Pain, opioid tolerance and sensitisation to nociception in the neonate

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Pain is commonplace in newborn infants. Opioid analgesics have become increasingly used to reduce different types of pain in neonates, including pain from surgery, medical procedures and chronic conditions. Adverse effects of opioids include respiratory depression, hypotension and tolerance. These adverse effects can be minimised by utilising specific administration techniques and constant monitoring. Recent studies have demonstrated that untreated pain can have long-term effects on infant pain behaviours months beyond the events, thus, opioid analgesics may have a beneficial role that extends beyond the immediate painful event(s).

Key words: infant–newborn; pain; opioid analgesics; hyperalgesia.

There are many situations in the life of a newborn infant where pain can occur. These include medical conditions such as traumatic deliveries and iatrogenic pain during hospitalisation. Opioid analgesics have become increasingly utilised in an attempt to decrease pain in this population.[1–3] The increase in the utilisation of opioid analgesics for

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neonatal pain management is due to increased awareness that neonates feel pain and that analgesics effectively decrease pain. In addition, there is a growing body of evidence demonstrating that untreated neonatal pain can lead to long-term changes in pain behaviours that persist throughout infancy and childhood. Recent international consensus statements have also supported the routine use of analgesics in this population.[4,5]

The purpose of this chapter is to review the literature on pain in the neonate, its management with opioid analgesics and the long-term effects of untreated pain. The first part provides a brief overview of the nociceptive system and pain measurement in newborn infants. In the second part, we review the use of opioid analgesia and research that deals with the adverse effects of opioids. We conclude with a review of the literature examining the long-term effects of untreated neonatal pain.

PAIN IN INFANTS

The neonatal nociceptive system

The neuroanatomical basis for pain perception is present at the time of delivery, even in preterm infants (for reviews, see Wolf[6] and Anand et al[7]). Briefly, it has been demonstrated that sensory neurons cover all fetal cutaneous and mucosal surfaces by 20 weeks' gestation.[8] At full-term, the density of cutaneous neurons in neonatal skin is at least as great as that of the adult.[9] Organisation of the dorsal horn cells and myelination of nerve tracts up to the level of the thalamus is complete by 30 weeks' gestation.[10] Synaptic connection between the thalamus and cortex occurs at 24 weeks' gestation.[11] Neuromediators such as substance P and endogenous opioids and their receptors, have been demonstrated in fetuses as well.

There is remarkable plasticity in the nociceptive system. In general, interplay between afferent neurons and descending central nervous system neurons modulates the incoming nociceptive signal, resulting in a dampened or increased nociceptive input. In the neonate, however, descending central inhibitory pathways and interneurons that modulate nociceptive inputs in the spinal cord may be relatively immature at birth.[12,13] Consequently, neonates, particularly preterm infants, may respond to stimuli that do not evoke a response in older, more developed infants and thus may experience pain in response to normally non-noxious stimuli.

Pain assessment

Newborn infants demonstrate consistent and reliable responses during acutely painful procedures that encompass three distinct domains: behavioural, physiological and neurochemical.[14] Behavioural responses include facial grimacing, crying, body writhing movements and withdrawal reflexes. Physiological responses include changes in heart rate, oxygen saturation, blood pressure and respiratory rate. Neurochemical responses include the release of a variety of hormones including cortisol, insulin, glucagon, endorphin and catecholamines.

In general, infant responses across the different domains are correlated.[15] As such, a number of composite measures have been developed that incorporate responses from one or more domains to generate an overall pain score. Examples of infant pain assessment tools include the Neonatal Facial Coding System (NFCS)[16], the Premature Infant Pain Profile (PIPP)[17] and the Scale for Use in Newborns (SUN).[18]

The responses of infants to acute pain are similar to those observed in children and adults and are designed to be short-lived and protective. Infant responses to

persistent or long-lasting pain have been less well studied. Persistent pain can occur in certain conditions that involve inflammation[14], such as birth-related fractures, cephalohaematomas, osteomyelitis and necrotising enterocolitis. In addition, persistent pain may be iatrogenic and result from repeated medical procedures (e.g. heel lancing). In adults, chronic pain is accompanied by altered sensory states such as hyperalgesia and allodynia. Similar states probably develop in newborn infants with the above inflammatory conditions and those exposed to repeated noxious procedures. In fact, newborn infants may be particularly sensitive to the effects of pain due to the immaturity of descending inhibitory pathways, rapid brain growth and the potential to permanently alter neuronal development and organisation.

CLINICAL USE OF OPIOID ANALGESICS

Opioid analgesics are commonly administered to newborn infants for the management of procedural pain, post-operative pain, disease-related pain and as sedatives to reduce the stress of intensive care in mechanically ventilated infants. Opioids provide pain relief and blunt the physiological effects of pain and stress. These include changes in the cardiorespiratory system (e.g. hypertension, tachycardia, hypoxaemia), endocrine (e.g. hypothalamic–pituitary–adrenocortical (HPA) activation) and metabolic processes (e.g. hyperglycaemia), the immune system and coagulation/hemostasis.[19]

Opioids decrease the physiological abnormalities that are associated with operative procedures and may lead to diminished overall morbidity and mortality. In two separate landmark studies, opioid analgesics were shown to decrease the stress response and improve clinical outcome when used during operative procedures in newborns.[20,21] It has been proposed by some authors that the benefits of opioids for operative procedures may be extrapolated to the neonatal intensive care unit, for indications such as sedation during mechanical ventilation. In support of this hypothesis are data demonstrating that cortisol levels in hospitalised preterm infants in the first week of life can exceed those seen in response to surgery.[22] Moreover, it has been demonstrated that increased stress hormone concentrations in sick preterm infants are associated with an increased risk of mortality (although it is not clear to what extent they reflect the severity of underlying illness).[23] Opioid analgesics have, therefore, been increasingly used for sedation and analgesia in ventilated preterm infants[24] with the hope that they will improve clinical outcome.

Two studies have investigated the effects of sedation with morphine on infant outcomes. In a randomised controlled study, Anand et al[25] found that infants that received morphine had significantly improved long-term outcomes (defined as a reduced risk of death and of major neurological morbidity) compared to infants that received midazolam or dextrose. Infants had been treated with either morphine, midazolam, or dextrose for up to 14 days (mean infusion duration among groups was 3–5 days). The investigators hypothesised that the beneficial effects of morphine were due to: decreased stress; blood pressure stability; ventilator synchrony (by decreasing spontaneous respirations and helping to synchronise breathing during mechanical ventilation); improved oxygenation.

Similar results, however, were not observed in other randomised controlled trials of opioid sedation/analgesia in ventilated pre-term infants. Quinn et al[26] found a decrease in pain response but no difference in long-term outcomes when morphine was compared to placebo. The average duration of morphine therapy was 56 hours. Similarly, Orsini et al[27] demonstrated decreases in pain response but not in neonatal

complications using a fentanyl infusion for the first 5 days of life (see also Dyke et al[28] and Richardson et al[29]). None of these studies included enough infants to rule out potential long-term (positive or negative) effects of opioid use and further research is clearly needed before any definite conclusions can be made.

Many studies have demonstrated the efficacy of single doses of opioid analgesics for decreasing pain and stress during noxious medical procedures, such as percutaneous venous or arterial catheter placement, peripheral arterial or venous cutdown, endotracheal intubation, endotracheal suctioning and chest tube insertion. The reader is referred to the 'Consensus statement for the prevention and management of pain in the newborn'[5] for specific details and references.

It should be noted that although opioids are commonly used in neonates, the optimal dose for a given infant and indication have not been determined. This is due to insufficient data regarding the concentration–response relationship of opioids. Even though various pain assessment tools have been developed and validated, there is no universally accepted method of pain assessment, thus, it has been difficult to assess pharmacodynamic response in this population. Determination of the concentration–response relationship also requires that multiple blood samples be collected to assay drug concentrations. However, ethical considerations limit the number of samples and total amount of blood that may be collected in neonates for research purposes. It should be noted, however, that even if the concentration–response relationship for opioid analgesics had been well characterised in neonates, developmental differences in pharmacokinetics and the ontogeny of the nociceptive system make the development of an appropriate dosage regimen for individual neonates difficult.[30]

Adverse effects of opioids

Short term adverse effects

The short-term adverse effects of opioid analgesics include respiratory depression, hypotension, bradycardia, glottic and chest wall rigidity, urinary retention, ileus and seizures. Although potentially serious and life-threatening, these adverse effects can be managed clinically. For instance, smaller bolus doses and/or prolonged infusion times can be used rather than large bolus doses with rapid injection times. In addition, combining opioid analgesics with interacting medications can be avoided. One such class of drugs are the benzodiazepines, which, when combined with opioids, increase the risk of hypotension and respiratory depression.[31] Furthermore, opioid use can be limited to infants receiving ventilatory support, so that respiratory depression is easily managed.

Tolerance

Chronic administration of opioids may be associated with tolerance that requires dose escalation to maintain analgesia and sedation. Tolerance occurs in patients that are given opioid analgesics on a long-term basis. The rate of development of tolerance is variable between patients, but may be as short as a few days after the beginning of therapy. Tolerance is believed to develop more rapidly with continuous infusions of opioids (rather than intermittent doses) and with the use of synthetic opioids (e.g. fentanyl).[32] According to various authors, the development of tolerance to fentanyl in neonates occurs after a cumulative fentanyl dose of 1.6–2.5 mg/kg, or after 5–9 days of continuous infusion therapy.[33,34] It has been suggested that the risk of developing opioid tolerance may be reduced by instituting other comfort measures concurrently that supplement opioid analgesia/sedation such as noise reduction[35], or by switching opioids and using sedatives (if appropriate).[32]

Withdrawal reactions

Abrupt discontinuation of opioid analgesics may be accompanied by withdrawal reactions in infants that are physiologically dependent. The main body systems affected in opioid withdrawal include the central nervous system, autonomic system and gastrointestinal system. In one retrospective study of the frequency of adverse effects following opioid use in neonates for ≥ 3 days, the most frequently observed symptoms were irritability, hypertonicity, diaphoresis, hyperthermia and vomiting with feeds.[36] Of the 18 neonates given morphine, 48% experienced withdrawal reactions as did 84% of the 15 neonates who received fentanyl. Withdrawal reactions were correlated with dose and duration of infusion and lasted from 1 to 11 days. Fentanyl was associated with a longer duration of withdrawal (mean = 3.9 days) compared to morphine (mean = 2.3 days).

Some authors have suggested tapering schedules for discontinuation of opioids. The rationale for this being that gradual removal of the drug will prevent withdrawal reactions. At present, there are no experimental data supporting one tapering method over another and individual patient needs should be considered. In general, more aggressive tapering schedules are advised for patients that have received short-term therapy compared to those taking opioids for longer durations. For short-term therapy, opioid doses are decreased by approximately 25–50% of the dose per day and the drug is discontinued within 2–3 days. Doses are decreased by 10–20% of the original dose per day for long-term therapy and infusion regimens may be switched to intermittent dosing regimens before discontinuation. An approach to weaning opioid infusions was recently published by Anand et al.[25] The same opioid that was used therapeutically is usually used during the weaning process. Continual observation and evaluation of withdrawal reactions is necessary throughout the tapering period. Many neonatal intensive care units have implemented tapering protocols to facilitate the process.[35] They use objective tools to monitor symptoms (for a review, see Suresh and Anand[32]) and tailor opioid dosing requirements accordingly. Withdrawal reactions are managed with opioids. Non-pharmacological interventions were added to supplement their effects. Non-opioid medications are less frequently used to manage withdrawal reactions.[32,37]

Behavioural disturbances

There has been a long-standing concern that using opioid analgesics in the neonatal period may lead to disturbances in parental–infant attachment and imprinting. These concerns are derived from studies of the ontology of various neurotransmitter systems in the nervous system demonstrating extensive postnatal development with increased plasticity in the neonate compared to the adult. Detrimental effects have been demonstrated in human and animal studies (see Rahman et al[38] and MacGregor et al[39]). Briefly, human studies have shown that infants born to opioid-abusing mothers may have cognitive and behavioural problems (although these data are confounded by other risk factors associated with drug abuse). Animal studies have demonstrated altered receptor number, analgesia and tolerance in the adult following exposure in early life.

It should be noted, however, that is possible that non-medical opioid exposure in the neonatal period may lead to different pharmacological effects compared to when it is used for painful conditions.[38] In a study that investigated long-term neurological and behavioural outcome in newborn infants exposed to opioids during clinical care (for 56 hours to 5 days), no adverse effects were observed. Infants who received morphine ($n = 57$) were not different from those who did not ($n = 30$) in intelligence quotient

(IQ), motor impairment or behaviour problems. In fact, there was a trend for better scores in the morphine-exposed group.[39] Moreover, it has been suggested that clinical use of opioids in neonates is protective against potential adverse long-term effects of untreated pain (see below).[40–42] Clearly, more research on the long-term effects of opioid analgesia are needed.

Central sensitisation

There is a growing body of basic science and clinical data in the adult literature describing the development of acute opioid tolerance and its relationship to opioid-induced facilitation. Recent advances in the basic science of pain are relevant to the efforts to prevent central sensitisation by preoperative administration of opioids. Opioid administration may lead to the development of acute opioid tolerance[43,44] and opioid-induced facilitation of nociceptive processing[45–47] thereby increasing the requirements for postoperative analgesia and enhancing postoperative pain. The effects of opioid agonist-induced hyperalgesia are operating at cross-purposes to the analgesic effects thereby reducing the overall magnitude of the analgesic effects of these agents. Strategies to maximise pain relief and minimise the development of acute opioid tolerance and opioid induced hypersensitivity include co-administration of *N*-methyl-D-aspartate (NMDA) receptor antagonists such as low-dose ketamine[48,49] or dextromethorphan and ultra low-dose opioid antagonists such as naloxone or naltrexone.[50,51] To our knowledge there are no studies in the infant literature that address the related issues of acute opioid tolerance, opioid-induced facilitation of nociceptive processing and their reversal by opioid antagonists or NMDA receptor antagonists.

LONG-TERM EFFECTS OF PAIN

The increase in utilisation of opioid analgesia for the management of pain in the neonate is supported by recent evidence suggesting that early pain experience results in behavioural and physiological changes in future pain responses. These studies can be divided into two groups: studies that investigated the effects of prolonged or repeated pain and those that investigated the effects of a single painful event. A brief review of their findings is provided below.

Effects of a single painful event

Studies on the long-term effects of a single painful event have focused on the effects of birth conditions and neonatal surgical procedures on pain responses during routine immunisation. It has been demonstrated that highly stressful, or suboptimal, birth conditions are associated with exaggerated cortisol responses to routine immunisation up to the age of 6 months.[52,53] Two studies have shown that male neonatal circumcision is associated with heightened pain responses during routine immunisation 4–6 months later.[54,55] In one of these studies, pre-treatment of circumcision pain with local anaesthesia partially attenuated the development of these heightened pain behaviours.[55] Most recently, Peters et al[40] demonstrated no difference in immunisation pain responses at 14 or 45 months between infants that had undergone major abdominal or thoracic surgery in the first 3 months of life and control infants. In the surgical group, infants had received morphine for post-operative pain and morphine administration may have prevented the development of alterations in pain threshold in the long term.

In summary, heightened behavioural responses to pain have been observed in neonates undergoing noxious procedures compared with neonates not subjected to these procedures. The results of one study suggest that the administration of a local anaesthetic during neonatal surgery obtunded the pain response to the subsequent procedure several months later, implying a causal relationship between the two experiences of pain.

Effects of prolonged or repeated pain

Several groups of investigators have examined the pain responses of preterm and full-term newborn infants that had undergone multiple painful procedures during hospitalisation in the neonatal intensive care unit. It has been demonstrated that both behavioural and physiological responses to pain may be altered over time although the direction of the changes that are observed is not always consistent for a given variable and changes in pain response are not consistently predicted by the number of painful procedures that the infants were exposed to. Differences in study designs and environmental conditions may explain the inconsistent findings. These studies are described in more detail below.

A recent study found that infants with pathological abdominal disease (unilateral hydronephrosis) demonstrated cutaneous abdominal sensitivity when compared to normal infants and that this hypersensitivity persisted up to 3 months after corrective surgery, suggestive of visceral hypersensitivity.[56] However, Anand and Birch[57] found no evidence of chronic pain behaviour or neuropathic pain syndromes in children and adults 3–23 years after brachial plexus injury at birth and speculated that relative neuronal immaturity in the newborn and central nervous system plasticity is protective against the subsequent development of chronic pain syndromes.[57]

In a study by Johnston and Stevens[58], the behavioural and physiological pain response patterns of preterm infants born at 32 weeks gestational age were found to differ from those of preterm infants aged 32 weeks who had been born 4 weeks earlier. The earlier-born infants demonstrated significantly less behavioural grimacing (i.e. brow bulge, eye squeeze, naso-labial furrow) compared to the newly born infants. Earlier-born infants exhibited significantly higher maximum heart rates and lower oxygen saturation values than the newly born infants. More recently, Grunau et al[41] found that exposure to a greater number of painful procedures correlated with diminished facial reactivity as well as heart rate variability during heel lance in preterm infants. Increased heart rate variability, however, was associated with increased exposure to morphine. These authors suggest that increased exposure to painful procedures diminished the pain response and that morphine exposure partially ameliorated these effects.

Three longitudinal studies have demonstrated that pain responses change over time in preterm infants exposed to repeated painful procedures as neonates. Fitzgerald et al[59] used the flexion reflex threshold (a nociceptive reflex involving noxious stimulus elicited limb withdrawal) to demonstrate that tactile responses were heightened in preterm infants after undergoing repeated painful cutaneous procedures. This hypersensitivity was prevented by pre-treatment of the damaged area with a topical anaesthetic cream. Johnston et al[60] and Porter et al[61] demonstrated increased behavioural responses in preterm infants over time.

To date, two studies have evaluated pain behaviours in former extremely low birthweight (ELBW) infants ($\leq$800 g) undergoing a procedure after discharge from the neonatal intensive care unit. Both studies included the same cohort of infants at 4 and 8 months corrected age.[42,62] In both studies, behavioural and physiological responses

were similar between former ELBW infants and term-born control infants. However, subtle differences in cardiac, autonomic and facial responses were observed.

While it has been suggested that early pain may cause changes in the processing of nociceptive stimuli, it is important to consider the role of classical conditioning in inducing these changes. It may be that infants learn to anticipate an impending noxious event and, therefore, exhibit anticipatory pain behaviours and it is these behaviours, rather than sensitisation of nociceptors and/or central sensitisation (hyperexcitability) of sensory structures involved in processing somatosensory input that accounts for the observed differences in pain behaviour over time. Few studies have examined this phenomenon. In one study, preterm infant responses to having their leg being picked up prior to heel lance were recorded over time.[63] Heart rate changes increased over time, supporting a conditioning theory. However, facial grimacing and body movements did not change over time. More recently, Taddio et al[64] demonstrated conditioning and hyperalgesia in full-term newborns exposed to repeated heel lances. Unlike the previous study, this study included a group of infants that experienced repeated pain and a control group that did not experience repeated pain. Investigators found that infants exposed to repeated heel lances had greater behavioural pain responses during the preparatory phase of a venipuncture (i.e. skin cleansing) and that the intensity of the pain they experienced in response to venipuncture was greater than that of normal infants.

CONCLUSION

Newborn infants have the capacity to perceive pain. Furthermore, their responses to pain can be objectively quantified. It is generally accepted that pain relief should be a part of the medical management of preterm and full-term infants. The major justifications for this view include the accumulating evidence that analgesics effectively decrease pain and that untreated pain and stress may have long-lasting effects on subsequent pain responses later in infancy. Opioid analgesics have been increasingly used to manage procedural pain, post-operative pain, disease-related pain and the stress of intensive care in mechanically ventilated infants. They may, however, be associated with serious adverse effects. In addition, the optimum dose is not known. Early experiences with pain may be associated with heightened or dampened pain responding later in infancy, depending, in part, on the infant's current state, developmental status (e.g. pre-term versus full term) and cumulative experience with pain. Preterm infants that are hospitalised as neonates and subjected to repeated painful procedures appear to have a dampened response to subsequent painful procedures later in infancy. In contrast, full-term infants exposed to extreme stress during delivery or who undergo surgery react to later noxious procedures with heightened behavioural responsiveness. Variability in infant characteristics, time frame within which infants were observed and outcome measures may explain certain discrepancies between study outcomes. It appears that there is the potential for early neonatal pain experience to cause changes in how infants respond to future painful procedures. The precise determinants of these changes, their extent and their permanence are not known but they appear to involve noxious stimulus induced peripheral and central sensitisation as well as classical conditioning. Continued investigation of the effects of early pain on nociceptive pathways and the potential effects of pre-treatment with opioid analgesics are needed.

Practice points

- opioid analgesics are commonly administered to newborn infants for the management of procedural pain, post-operative pain, disease-related pain and as sedatives to reduce the stress of intensive care in mechanically ventilated infants
- the short-term adverse effects of opioid analgesics include: respiratory depression; hypotension; bradycardia; glottic and chest wall rigidity; urinary retention; ileus; and seizures. The risk of adverse effects can be minimised by using smaller bolus doses and/or prolonged infusion times and avoiding co-administration with interacting medications such as benzodiazepines
- chronic administration of opioids may be associated with tolerance that requires dose escalation to maintain analgesia and sedation
- abrupt discontintuation of opioid analgesics may be accompanied by withdrawal reaction in infants that are physiologically dependent. The main body systems affected are the central nervous system, autonomic system and gastrointestinal system. Tapering schedules are used to minimize the risk of withdrawal reactions
- highly stressful or suboptimal birth conditions and neonatal circumcision may be associated with exaggerated response to routine infant immunization up to the age of 6 months. The pain response of preterm and full-term newborn infants that have undergone multiple painful procedures during hospitalisation in the NICU may have altered behavioural and physiologic responses to pain over time. In addition, infants exposed to repeated painful procedures may learn to anticipate an impending noxious event, and therefore exhibit anticipary pain behaviours
- there is a long-standing concern that using opioid analgesics in the neonatal period may lead to disturbances in parental–infant attachment and imprinting. However, it has also been suggested that clinical use of opioids for the management of neonatal pain may be protective against the long-term adverse effects of pain

Research agenda

- further research is warranted to evaluated the optimal dose of opioid for a given infant and indication and the optimal tapering method for infants receiving chronic opioid administration
- the potential long-term (positive or negative) effects of the clinical use of opioid analgesia in neonates requires research in order to ensure that they are used optimally
- the mechanisms underlying potential differences in pain behaviour over time in infants exposed to stress and pain requires further investigation so that interventions may be implemented to avoid the potential adverse effects of pain

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