Infant pain management: a developmental neurobiological approach

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SUMMARY

Infant pain is a clinical reality. Effective pain management in infants requires a specialist approach—analgesic protocols that have been designed for older children cannot simply be scaled down for CNS pain pathways and analgesic targets that are in a state of developmental transition. Here, we discuss the particular challenges that are presented by an immature CNS for the detection and treatment of pain. We show how the application of neurophysiological and neuropharmacological approaches can help to overcome the problems inherent in measuring and treating pain in infants, and how research data in these areas can be used to devise age-appropriate methods of assessing pain as well as strategies for pain relief. The evidence that untreated pain in infancy results in long-term adverse consequences is presented, thereby emphasizing the need for a longer term view of infant pain management.

KEYWORDS analgesia, development, nociception, pain, sensitization

REVIEW CRITERIA

Searches of the PubMed and Cochrane databases were conducted for each of the main topics included in the Review. Searches were limited to articles published in English and focused on papers published since 2000. Initial searches were broad, based on the terms "neonate, infant and child" and "nociception", alongside "development", "pain measurement", "neurodevelopmental outcome" and "developmental pharmacology". Recent reviews, evidence-based guidelines and bibliographies of relevant papers were hand checked for relevant scientific and clinical data.

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'For how can I go so far as to try and use language to get between pain and its expression?'
(Ludwig Wittgenstein, 1889–1951)

INTRODUCTION

Pain most commonly arises from tissue or nerve damage and trauma and falls under all branches of neonatal and pediatric medicine. As we emerge from a period of relative neglect in the study of infant pain,[1] we now face the challenge of how to manage this problem effectively. Clear evidence of infant pain expression and sensitivity to noxious stimuli,[2] together with findings that untreated pain has the potential to damage the developing nervous system,[3] has convinced clinicians of the need to manage pain more effectively in this vulnerable patient group.[4] Although pain management in children is benefiting from an increasing amount of evidence-based data,[5] many treatments for the youngest patients are currently extrapolated from data obtained from older children or adults, which can be inappropriate for the very young.[4,6,7] There is an urgent need for more 'proof of principle' studies and clinical trials of analgesic protocols in infants; however, for these to be useful, the outcome measures require re-evaluation and this, in turn, requires a better understanding of the neurophysiology and neuropharmacology of developing pain pathways.

Two major issues lie at the heart of the problem of infant pain management. First, the infant has no language, and measuring pain expression in a quantitative and reliable manner is especially challenging in this patient group. While other physiological expressions of pain and stress can be measured and together provide convincing evidence that an infant is experiencing pain,[8] these surrogate measures must be viewed in the context of CNS sensory circuits and motor pathways that are undergoing considerable structural and functional maturation over the postnatal period.[9,10] Second, analgesic protocols that have been designed for older patients may be of limited applicability in neonates and infants, not only because of differing metabolism, but also because many analgesic targets in the brain are still undergoing developmental changes during infancy.[4,11] Progress in both the measurement of pain and the use of analgesic protocols in infants depends critically on an increased understanding of the developmental biology of pain and analgesia. The aim of this Review, therefore, is to highlight those features of the developing pain system that create challenges for management of infant pain and to discuss how knowledge of the developmental neurobiology and neuropharmacology that underlie infant pain can inform treatment in the future.

CURRENT PAIN MANAGEMENT STRATEGIES IN INFANTS

In the past, clinicians treating infants and neonates were faced with a dilemma: inadequate analgesia in this age-group was known to be associated with adverse perioperative outcomes, but use of analgesics in these young patients was limited by fear of adverse effects.[12] Since then, however, there have been notable changes in clinical practice,[6,13–15] and pediatric perioperative analgesia is being increasingly based on current best evidence.[5,16] However, the number of controlled trials of analgesics in neonates is still limited by ethical and methodological restraints, lack of large homogeneous populations, and the reduced sensitivity and specificity of the observer-based outcome measures that are used.[4] Postoperative, procedural and intensive-care pain management in infants is still based largely on clinical experience, and published evidence on which to base management is limited.

Postoperative pain

Opioids are the mainstay of perioperative analgesia when major surgery is performed in neonates and infants, but, as in adult practice, multimodal analgesia is being increasingly used.[5] Epidural infusions of local anesthetic can be used following major surgery. For minor surgery, intraoperative wound infiltration or regional blocks (such as caudal injection) with local anesthetic can provide sufficient perioperative analgesia. The addition of opioids or nonopioid spinal analgesics (such as clonidine or ketamine) to epidural local anesthetic has been shown to improve analgesia in older children, but the efficacy and safety of these agents in the neonatal period has not been extensively investigated. In children, paracetamol (acetaminophen) is used alone for mild pain, or in combination with regional local anesthetic techniques or opioids during major surgery. Combinations of paracetamol and opioid have been shown to reduce opioid requirements following surgery in adults, but this benefit is yet to be confirmed in neonates.[17] NSAIDs are used in neonates to promote closure of a patent ductus arteriosus, but analgesic effects in early life have not been fully investigated, and the balance of analgesic benefit versus the risk of adverse effects with these agents is unclear in neonates and infants under 3 months of age.

Procedural pain

Repeated exposure to pain and stress is common for neonates in intensive care, particularly for infants born preterm.[18,19] Procedural interventions, such as heel sticks, and insertion of intravenous and arterial lines and tracheal and nasogastric tubes, are essential for monitoring and for intensive care management, but they are invasive and produce measurable cortical pain responses in even the youngest preterm infant.[20] Analgesics can reduce the adverse physiological consequences secondary to cardiorespiratory responses and the alterations in cerebral perfusion that can occur following procedural interventions, but the acute noxious effects of the interventions are difficult to control. Regular assessment of pain[21] and implementation of local practice recommendations[22]—which can be formulated from evidence-based guidelines—have increased analgesic use in neonates,[5] although frequently no or minimal analgesia is used in this group.[22,23]

Sucrose, nonnutritive sucking, and breastfeeding have been shown to reduce distress and the behavioral response to procedural interventions in neonates.[24,25] However, the relative efficacy of these different interventions alone or in combination with pharmacological therapies, their acute and long-term safety and efficacy with single and repeated use, and the mechanisms that underlie the infant response to the interventions, require further evaluation. Topical local anesthetic preparations can be safely used in neonates,[26] although they are more effective when used for venepuncture than for heel lance[27] or intramuscular injection.[28] In awake neonates undergoing circumcision, pain is reduced but not eliminated by topical local anesthetic, and a dorsal penile local anesthetic block is more effective.[29]

The capacity of opioids to control procedural pain in neonates continues to be debated. Responses to heel stick and tracheal suctioning have been variably reported to be decreased[30] or unaltered[18,31] in ventilated neonates who receive intravenous morphine infusions. Timed bolus administration of rapid-onset lipid-soluble opioids, such as fentanyl, may be more effective than these strategies,[14] but further evaluation of the efficacy, dosing requirements and safety profile of this intervention is required.

Pain in ventilated neonates in intensive care

The use of morphine infusions in neonates in intensive care has expanded from a specific analgesic role to provision of sedation, aimed at improving cardiorespiratory stability and tolerance of mechanical ventilation. Results from a pilot study suggested that neurological outcome is improved with morphine infusions.[30] The subsequent large, multicenter NEOPAIN (Neurologic Outcomes and Pre-emptive Analgesia in Neonates) study randomly assigned children to receive placebo or morphine infusions (at doses of up to 30 μg/kg per hour, which is higher than perioperative requirements[32]); children in both groups could receive open-label morphine boluses for analgesia according to clinical need. No difference in outcome was found between the placebo and morphine groups, but an association between bolus morphine administration and worse outcome was initially reported.[33] Subsequent analysis has shown that the poor neurological outcomes were related to pre-existing hypotension and that morphine therapy was not a contributory factor.[34] However, morphine infusions can produce hypotension, and the safety, efficacy and long-term outcomes of analgesia and sedation in ventilated neonates require further evaluation. Although there is insufficient evidence to support routine morphine infusions, morphine seems safer than midazolam for sedation, and selective use of opioids on the basis of clinical judgment and assessment of pain has been recommended.[35]

Midazolam infusion is frequently used for sedation in older patients in intensive care, but in ventilated preterm neonates routine infusion of this drug has been associated with an increased incidence of poor neurological outcome.[30] A meta-analysis found that midazolam had variable sedative effects in neonates and identified insufficient data to support the drug's routine use in this group; the paper also raised concerns over the safety of infusion with this agent in neonates.[36] A follow-up study of children born preterm found that, after adjustment for gestational age and risk factors, prolonged sedation and/or analgesia was not detrimental to 5-year neurodevelopmental outcome, although limited data about the type and doses of drugs administered were provided (developmental toxicity is covered in more detail later in the text).[37]

Repeated procedural interventions, surgical interventions, and complications such as infection, can all contribute to development of persistent hyperalgesia[38] or chronic pain during intensive care. Current tools for assessing pain in neonates are directed at acute behavioral and physiological changes associated with procedural or postoperative pain and have not been validated for chronic pain. The incidence, presentation, assessment, and management of persistent pain during neonatal intensive care have not been extensively investigated and are not the focus of this Review. However, the long-term impact of pain in children who required intensive care as neonates is discussed later.

CHALLENGES IN DETECTING AND TREATING PAIN IN NEONATES

The immaturity of the CNS in infants means that the relationship between noxious input and behavioral response is not always predictable, and this uncertainty presents challenges for the measurement of pain and assessment of the effectiveness of analgesia. The lack of language to express pain accentuates the need for age-appropriate physiological measures. In addition, the effects of treatments can be confounded by age-dependent changes in metabolism of analgesic agents. Adequate detection and treatment is especially important in this age-group as the plasticity of the infant CNS means that the effects of pain during infancy can outlast the injury period and have prolonged consequences.

The immaturity of the pain signaling and response systems

In adults, noxious or tissue-damaging stimuli and the resulting release of inflammatory and trophic molecules activate and sensitize nociceptors in the damaged region, leading to a barrage of nociceptive afferent input into the CNS.[39,40] This process excites central nociceptive circuits in the spinal cord, brainstem, thalamus and brain areas including the somatosensory cortex, cingulate cortex and amygdala, which together contribute to the 'pain matrix'.[41,42] Unlike other sensory stimuli, relatively brief trains of activity in peripheral nociceptors have the capacity to

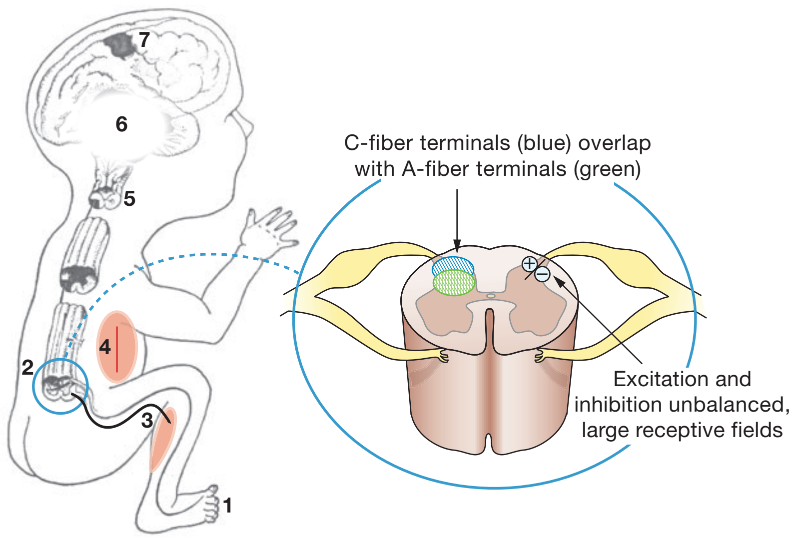

Figure 1 Key sites of developmental transition in infant pain pathways. The areas of the nervous system are indicated where developmental changes and plasticity impact pain detection and treatment in this group. (**1**) Peripheral innervation is vulnerable and sensitive to tissue injury. (**2**) Dorsal horn sensory pathways undergo considerable postnatal reorganization. (**3**) Nociceptive reflex pathways are diffuse and poorly tuned. (**4**) Primary hyperalgesia develops before secondary hyperalgesia. (**5**) Endogenous descending controls via the brainstem are unbalanced. (**6**) Extensive cortical development begins postnatally, but little is known of the development of intracortical network connections in infancy. (**7**) The somatosensory cortex is activated by noxious stimulation from an early age, but little is known of activation in other cortical regions.

trigger long-term changes in CNS circuitry and to cause prolonged states of hypersensitivity. This 'central sensitization' contributes to an amplification of the noxious input and a spread of pain into areas outside the original damaged region (hyperalgesia) and the onset of pain from normally innocuous stimuli (allodynia).[43] The central sensitization arises from prolonged increases in membrane excitability, strengthened excitatory synaptic inputs, and reduction of inhibitory interneuronal activity,[44–46] which processes are in turn regulated by shifts in gene expression and by the production and trafficking of key receptors, channels and downstream neuronal signaling pathways.[47]

While much of the system described in adults is also functional in newborns, the postnatal period is a time of great structural and functional change in pain pathways, and, as a result, noxious stimulation does not evoke the same pattern of activity as it does in the adult CNS.[9,10] The immaturity of synaptic connections and integrated circuits in the newborn means that in many ways the infant pain experience is more diffuse and less spatially focused than that in adults, but it is also under less endogenous control (see below) and is, therefore, potentially more powerful. Animal models can tell us much about infant pain mechanisms; the CNS of the 7–10-day-old rat or mouse approximately equates to that of a preterm human infant of 28 weeks postmenstrual age.[48] In the spinal cord of the young rat, the central terminals of low-threshold tactile and nociceptive inputs are relatively diffuse and initially overlap with those of nociceptive C fibers in lamina II of the neonatal dorsal horn, slowly becoming pruned over the postnatal period.[49,50] The separation of the two types of sensory terminals is not complete until the rats are 3–4 weeks old; before that time, discrimination between noxious and non-noxious stimuli is less efficient. The underdeveloped myelination and slower synaptic transmission from immature ion channel kinetics cause sensory and motor neurons in the CNS to respond at longer and more-variable latencies, producing less-synchronized responses to peripheral stimulation.[51–54] In addition, the cutaneous receptive fields of individual spinal sensory neurons are larger in young rats and gradually become smaller and more organized with postnatal age. Contralateral inhibitory receptive fields, which in the adult mirror the excitatory fields, are mismatched in young spinal cords.[51,55] These properties together mean that in young rat pups noxious skin stimulation can excite many more neurons than it can in older animals but that this excitation may be poorly integrated both spatially and temporally such that the final output, in terms of motor behavior, is less reliable. These animal data can probably be extrapolated to humans, since the gradual postnatal maturation of more focused and accurate nociceptive reflexes can be observed in both young rats and human infants.[9] The key sites of developmental transition in infant pain pathways are summarized in Figure 1.

The central pathways that are responsible for sensitization and hyperalgesia are functional in the newborn but differ from those in adults. Primary hyperalgesia in sites of surgical injury or inflammation is evident from birth in both rat pups and human infants,[56–58] but secondary hyperalgesia that spreads outside the area of injury is slower to mature and may be less obvious in infants.[59] The capacity for referred hyperalgesia, whereby visceral pathology evokes abdominal reflex hypersensitivity, also increases with postnatal age in human infants.[60] Although recovery from mechanical hyperalgesia following skin incision is more rapid in younger than in older animals,[58] central sensitization can build up, and newborn infants who have undergone repeated painful procedures react more during a painful procedure than do those who have not undergone repetitive painful experiences.[61] As yet, little is known about the maturation of the underlying signaling pathways, although both cyclo-oxygenase 1 activity evoked by noxious stimuli[62] and extracellular signal-regulated kinase phosphorylation are known to be developmentally regulated.[59]

An important aspect of CNS pain processing is the system of endogenous control that modulates nociceptive activity through descending modulatory systems and endogenous opioids.[63–65] Through this mechanism, a noxious stimulus or injury not only excites neuronal networks but also activates local inhibitory circuits and alters the balance of brainstem descending inhibitory and excitatory activity, thus contributing to a homeostatic feedback mechanism of control.[42] These descending and endogenous pain-modulatory pathway controls are the mechanisms by which factors such as attention and distraction, suggestion and expectation, stress and anxiety, and context and past experience influence pain responses.[66] In rat pups, there is little descending inhibitory tone from higher CNS centers in the first weeks of life and no analgesia is produced from periaqueductal gray stimulation until 3 weeks of age.[67] A lack of balance between inhibitory and excitatory supraspinal controls[68,69] may mean that infants are less able to mount effective endogenous control over noxious inputs than are adults.

While many people feel intuitively that neonates experience pain in a similar way to adults, anatomical data show that neuronal connections to the cortex are formed relatively late in gestation at around 22 weeks,[70] which suggests that higher pain processing may be limited during infancy despite the presence of a behavioral response. Imaging of cortical activity in response to noxious stimulation has provided important insights into pain processing in the adult human brain,[42,71] but its use in early development has been hindered by uncertainty about neurovascular coupling in young individuals. Comparison of functional MRI measurements and electrophysiological recordings following somatosensory stimulation in young rats shows that the regional blood-oxygen-level-dependent, or BOLD, response (which indicates areas of brain activity) undergoes a systematic decline in latency and growth in amplitude from the second week of life to adulthood.[72] Direct hemodynamic responses can be recorded at the cot side, with near-infrared spectroscopy (NIRS). This technique has shown that clinically essential noxious heel lances in newborn infants evoke a response in the contralateral somatosensory cortex, thereby suggesting that higher-level brain activity and, thus, processing of pain, may occur at a young age.[20] The response is specific for noxious stimuli—it is not seen following application of non-noxious mechanical stimuli to the heel. Electrophysiological evidence or analysis of real-time neuronal activity in infant cortical circuits in response to noxious stimulation will provide important insights in this area.

Measuring pain in the absence of language

Measurement of pain in preverbal infants has long been recognized as a challenge. The standard self-report scales that are used in adolescents and adults are not an option in infants, as infants cannot report their pain. Extensive research and validation has led to the development of a number of effective pain assessment 'tools' that make use of the behavioral and physiological body reactions to a noxious stimulus. While these tools have made a major contribution to the understanding and treatment of infant pain, it is unclear whether they are specific and sensitive enough to provide an end point for proof-of-principle studies and comparative clinical trials of analgesics.

The majority of the currently available infant pain assessment tools use a combination of behavioral measures (e.g. leg movements, crying), physiological measures (e.g. heart rate, oxygen saturation) and characteristic facial expressions of pain as originally described by Grunau and Craig,[73] with added factors for sleep state and extreme prematurity (see Figure 2). Current tools include the PIPP (Premature Infant Pain Profile), NIPS (Neonatal Infant Pain Scale), CRIES (Crying, Requires oxygen, Increased vital signs, Expression, and Sleepless), COMFORT (which measures alertness, calmness, muscle tone, movement, facial tension and respiratory response), and BIIP (Behavioral Indicators of Infant Pain) scales (see Howard *et al.*[5] and the NHMRC website[74] for reviews of these scales). Unlike in older children, pain assessment tools in neonates have not yet been subjected to a systematic review, and there is no gold standard

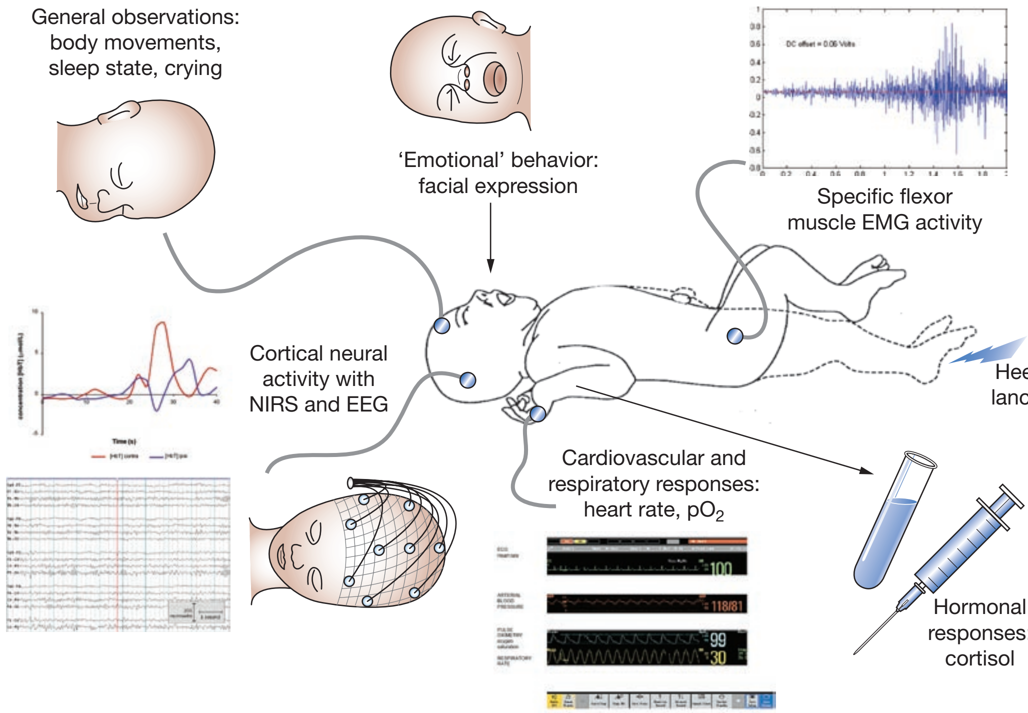

Figure 2 Methods of assessing infant pain. In the absence of language, infant pain is assessed by a number of different physiological methods. Some of these methods are integrated into current clinical pain assessment tools. The neurophysiological techniques EMG, EEG and NIRS are not used for routine pain assessment but are increasingly being used in research studies of infant pain. Abbreviations: EMG, electromyogram; NIRS, near-infrared spectroscopy; pO_2, partial pressure of oxygen.

with which to evaluate one against another. Most of the tools have been developed for assessment of acute procedural pain, although the PIPP, CRIES and COMFORT scales have also been widely used for postoperative pain.

Developmental pharmacokinetics and dynamics

Safe and effective administration of any drug is dependent on an understanding of its pharmacokinetic and pharmacodynamic profile. Developmentally regulated changes have an additional major impact on analgesic dose requirements in early life. Dose guidelines for morphine infusions initially focused on plasma concentrations that minimized the risk of respiratory depression[75] and on the changing clearance and metabolism of this drug with age.[76] However, interindividual variability in kinetics[77] and the poor correlation between pain score and plasma concentration[78] emphasize the need for further titration of morphine dose against analgesic effect in each patient. Tolerance and withdrawal occur after prolonged infusions, and signs of withdrawal can be recognized in even the youngest infants.[15] Pharmacogenomic changes and occurrence of a polymorphic variant in the cytochrome P450 *CYP2D6* gene can result in reduced metabolism and efficacy of codeine[79] and tramadol.[80] Age-related changes in enzyme levels can further reduce drug efficacy in early life. Following oral, rectal[81] or intravenous[82,83] administration the pharmacokinetic profile of paracetamol changes markedly, and doses based on post-conceptional and postnatal age are aimed at avoiding hepatic toxicity.[5] The effect site and plasma concentration of paracetamol that produces analgesia in children is greater than is required for an antipyretic effect,[84] but analgesic efficacy data for this drug in neonates are limited.

Assessing the long-term impact of infant pain

Evidence exists that, in many infants who have been subjected to a painful stimulus, prolonged changes in pain sensitivity occur that long outlast the initial injury—a phenomenon that creates an additional challenge for pain management in this group. For instance, neonatal circumcision has been associated with an increased behavioral response to immunization several months later, which was reduced by local anesthesia at the time of initial insult in a double-blind, randomized, controlled trial of 87 infants.[85] In addition, retrospective cohort studies of infants who were previously in neonatal intensive care show that areas that have undergone repeated procedures can have flexion reflex hypersensitivity for at least a year afterwards[86] and that enhanced perceptual sensitization to a prolonged thermal stimulus is present at thenar and trigeminal sites at 8–12 years.[87] In a cross-sectional study of 164 neonates and infants who were undergoing surgery, higher observational pain scores and increased perioperative analgesic requirements were observed in those who had undergone previous surgery before 3 months of age, but only if the surgery had been performed in the same dermatome as the current procedure.[88] These reports of hypersensitivity to noxious stimulation are accompanied by evidence of underlying hyposensitivity to normal, physiological levels of sensory stimulation in children exposed to early tissue injury and pain; sensory threshold testing of neonatal-surgery groups at 9–12 years has shown that there is long-term thermal and mechanical hypoalgesia adjacent to neonatal surgical scars,[89] and a larger cohort study of children born extremely preterm has suggested that this hyposensivity depends on the degree of initial local tissue injury.[90] In addition, children exposed to early tissue injury and pain have generalized decreases in thermal sensitivity, suggestive of centrally mediated alterations in modulation of C-fiber nociceptive pathways.[87,91]

Long-term changes in behavioral responses to pain have been reported in children who required intensive care in the neonatal period. Parents report that children who were born preterm have reduced sensitivity to everyday bumps at 18 months when compared with other children,[92] and that they have increased somatization at 4 years but not at older ages.[93] However, these children show more pain catastrophizing than controls do and their mothers are more likely to engage in solicitous pain-related behavior,[91] which could promote maladaptive pain-related behavior. This factor, combined with other reported cognitive and behavioral impairments in infants who were born preterm,[94,95] means that postnatal factors and not solely early pain experience may influence later behavioral responses to pain.[93]

DEVELOPMENTAL NEUROBIOLOGY AND INFANT PAIN MANAGEMENT

Overcoming the challenges presented by infant pain requires the application of developmental neurobiological and neuropharmacological knowledge to the clinical setting. This knowledge can underpin the design of appropriate methods of pain measurement and ensure that the data are interpreted appropriately in the context of CNS development. Furthermore, this knowledge can provide important insights into infant CNS responses to pain of different origins, such as inflammation and nerve damage, which are of great clinical relevance. Lastly, understanding of neuronal synaptic plasticity in developing pain pathways, gained from laboratory studies, is essential if we are to interpret and prevent the long-term effects of early pain upon adult sensory processing.

Improving the detection of immediate pain responses

To date, clinical tools for infant pain assessment have depended on surrogate measures that do not directly measure the sensory pain experience. These tools rely to a greater or lesser extent on coordinated, integrated and directed sensory and motor responses to a noxious input. The lack of spatial and temporal integration in immature pain pathways as discussed above will inevitably affect these responses, and the relationship between noxious stimulus and coordinated motor response will be less reliable in the infant than it is in the adult. This point has been clearly illustrated in a study in which a direct comparison was made between evoked somatosensory cortical activity (as indicated by a hemodynamic change measured with NIRS) and behavioral facial coding in individual infants following noxious stimulation.[96] A good correlation was generally found between these two measures but, importantly, some infants who displayed no behavioral response to a heel lance did have a robust cortical response, which suggests that CNS pain processing can occur in the absence of linked motor behavior. NIRS measures may, therefore, provide a more sensitive outcome measure than behavioral observation in future clinical trials.

Recognition of the underlying development of the sensory inputs and motor outputs related to pain signaling and behavioral responses in infants will improve the design of pain assessment tools in this group. Direct recordings of neural activity have advantages over observational measures as they can be measured objectively and quantitatively and, most importantly, they have direct parallels in rodent models, in which underlying pain mechanisms can be investigated. For example, electromyographic studies in both humans and rodents have shown that lower limb nociceptive reflexes are of longer latency, lower threshold and greater amplitude in infants than in adults. In addition, in both species, nociceptive reflexes are more variable in the young and can be accompanied by a wide range of muscle activity in the rest of the body, not normally observed in adults.[97,98] The advantage of these reflex studies is that they can be used to investigate the hyperalgesia or tactile hypersensitivity that follows tissue injury.[56,97,99,100] Tenderness and pain following repeated noxious procedures, surgical incisions or chronic tissue inflammation both around and distant from the site of injury can be measured in the youngest infants through demonstration of a drop in threshold and an increased reflex response to calibrated von Frey hairs.[60,97,101,102] This sensory reflex hypersensitivity is a quantitative measure of peripheral and central sensitization of pain pathways and can be used in clinical studies and trials. The recent demonstration that specific noxious-evoked activity can be recorded from the somatosensory cortex of the youngest preterm infants may lead to direct neurophysiological methods of measuring the 'pure' sensory aspects of pain intensity in young infants, although this requires considerably more research.[20,96]

Understanding the mechanisms that underlie different types of infant pain

The number of animal models of infant pain is increasing, providing insight into the developmental profile and mechanisms that underlie infant pain of varying intensities and time course, including nociceptive pain,[59] inflammatory pain,[57,103] surgical incision pain,[58,104] and neuropathic pain.[105,106] Neurophysiological investigations of the maturing network activity that underlies these types of pain help us to understand infant pain behavior in different pain states.[9,107] Investigations in a range of models—including spared nerve injury, chronic constriction injury, partial sciatic ligation, and spinal nerve ligation—have demonstrated that injury to peripheral nerves in the first 4 weeks of life does not produce the marked allodynia that is seen in adults.[105,106,108] This finding is in stark contrast to the robust response to tissue damage and inflammation that is seen in infants. The observed lack of allodynia is consistent with the observation that brachial plexus root and nerve damage in human neonates caused during delivery does not result in long-term neuropathic pain.[109] Self-mutilation behavior, which may be a correlate of the autotomy behavior following axotomy that is seen in adult animals, has been noted in a small proportion (<4%) of infants in the months following brachial plexus reconstruction surgery,[110] but whether this represents a reaction to pain is unclear. This relative resistance to neuropathic pain—a pain that is intense in adults—seems likely to be due to the immaturity of spinal cord immune activation.[111,112] The development of neuroimmune interactions and pain will be an important area of future research.

Understanding the long-term impact of early pain

Clinical observations of possible long-term effects of infant pain are informed by the use of animal models that permit analysis of the prolonged effects of specific noxious injuries, the importance of age of insult, and the underlying mechanisms, while controlling for handling and maternal separation.[113]

Many of the postnatal developmental changes in nociceptive processing depend on a normal balance of neural sensory activity and fail to occur if the patterns of activity are disrupted. In rat pups in which spinal NMDA receptors are chronically blocked and in mutant mice in which the CaMKIIα enzyme does not autophosphorylate, nociceptive processes remain immature.[49,114] Furthermore, maturation is delayed by blockade of low-threshold sensory afferents with peripheral anesthetic.[115] Thus, dorsal horn nociceptive circuits are not fixed or preset at birth but are in a plastic or transitory stage, responsive to the sensory experience.[50] In this way, early tissue injury can lead to changes in somatosensory processing and pain signaling and hence influence future analgesic responsiveness.

In the rodent, a number of somatic, visceral, and neuropathic injuries during the neonatal period are associated with persistent changes in sensory processing or in responses to future noxious stimuli. The long-term sensory outcomes associated with initial injury to different sites are summarized in Figure 3.

The complexity and diversity of persistent changes in pain responses have been demonstrated in clinical as well as preclinical studies. It is too simplistic to expect that early pain experience will reliably either increase or decrease sensitivity, as multiple contributory factors may interact to influence nociceptive processing and/or the behavioral response to pain. The behavioral outcomes of early pain experience in animal models, as summarized in Figure 3, are consistent with observations in human studies. These findings can, therefore, be used to evaluate mechanisms that underlie persistent sensory changes and to assess the capacity of analgesia to modulate long-term effects; this information can then be translated into clinical trials to inform future practice.

A SCIENTIFIC BASIS FOR INFANT-SPECIFIC ANALGESIA

Improvements in clinical analgesic use in infants can be enhanced through an understanding of the mechanisms that underlie age-related changes in efficacy and susceptibility to adverse effects. The developmental regulation of expression, distribution and function of the transmitters and receptors that are required for analgesic action has a major impact on the pharmacodynamic profile of analgesics during postnatal development, and understanding these processes can inform and improve the design of subsequent clinical trials.[116] In adult practice, it has been suggested that a move away from the empirical approach of suppressing sensory symptoms towards the targeting of specific pain mechanisms of inflammatory and neuropathic pain may improve outcomes.[117] In a broader sense, this comment is also applicable to pain in early life, as age-related changes in analgesic targets necessitate a specific approach. Quantification of analgesic efficacy in a range of animal injury models and comparison of the relative efficacy of different agents is especially useful for determination of analgesic regimens that are appropriate for infants. Whereas adults with acute pain can readily report the degree to which pain is reduced by a drug or intervention, current neonatal assessment tools readily determine if pain is present but have limited sensitivity for quantifying the degree of pain reduction. A 35–50% reduction in self-reported pain score represents a clinically detectable and relevant degree of change for adult patients,[118] but the behavioral or physiological change that represents a clinically significant impact on pain experience cannot be evaluated in preverbal patients. The clinical efficacy of different analgesics in adults can be compared through compilation of data across a number of acute pain intervention trials and construction of league tables. Comparative efficacy is difficult to determine from neonatal and infant clinical studies, but preclinical data can highlight the most effective analgesic strategies at different developmental stages. Preclinical studies are also essential for identifying and evaluating age-related side-effect profiles and the potential toxic effects of drugs.

The postnatal development of drug receptor interactions

Developmentally regulated changes in the expression and distribution of opioid receptors in the brainstem and dorsal horn contribute to the increased sensitivity (i.e. lower dose requirements for analgesic efficacy) to morphine in the young that has been demonstrated in laboratory and clinical studies.[119,120] Functional expression of opioid receptors in dorsal root ganglion mechanoreceptors as well as nociceptors further increases sensitivity to analgesia and may also produce some blunting of general sensory processing.[121] Glutamate receptors, including NMDA receptors, are highly regulated postnatally,[11] and this could lead to differing efficacy and actions of ketamine in young infants when compared with older children and adults. Cyclo-oxygenase 1 inhibitors are less efficacious in younger than older rats,[62] which may have implications in relation to the dose requirements and potential risk–benefit profile of NSAIDs in infants. Voltage-gated sodium channels shape and activate the pain networks from early on in development, and expression of these channels is postnatally regulated.[122] Local anesthetic block can last longer in young nerves, and the central antihyperalgesic effects may necessitate lower doses in infants.[123–125] The dose reduction necessitated by reduced protein binding and clearance in early life, therefore, may be achieved without compromising efficacy.

Animal models give additional insight into increased susceptibility in the young to adverse effects. $GABA_A$-receptor subunit content and reduced Cl^- transport contribute to postnatal changes in inhibition of pain circuits,[11,53,54,69,126] and high levels of circulating neurosteroids in the immature CNS regulate $GABA_A$-receptor function.[52] Midazolam enhances rather than

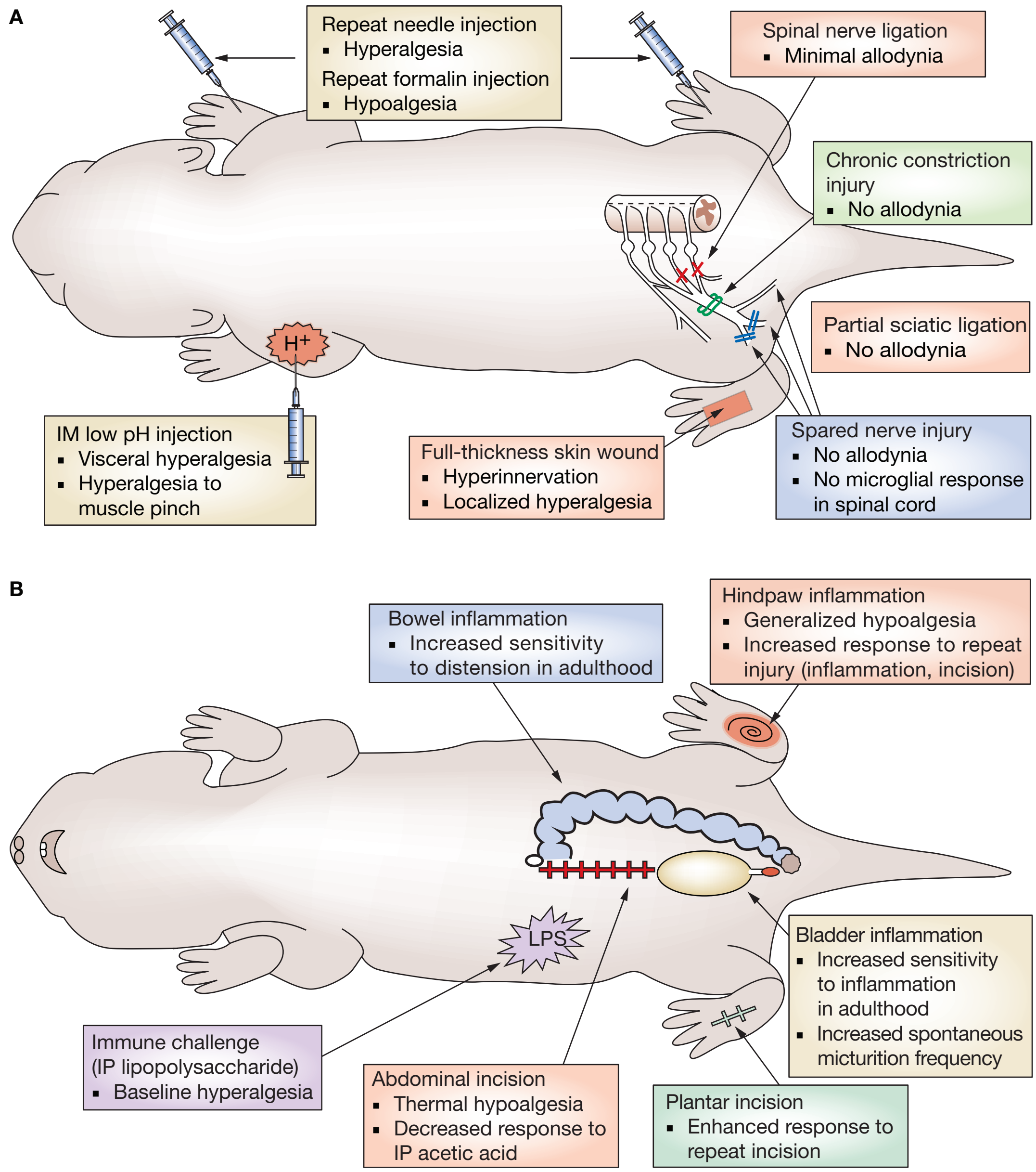

Figure 3 The long-term impact of infant pain. Animal models have illustrated how a variety of different types of early pain and injury can have a long-term impact on future somatosensory and pain processing. Here, the different sites and forms of injury and the long-term effects are summarized. (**A**) Dorsal and (**B**) ventral aspects of a rat pup. Severe hindpaw inflammation in rodents produces long-term structural changes in nociceptive pathways,[150,151] whereas milder inflammation during the first postnatal week produces generalized hypoalgesia[103] and an increased hyperalgesic response if the previously injured paw is inflamed[103] or surgically incised[152] during adulthood. Repeated hindpaw injection with a needle in the first postnatal week has been reported to produce a persistent increase in sensitivity,[153] and daily intramuscular injection of a low pH solution over the period of 1–3 weeks of age produces hyperalgesia to either muscle pinch or visceral distension in adult rodents.[154] Full-thickness skin wounding in the first postnatal week produces localized hyperalgesia[155] that is associated with alterations in growth factor expression and skin hyperinnervation.[156] Hindpaw plantar incision in the first postnatal week is associated with an enhanced response to future incision in the same paw (SM Walker *et al.*, unpublished data). Neonatal laparotomy in mice is associated with decreased sensitivity to thermal and visceral stimuli in adulthood,[104] and irritation of the bowel or bladder by chemical or mechanical stimuli in the first 2–3 weeks after birth produces an increase in visceral sensitivity that persists into adulthood.[157–159] Neonatal exposure to an immune challenge (i.e. intraperitoneal lipopolysaccharide) produces persistent changes in centrally mediated inflammatory responses and increased sensitivity to mechanical and thermal stimuli in the adult.[160,161] Abbreviations: IM, intramuscular; IP, intraperitoneal.

suppresses the spinal reflex response and does not produce sedation in young rat pups,[127] which may contribute to the variable levels of sedation reported with midazolam infusion in clinical studies.[35]

Specific developmental toxicity that is not seen at older ages may also be revealed by preclinical studies, which are also essential to evaluate the potential for toxic effects with novel drugs or routes of administration. For example, the increased efficacy of epidural dexmedetomidine in young rats[128,129] suggests that spinally administered α_2-adrenergic analgesics could have clinical utility in early life, although developmental spinal toxicity also needs to be evaluated preclinically before this method is put into routine clinical use.[130]

Neuronal cell death

Neurons that do not form functional synapses in the immature nervous system undergo programmed cell death or apoptosis, a process that differs from excitotoxic or ischemic cell death. Drugs that act as NMDA antagonists and/or GABA agonists can markedly increase the degree of neuronal apoptosis in the developing brain, and this mechanism may underlie the neurodevelopmental deficits related to prenatal exposure to alcohol and antiepileptic drugs.[131] Many general anesthetics act as NMDA antagonists (e.g. ketamine, nitrous oxide) or GABA agonists (e.g. isoflurane, propofol) and have also been shown to increase apoptosis in the developing brain of rodents and primates.[132,133] Effects are age-dependent, with peak susceptibility at around the seventh postnatal day in rodents, are more marked when combinations of drugs are used, and have been associated with long-term learning deficits.[134,135] Early studies exposed pups to 6 h of anesthesia, which may represent a much longer developmental exposure than is seen with clinical anesthesia;[136] however, subsequent studies have confirmed that dose-dependent apoptosis can be precipitated by single doses of ketamine[137] or by 1 h exposures to isoflurane.[138] Anesthetic agents trigger intracellular cascades specific for apotosis rather than excitotoxic injury, and this process occurs in the absence of hypoxia, hypoglycemia, or changes in cerebral blood flow.[137–139]

The prolonged drug exposure in some laboratory studies may be more relevant to neonates who require prolonged intensive care. Midazolam, which is a $GABA_A$ agonist, has been shown to produce apoptosis in rodents,[135,137] and this mechanism may contribute to the poor neurodevelopmental outcomes associated with prolonged infusion with this agent in neonatal intensive care.[30,35,37] As previously discussed, prolonged infusions of opioids have also been linked with poor neurodevelopmental outcomes, but specific developmental effects and the molecular mechanism of putative neurotoxicity have not been well documented.[140,141] Opioids have been shown to have variable effects on neuronal survival and proliferation. In contrast to general anesthesia with isoflurane, midazolam, and nitrous oxide, prolonged infusion with fentanyl did not produce apoptosis during the period of peak synaptogenesis in the guinea pig.[142] By contrast, neuronal apoptosis has been demonstrated following prolonged exposure to opioids in models of drug abuse and opioid tolerance in adult rodents.[141,143] Although morphine produces apoptosis in cultured neurons from human fetal tissue, the relevance of doses *in vitro* are difficult to extrapolate to clinical exposure,[144] and further studies are required to investigate the specific age-dependent and dose-dependent effects of opioids on neuronal survival in early life.

Neurodevelopmental outcomes

Evaluation of the potential impact of clinical anesthetic and analgesic use on neurodevelopmental outcome remains difficult, and conflicting results continue to be reported.[35,37] Issues including species differences in susceptibility to injury, the duration and timing of exposure, and lack of a surgical stimulus in many experimental designs, continue to be debated.[132,136,145] Surgery in preterm infants has been associated with an increased risk of poor neurodevelopmental outcome,[146] and preterm neonates with complications have a higher rate of impairment, which is further increased if surgical rather than medical treatment of patent ductus arteriosus[147] or necrotizing enterocolitis[148,149] is required. However, evaluation of the specific contributions of anesthesia or analgesia to these findings is difficult because of multiple confounding factors, such as illness severity, intercurrent disease, infection, and cardiorespiratory instability. Preclinical studies permit the specific manipulation of a range of potential contributory factors (such as surgical injury, immune challenge, and drug administration) and can direct clinical trials and therapy towards the most important mechanisms. As discussed earlier, prolonged infusion with midazolam and with opioids in ventilated neonates has also been associated with poor neurodevelopmental outcomes,[35] but the recent EPIPAGE study found no association with poor 5-year neurological outcome after adjustment for the propensity score (a regression model that includes multiple confounders related to neonatal and pregnancy factors, place of birth, and postnatal complications).[37] These conflicting results may relate to variation across neonatal follow-up studies in inclusion criteria, age at time of assessment, definitions of poor neurological outcome, sensitivity of assessment methods, and the extent to which corrections are made for illness severity. Inadequate anesthesia and analgesia are known to sometimes adversely effect acute outcomes[12] and may contribute to prolonged alterations in sensory function or enhanced responses to future injury,[85] so the risks of therapies must be carefully balanced against their potential benefit. Determination of the most appropriate type and dose of drug in the different clinical contexts of anesthesia for surgery, analgesia for postoperative and procedural pain, and sedation of ventilated neonates, and evaluation of the risk–benefit profile of prolonged use at critical developmental stages, are major ongoing challenges for scientists and practitioners investigating the impact of pain in early life.

CONCLUSIONS

Pain in infancy is an important clinical problem with an increasing patient population, but the assessment of pain in this group is particularly problematic. Untreated pain in infancy can have wide-ranging consequences, some of which can last into adulthood. The application of developmental neurobiological and neuropharmacological knowledge through the use of animal models of infant pain will benefit the development of new and more sensitive outcome measures based more directly on the changing patterns of neural activity in the CNS. This knowledge will also provide insight into the mechanisms and prevention of pains of different origin and clarify the long-lasting impacts of early pain on adult sensory processing. Finally, efforts to improve the efficacy and side-effect profile of analgesia in infants will benefit from increased understanding of the developmental synaptic pharmacology of pain. The knowledge that we have gained regarding pain assessment in infants and the potential actions of analgesic drugs must now be used to conduct proof-of-principle studies and to underpin clinical trials.

KEY POINTS

- Neonatal and infant pain management is largely based on clinical experience and extrapolation of data from older age-groups; improvements in perioperative analgesia are being increasingly made on the basis of evidence-based recommendations, but further research is required to establish the most effective analgesic protocols in early life, particularly for management of procedural pain and sedation in ventilated neonates in intensive care
- A considerable challenge to infant pain management is presented by the fact that maturation of CNS pain pathways and postnatal changes in neural processing have a major impact on infant pain sensation and behavior and sensitivity to analgesia
- Measurement of pain with observational tools in preverbal infants requires informed analysis, as interpretation of the data depends upon the maturational stage of pain behavior
- Neurophysiological analysis of developing pain pathways can provide important insights into pain measurement in infants and provide new knowledge about persistent inflammatory and neuropathic pain states in infancy
- Postnatal changes in the expression, distribution and function of transmitters and receptors required for analgesic action have a major impact on the pharmacodynamic profile of analgesics, and understanding these processes can inform and improve the design of future clinical trials
- The fact that neural pathways are still undergoing maturation in early life means that tissue injury can alter the normal course of development, leading to long-term changes in somatosensory processing and pain sensitivity; laboratory studies give an increased understanding of the factors that trigger these changes and how to prevent them

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