Management of pain in ventilated neonates: current evidence

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Abstract

Management of pain in neonates has gained importance in the last two decades. We have just begun to understand the expression of pain by the neonates and we are still exploring pharmacologic and non-pharmacologic management strategies. This article reviews the pharmacological treatment of pain in ventilated neonates, the clinical and neuro-developmental impact of most used drugs for analgesia and sedation and discusses various options and recommendations.

Keywords analgesia; pain; pain assessment; newborn; ventilated neonates

Introduction

Pain management has rightfully been the subject of many research articles. Newborn infants have the anatomical and functional components to perceive painful stimuli at an early gestation. These pathways are completely myelinised by approximately 30 weeks gestation. Near-infrared spectroscopy directly measures the cortical haemodynamic response to noxious stimulation. A clear cortical response is seen from 25 weeks gestation whose magnitude increases and latency decreases with age. In premature newborn infants repeated exposure to painful stimuli leads to persistent behavioural changes that suggest a long term effect on the developing brain. Pain

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exposure is a major source of distress for neonates admitted in a neonatal intensive care unit (NICU). The most frequently described painful procedures are endotracheal and naso-pharyngeal suctioning, heel lance, removal of adhesive tape, insertion of an intravenous cannula and the manipulation on CPAP (prongs insertion/reinsertion). The number of such procedures to which a neonate is exposed varies from 2 to 17 per day and is more frequent in the most premature.

Appropriate and accurate assessment of ongoing pain is a necessary and routine element in deciding the need for an adequate analgesic and sedative treatment especially in the sickest and most premature neonates often requiring prolonged periods of mechanical ventilation.

There are at least 37 published scales of assessment for pain in newborn infants. The basic component included physiological parameters (Heart rate (HR), Respiratory rate (RR), Oxygen Saturation (sats), Blood pressure (BP)) and behavioural observations (facial grimace, body movement, and cry). Clinical use of these scales is based upon the ease of use of the scale at the bedside and validity in the given population. The Association of Paediatric and Anaesthetists of Great Britain and Ireland recommended use of PIPP, NFCS, FLACC and COMFORT scales.

In 19 ventilated preterm infants the COMFORT scale appeared to be a valid and reliable measurement tool to assess the stress of ventilated prematurely newborn in the acute setting and was the preferred assessment tool by NICU nursing staff. The COMFORTneo scale has been adapted to be more relevant to NICU giving a score of 1−5 is given for 6 domains. In 286 newborns from 24 to 42 weeks gestation a score of 14 out of 30 had sensitivity of 0.81 and specificity of 0.9 to determine a painful response.

Appropriate and accurate assessment of ongoing pain is a critical element in deciding the need for and the adequacy of analgesic and sedative treatment. Despite well conducted studies in ventilated preterm infants there is still controversy on the use of analgesia in this population.

General principles

The overriding principles are covered in detail in the Association of Paediatric Anaesthestists good practice guideline 2012. Planning for painful procedures and experience, Routine validated assessment, cohorting of necessary interventions, the use of prophylactic and reactive methods, appropriate use of non-pharmacological and pharmacological methods are the basis for a biological, psycho social and medical model of pain management. There are short and long term adverse consequences of pain in the newborn that should be balanced with the known adverse effects of any management strategy. Of note is that neuronal apoptosis is seen for almost all pharmacological measures. However the quantity of apoptosis related to the specific drug, the long term neuro-developmental effects are not clearly defined. These adverse effects should be balanced with the detrimental effects of pain experience on NICU.

OPIODS

Morphine

Morphine is commonly used for pain and sedation in NICU. It produces analgesia and sedation by acting on brain stem, dorsal

horn of the spinal cord, and neuronal membrane potentials peripherally. The half-life in neonates varies between 6 and 12 hours depending on the gestational age.

There are three well-designed randomized controlled trials (RCT) comparing morphine with placebo in preterm ventilated infants. The Neonatal Outcome and Prolonged Analgesia in Neonates trial (NOPAIN, 1999) studied 67 neonates from 24 to 32 weeks' gestation who were intubated and ventilated for less than 8 hours at enrolment. The newborns were enrolled within 72 hours of delivery and randomized to receive midazolam, morphine, or placebo. A loading dose of 100 μg/kg of morphine followed by an infusion of 10, 20, or 30 μg/kg/hr was given to newborns 24−26, 27−29, and 30−32 weeks gestation, respectively. Severe intraventricular haemorrhage (IVH), periventricular leucomalacia (PVL) and death occurred in 24% of newborns in the placebo group, 32% of newborns in the midazolam group, and 4% of newborns in the morphine group, with no differences in the neurobehavioral outcomes at 36 weeks. An infusion of 10−30 μg/kg/hour of morphine significantly reduced the Premature Infant Pain Profile scores (PIPP) during endotracheal tube suction compared with the placebo group.

The NEurologic Outcomes and Preemptive Analgesia in Neonates trial (NEOPAIN, 2004) was multicentre, blinded, randomized trial that recruited 898 preterm neonates born between 23 and 32 weeks of gestation who were intubated within 72 hours of delivery and were randomized to receive morphine or placebo. A loading dose of 100 μg/kg of morphine followed by an infusion of 10, 20, or 30 μg/kg/hr was given to 449 infants 24−26, 27−29, and 30−32 weeks gestation, respectively. Open-label morphine could be given, based on clinical judgment. Newborn response to tracheal suction was assessed using PIPP before the start of the infusion, at 24 hours, 72 hours and 12 hours after the end of the infusion. In addition HR, RR, and Sats were recorded before and 2 minutes after tracheal suction. PIPP scores were significantly lower in the morphine group at 24 hours of infusion but no evidence of morphine analgesic effects was noted in relation to ETT suction, particularly when measured by heart rate changes and PIPP scores. Newborns in the morphine group required a longer duration of mechanical ventilation, took longer to tolerate full enteral feeds and showed hypotension more frequently than the placebo group both with the loading dose and at 24 hours. Continuous morphine infusion did not change the frequency of the primary outcome (composite of neonatal death, severe IVH, or PVL) in the two groups. A post hoc analysis demonstrated that the increased IVH noted in the 27−29 week group was related to gender, antenatal steroids, CRIB score, maternal chorioamnionitis and gestational age.

Intravenous morphine poses the newborn risks of apnoea, respiratory depression, delayed gastric motility and urinary retention. In addition clinically significant hypotension is more common in newborns of 23−26 weeks gestation, with preexisting hypotension and in high dose (>100 μg/kg). Whilst the first two are significant, an intubated newborn will be protected from these. Developmental follow-up of NEOPAIN infants ($n = 572$) at 36 weeks postmenstrual age found higher popliteal angle cluster scores, indicative of increased tone, in neonates randomized to morphine. This finding was confirmed by a retrospective analysis showing that larger total morphine dose correlated with poorer motor development at 8 months but not at 18 months. A 5- to

7-year follow-up of 20 newborns from NEOPAIN (morphine treated {$n = 14$}, placebo treated {$n = 5$} found that IQ and academic achievement did not differ between the groups. A further 5-year follow-up study showed no significant differences in intelligence, visual-motor integration, behaviour, chronic pain or health-related quality of life between children who as neonates had received either morphine or placebo. However visual analysis as a subtest of IQ test was significantly worse in newborns who received morphine. Whilst the Cochrane review states that routine use of morphine cannot be recommended, specific indications such as post surgery, post birth asphyxia or during routine invasive procedures (i.e. Intubation and ventilation) that have been recommended in other publications highlight that morphine is a basic part of pain management on NICU.

Synthetic opioids − fentanyl, alfentanil and remifentanil

Fentanyl is a synthetic μ-opioid agonist that is more potent, has a faster onset and shorter duration of action compared to morphine. It is mainly cleared by the kidneys and less by the liver and so the half long is prolonged if either of these systems is impaired. In NICU fentanyl reduces stress markers, decreases behavioural scores, decreases oxygen desaturation without adverse neurological impact. A large RCT of 163 ventilated neonates found similar mortality and rates of severe IVH in both morphine and fentanyl groups. Fentanyl infusion has less of the detrimental effects of morphine but there is greater tolerance and withdrawal by opioid receptor desensitization and up-regulation of the cAMP pathway. Fentanyl requires regular increases in infusion rate to maintain satisfactory sedation in newborns and so its routine use as an infusion on NICU has been limited.

Remifentanil and alfentanil are alternatives to fentanyl infusion. Their duration of action is shorter (3−5 minutes and 20−30 minutes respectively) and are rapidly eliminated by esterases resulting in lack of accumulation and a rapid offset rather than being organ dependent. A cohort of 46 ventilated infants less than 33 weeks gestation demonstrated that time to extubation following discontinuation of remifentanil infusions was 36 minutes after a median treatment period of 5.9 days (range 1−20). Other studies have also found the mean time to extubation following discontinuation of remifentanil is shorter compared with fentanyl but varied in the time taken (remifentanil 80 minutes vs. Fentanyl 782 minutes). In addition the time to extubation was 12.1 times faster in those receiving remifentanil compared with morphine infusions. The dose required to achieve sedation has ranged approximately two fold from 0.1 μg/kg/minute and this is likely to reflect maturation in the metabolism pathway.

Remifentanil has also been used as a short term analgesic for painful procedures in the preterm neonates. For PICC line placement in self-ventilating neonates of 28 week gestation a small RCT showed 0.03 μg/kg/minute infusion of remifentanil resulted insignificantly lower pain scores compared with placebo whilst no difference in clinical observations were noted. A cohort of 6 preterm infants undergoing laser therapy received a midazolam bolus followed by a remifentanil infusion of 0.75−1 μg/kg/minute, increasing to 3−5 μg/kg/minute during the procedure. This regime provided adequate analgesia without haemodynamic side effects, nor chest rigidity and the patients were back to their pre-operative status within 2 hours of the procedure. Alfentanil has been used in similar settings and is

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considerably cheaper at the present time. A bolus of 20 μg/kg decreased the heart rate response, pain score and plasma adrenaline compared with placebo in a small group of premature infants.

Benzodiazepines

Midazolam infusion

Midazolam, a short-acting benzodiazepine, is used as premedication for intubation and as sedative in newborn infants requiring prolonged mechanical ventilation and prior to invasive procedures. The drug exerts its clinical effect by binding to a receptor complex which facilitates the action of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Midazolam is excreted primarily by the kidneys. Its elimination half-life varies with gestational age and ranges between 6 and 12 hours. Midazolam is sedative, anxiolytic and antiepileptic but can lead to seizure activity in neonates especially in preterm due partly to reduced number of GABA (A) receptors and partly reversal of mode from excitatory to inhibitory.

The adverse events associated with midazolam include hypoventilation, decreased oxygen saturation, apnoea, hypotension and decreased cerebral blood flow velocity. In a placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies the midazolam group had significantly lower blood pressures than newborns in the placebo group. In NOPAIN the incidence of poor neurological outcome (death, severe IVH, PVL) was higher in the midazolam group compared to the placebo and the morphine groups. A recent review has highlighted the increased risk of myoclonus in neonates compared to older populations, due to decreased number of GABA (A) receptors. Animal studies have described long term effects on brain development due to widespread neuroapoptosis and suppressed neurogenesis elicited by early benzodiazepine exposure. Whether neonatal exposure to midazolam also induces long-term behavioural or cognitive deficits remains unknown. On the basis of these findings midazolam infusion cannot be recommended on NICU.

In spite of the issues with an infusion, Midazolam has been successfully used in Paediatrics and Neonatal Intensive Care Units and Emergency Departments for acute sedation. The bioavailability is increased by nasal route. An intranasal dose of 200−400 μg/kg midazolam has been successfully used to sedate newborns during physiotherapy, children for dental extraction, laceration repair, venepunctures, burn dressing and retinopathy of prematurity screen. Intranasal administration has not been associated with adverse effects of respiratory depression or hypotension seen with intravenous use. The use of bolus midazolam for sedation on NICU is part of an ongoing trial (NCT01517828).

Alpha 2 adrenergic agonist

Clonidine and dexmedetomidine

Clonidine is a lipid soluble partial alpha 2 adrenergic agonist with antihypertensive, sedative and analgesic properties. A study of 30 ventilated children under 10 years of age in 2000 demonstrated that doses of 0.2−2 μg/kg/hour with a background of midazolam 50 μg/kg/hour provided adequate sedation without any haemodynamic side effects. Clonidine is often used as a replacement in opioid tolerance or in children who are difficult to

sedate or suffering opioid withdrawal. A single centre retrospective review of children post cardiac surgery with a mean age of 5 months, demonstrated that a clonidine infusion commenced on day 5 after surgery normalized the haemodynamic parameters and enabled opioid and benzodiazepine sedation to be stopped after 4 days of treatment with clonidine. The SLEEPS trial is a prospective multi-centred double blind equivalence study comparing clonidine with midazolam as intravenous sedative agents in children requiring mechanical ventilation will hopefully provide much needed safety data on both of the sedatives.

Dexmedetomidine is a more specific alpha 2 adrenergic agonist compared to clonidine with limited data in NICU. Dexmedetomidine recipients required less adjunct sedation, experienced less respiratory depression, less clinically significant haemodynamic effects, were quicker to establish enteral feeds and could be extubated whilst on the infusion compared with fentanyl. In a case report in a 24-week gestation newborn an infusion of 0.7 μg/kg/hour maximum allowed effective weaning from opioid and benzodiazepine with exubation after a 19 days use. In addition there is preliminary data suggesting neuroprotection following hypoxic-ischaemia events in the rodent model.

Ketamine

Ketamine acts as an N-methyl-D-aspartate (NMDA) receptor non-competitive antagonist. It is a dissociative anaesthetic combining profound analgesia with light sleep. Unless given in high doses respiratory reflexes are relatively maintained with transient increases in blood pressure and heart rate with bronchodilation and no effect on cerebral blood flow. These features have made it popular to maintain cardiac stability and in asthma or persistent pulmonary hypertension. Ketamine may be administered via intravenous, intramuscular, oral, rectal, epidural, and intranasal routes. Intravenous Ketamine demonstrates a rapid onset and peak effect followed by a relatively short and predictable duration of action. A small study demonstrated that the an intravenous dose of 0.5 ± 2 mg/kg given to neonates was ineffective in preventing the heart rate and blood pressure changes associated with endotracheal suctioning.

Salivary and tracheobronchial secretions are increased by Ketamine and can be attenuated with atropine or glycopyrrolate. It produces epileptiform electroencephalogram patterns in the human limbic and thalamic regions, suggesting that ketamine is a proconvulsive agent. However, there is no evidence that ketamine effects cortical regions nor that clinical seizures are more likely to occur. Ketamine has been reported to produce skeletal muscle hypertonicity and rigidity. The effect on muscle tonicity is dose related. Animal studies demonstrate that ketamine produced acute neuronal apoptosis and evidence of persistent changes in neuronal function.

In spite of these concerns, a 2 mg/kg IV dose of Ketamine given over 1 minute will produce 'surgical' anaesthesia after 30 seconds lasting approximately 10 minutes. In cryotherapy for retinopathy of prematurity an IV dose of 1 mg/kg with vecuronium allowed intubation and anaesthesia for at mean gestation of 36 weeks and mean weight of 1585 g. In addition a combination of nasal ketamine and midazolam has also been successful for the same. Ketamine is a potent anaesthetic that has received minimal study in neonates. The use of bolus ketamine for sedation on NICU is part of an ongoing trial (NCT01517828).

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Propofol

The UK Medicines Control Agency and Committee on safety of medicines have in 2001 determined that propofol *infusion* in under 16 year olds for sedation was contraindicated.

Infusions of Propofol have been associated with 'propofol infusion syndrome' that is characterized by metabolic acidosis, arrhythmia, hyperkalemia, hepatomegaly, rhabdomyolisis, cardiac and renal failure. Although this is a rare complication is it invariably fatal. Propofol has however been used as an induction agent for intubation and this is discussed in the following section.

Paracetamol

Paracetamol (N-acetyl-p-aminophenol) is a readily available anti-pyretic and analgesic agent. It acts by inhibiting the cyclo-oxygenase (COX) enzymes in the brain. It is the most frequently prescribed analgesic and anti-pyretic in children, infants and neonates. It can be administered by the oral, rectal, or intravenous route. Parenteral Paracetamol is an attractive analgesic for neonatal use in the postoperative period and for those with restricted oral intake. It is used as an alternative or supplement to opioid analgesia in term or preterm neonates where reduction of opioid associated side effects is frequently desirable. In a randomized control trial on 71 neonates, the cumulative median morphine dose in the first 48 hours postoperatively was 121 µg/kg in the paracetamol group ($n = 33$) and 357 µg/kg in the morphine group ($n = 38$), $P < .001$, with a between-group difference of 66% lower in the paracetamol group (95% CI). Pain scores and adverse effects were not significantly different between groups. The recommended doses are 10–15 mg/kg orally or 20–25 mg/kg rectally up to four times per day. Intravenous doses rely on a loading dose of 20 mg/kg followed by 10 mg/kg up to four times per day with a total daily dose less than 40 mg/kg in newborns of less than 32 weeks gestation and 60 mg/kg in newborns of 32–42 weeks gestation. Some caution should be exercised because of immature hepatic enzymes as toxicity can occur rarely.

Sucrose

Oral sucrose has been used for effective analgesia in term and preterm infants. A Cochrane Review included 3496 newborns and concluded that "Sucrose is safe and effective for reducing procedural pain in neonates. The analgesic effect is equivalent to other non-pharmacologic interventions such as facilitated tucking and kangaroo care. A combination of these techniques might provide synergy. An effective dose ranges from 0.1 ml of 24% to 1 ml of 30% sucrose. However 0.24 g of sucrose given 2 minutes before an intervention was effective for up to 7 minutes. Some concern has been raised about repeated doses linked to necrotizing enterocolitis, poor neuro-developmental outcome and long term detrimental effects of early dietary exposure to sugar.

Topical Local anaesthetics

Several topical agents such as 4% tetracaine gel, liposomal lidocaine, and LMX4 are effective in reducing the pain from venepuncture and other skin puncturing procedures. None of these have been effective for heel lancing (a spring loaded lance on the plantar surface of the heel are most effective). 4% tetracaine has been used safely in newborns of 27 weeks gestation.

Premedication for intubation

Endotracheal intubation is a potentially injurious procedure and is associated with pain and cardiorespiratory instability. Therefore the best possible intubating conditions are required to minimize the risk injury and number of attempts as much as possible. The use of premedication significantly improves intubation conditions enabling jaw relaxation, the vocal cords to be open and immobile as well as the pharyngeal and laryngeal reflexes to be suppressed.

In the UK and Australia morphine followed by fentanyl are the most common analgesics. Suxamethonium is most widely used muscle relaxant and Atropine is used in half of the NICU's using premedication regimes. However these drugs take time to draw up and administer and do not provide 'ideal' intubation conditions. There is no definition of an ideal intubating condition but safety profile in NICU, time to draw up and administer drugs, rapid onset of sedation and paralysis, short duration of action are common themes. These conditions have been highlighted by a move to endotracheal intubation with surfactant application and early extubation (the INSURE procedure) in many NICU's.

Inhalation anaesthetic agents such as nitrous oxide and sevoflurane have the advantage of ease of administration, rapid onset, short duration of action, and minimal side effects. However they are not routine available for use on most neonatal intensive care units and there is data on their detrimental effect in prolonged use on ambulatory EEG.

In terms of a sedative, morphine and placebo were similar in effect on physiological parameters during intubation. In addition the time is onset is approximately 5 minutes with peak effect at 15 minutes makes morphine a less than ideal drug for intubation.

Fentanyl has a faster onset of action and shorter duration than morphine. Chest wall rigidity and laryngospasm are associated with fast administration and can be alleviated by slower infusions or concomitant use of a paralytic agent (a prospective cohort study of fentanyl with atropine and succinylcholine demonstrated excellent or good intubation conditions in 91.7% of infants).

Recent trials have commonly used remifentanil as a premedication given its advantage of a static and short context sensitive half time of 3–5 minutes. It therefore doesn't accumulate in the peripheral tissues and has a rapid offset making it an attractive option for the INSURE procedure. A pilot study of 21 preterm infants receiving remifentanil demonstrated that it provided good intubating conditions, had no serious side effects and the average extubation time post intubation was 16.9 minutes (1–45 minutes) following which no infants had to be re-intubated. Alfentanil has been used in similar settings and is considerably cheaper at the present time. A bolus of 20 µg/kg decreased the heart rate response, pain score and plasma adrenaline compared with placebo in a small group of premature infants.

Propofol has been used as a bolus agent. One study in newborns of mean gestation 27–28 weeks found time to achieve successful intubation quicker compared with a standard regime (as above) 120 vs. 260 seconds. However there are conflicting findings from small studies re-adverse effects. Invasive blood pressure monitoring did not find evidence of post propofol hypotension compared to oscillatory blood pressure studies. In addition transient bradycardia and oxygen desaturation have been noted.

Ketamine produces 'surgical' anaesthesia after 30 seconds lasting approximately 10 minutes with 2 mg/kg IV dose of

Ketamine given over 1 minute. An intranasal dose of 200—400 µg/kg midazolam has been successfully used to sedate newborns. Both agents are part of an ongoing trial (NCT01517828) for sedation on NICU but not specifically for intubation.

Each of these agents in isolation would provide the ideal intubating conditions described above. However, many neonatologists or advocates of premedication strategies for NICU would suggest that a combination of drugs that includes a neuromuscular blocking agent is ideal. One must consider whether the additional time for administration is in the best interests of the newborn or facilitates intubation.

The choice of neuromuscular blocking agent if determined necessary has a number of options. The most pertinent consideration with a neuromuscular blocking agent is having the skills to manage a paralyzed newborn when intubation has failed. Suxamethonium is most widely used agent with a short onset (<30 seconds) and duration of action (usually <5 minutes). It is a depolarizing agent which results in neuromuscular blockade by its agonistic effect at the cholinergic receptor of the neuromuscular junction. Therefore atropine is required to limit adverse effects (particularly bradycardia). Whilst the rapid onset facilitates intubation, the limited duration of action and side effect profile is not ideal on NICU. The side effects are more common when repeated doses are given. There are many non-depolarizing neuromuscular blocking agents (atracurium, mivacurium, vecuronium, rocuronium and pancuronium). Each has a longer time to onset of action than suxamethonium (not ideal) but a longer duration of action that allows for a second attempt at intubation if required. Agents such as neostigmine and atropine or Sugammadex (for rocuronium and vecuronium) can reverse paralysis but do take some minutes to be effective.

A blinded RCT showed significantly better intubating conditions with a rapid sequence induction (RSI) combination of glycopyrrolate, thiopental, suxamethonium and remifentanil compared with morphine and atropine. Of note, one infant received an accidental 10-fold overdose of thiopental, highlighting the difficulties of complicated drug prescriptions in semi-urgent situations. In an RCT of preterm infants comparing remifentanil and midazolam with morphine and midazolam the probability of excellent intubating conditions was significantly higher in the remifentanil group. Though when compared with fentanyl a double-blind RCT found no difference in number of successful intubations. It is noteworthy that there were cases of chest wall rigidity in the remifentanil group though the fentanyl group were given succinylcholine which may have biased the results in fentanyl's favour. However the adjunct use of a muscle relaxant would counteract such side effects.

Mivacurium in combination with fentanyl and atropine has maintained oxygen saturation above 90%, fewer intubation attempts and shorter overall intubation time than attempts without mivacurium. The onset of muscle relaxation is longer and more variable than suxamethonium (approximately 90 seconds) and the duration of action longer (approximately 16 minutes).

Conclusion

Newborn infants have the anatomical and functional components to perceive painful stimuli at an early gestation. In NICU painful experiences are acute (procedural) and longer term (postoperative, ventilation). Both need appropriate management from a biological, psycho social and medical model of pain management with planning, routine validated assessment, cohorting of necessary interventions, the use of prophylactic and reactive methods, appropriate use of non-pharmacological and pharmacological methods. In addition there are short and long term adverse consequences of pain in the newborn that should be balanced with the known adverse effects of any management strategy.

The challenge is that this area does not have large studies to address every issue on NICU yet there is relevant data that has not been translated into NICU practice. Many papers conclude that further research is needed in order change the care of the sickest newborns and so specific recommendations are not forthcoming. ◆

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Practice points

However on the basis of the articles reviewed for this publication one might consider:

1. For ventilated newborns: infusion of morphine $+$ neuromuscular blocking agent.

2. For intubation Midazolam $\pm$ atracurium with:
    a. Alfentanil in cardiovascular stable newborns
    b. Ketamine in cardiovascular unstable newborns

3. For procedural pain a combination of range of planning, prophylactic and reactive methods as described above as they are.

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