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 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 nasopharyngeal 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

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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

