods on higher does of morphine are unlikely to do any harm if the baby is still agitated on 40 micrograms/kg/hr.
3. In preterm babies (<33weeks) consider changing to Fentanyl:
   - Change the drug, don’t add another in, there is little point in giving two drugs.
   - Give a loading dose of 3-5 micrograms/kg.
   - Continue infusion at 1.5 micrograms/kg/hr. Because this drug can accumulate, constant efforts should be made to minimise to a dose compatible with adequate sedation.
   - Remember the risk of chest wall muscle rigidity and laryngospasm. Tolerance and withdrawal symptoms can occur.
4. In term babies (>32 weeks) consider changing to Midazolam.
   - Midazolam should not be used in preterm babies (<33 weeks) until there is clearer evidence of its safety.
   - Give a loading dose of 100 micrograms/kg.
   - Continue infusion at 10 micrograms/kg/hr. Can increase to 60 micrograms/kg/hr depending on response.
   - Tolerance and withdrawal symptoms can occur.

**Key points:**

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<tr>
<th>Key Point</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Sedation/analgesia and muscle relaxation prior to intubation makes the procedure easier, quicker and less likely to be traumatic.</td>
<td>1-4</td>
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<td>Ongoing sedation/analgesia of ventilated babies reduces their observed distress and also reduces blood levels of stress hormones</td>
<td>13-16</td>
</tr>
<tr>
<td>Midazolam should not be given to very preterm infants.</td>
<td>18</td>
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</tbody>
</table>

**References**

5. Hancock S, Newell S, Brierley J, Berry A. Pre-medication for neonatal intubation: current practice in


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