



# Improving the treatment of infant pain

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## Purpose of review

Pain management presents a major challenge in neonatal care. Newborn infants who require medical treatment can undergo frequent invasive procedures during a critical period of neurodevelopment. However, adequate analgesic provision is infrequently and inconsistently provided for acute noxious procedures because of limited and conflicting evidence regarding analgesic efficacy and safety of most commonly used pharmacological agents. Here, we review recent advances in the measurement of infant pain and discuss clinical trials that assess the efficacy of pharmacological analgesia in infants.

## Recent findings

Recently developed measures of noxious-evoked brain activity are sensitive to analgesic modulation, providing an objective quantitative outcome measure that can be used in clinical trials of analgesics.

## Summary

Noxious stimulation evokes changes in activity across all levels of the infant nervous system, including reflex activity, altered brain activity and behaviour, and long-lasting changes in infant physiological stability. A multimodal approach is needed if we are to identify efficacious and well tolerated analgesic treatments. Well designed clinical trials are urgently required to improve analgesic provision in the infant population.

## Keywords

analgesia, infant, nociception, pain

## INTRODUCTION

Improved neonatal care has led to an increase in the number of invasive diagnostic tests and clinical interventions undertaken in infants. These procedures can be acutely painful, yet pharmacological analgesia is infrequently and inconsistently provided [1]. Chronic exposure to noxious stimuli during the preterm period is developmentally unexpected, and may drive changes in the maturation and organization of functional neural circuitry [2]. Given that infant pain is associated with short-term physiological instability [3] and long-term negative consequences, including changes in white matter microstructure [4,5] and altered cognitive development [5,6], effective analgesic provision is a clinical priority. Nevertheless, testing analgesic efficacy in infants requires a bespoke approach as verbal pain report clearly cannot be used and we cannot assume that analgesics used in adults and children will provide effective analgesia, because of differences in pharmacodynamics and pharmacokinetics [7].

Despite significant advances in our understanding of the neurobiology of pain, there remains a paucity of evidence-based analgesics available for use in infants [8,9]. Only in the past few decades have clinical trials been performed to assess the analgesic efficacy of pharmacological agents

commonly used in neonatal care [10]. These trials use a range of validated and unvalidated pain scores, comprised of behavioural and physiological response variables, as endpoints to quantify pain experience [8,9]. They have yielded conflicting and controversial results, and positive effects have often been overshadowed by concerns over potential adverse drug effects [11]. This has led to extreme variation in analgesic practices both between and within countries [12–14]. A new approach is needed. Here, we emphasise that the assessment of analgesic efficacy in infants requires well designed age-appropriate clinical trials, using objective and sensitive endpoints assessed across multiple modalities to better quantify infant pain. We discuss evidence relating to the use of

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## KEY POINTS

- The short and long-term consequences of pain exposure in the neonatal period necessitate fundamental change in infant analgesic provision.
- Randomized controlled trials of commonly used pharmacological analgesics provide conflicting evidence of efficacy in infants, but trial methodology is inconsistent making comparison difficult.
- As painful procedures elicit an array of responses across the nervous system, a multimodal approach to assessing analgesic efficacy is optimal.
- Measuring noxious-evoked brain activity, together with behavioural and physiological responses, will lead to a better understanding of the infant pain experience.

analgesics in neonatal practice and consider approaches to quantify analgesic efficacy using measurements of noxious-evoked change in infant physiology, behaviour and brain activity.

## NOXIOUS-EVOKED ACTIVITY IN THE NEWBORN INFANT

Pain elicits an array of neurophysiological, behavioural, and physiological responses designed to protect the body from harm. When an infant undergoes a painful procedure, noxious information is transmitted from the periphery to the spinal cord via nociceptors, triggering a spinal reflex, which can be observed as bilateral limb withdrawal from the offending stimulus [15,16]. The noxious information passes to the brainstem, triggering physiological changes, as well as reflexive facial grimacing and vocalizations, which alert the caregiver. It is then transmitted via the thalamus to various cortical brain regions [17<sup>a</sup>,18], which in adults, are thought to encode the sensory and emotional aspects of pain [19]. Cortical and subcortical brain regions also have a top-down modulatory effect on the nociceptive signal [20], which changes with development [21,22]. Physiological stability can be disrupted for several hours after the nociceptive event, with increased prevalence of episodes of tachycardia or bradycardia, oxygen desaturations, and apnoeas [23,24]. Up until recently, much of our understanding of clinical pain assessment and management in infants has been based upon the scoring of noxious-evoked behaviour and physiological responses [10]. These pioneering studies have been highly influential in raising the profile of infant pain and have provided good evidence for the use of non-pharmacological comfort techniques [25,26,27<sup>a</sup>]. However, when these measures have been used to

test pharmacological agents they have yielded inconsistent results, and have contributed to a continual state of equipoise for most analgesics.

## SEARCHING FOR ANALGESIC EFFICACY: MORPHINE – A CLASSIC EXAMPLE

Analgesic agents have mostly been introduced into neonatal practice unconventionally, with limited understanding of their pharmacokinetics and pharmacodynamics, and without clinical trials establishing their efficacy [10]. Doses of many commonly used drugs are often extrapolated from adult and paediatric regimens [10]. Morphine, the archetypal opioid, is the most frequently used analgesic in infants [13<sup>a</sup>] and while it has been shown to reduce physiological instability and hormonal stress responses [28–31], and improve ventilator synchrony [32] in premature infants, its analgesic efficacy remains controversial [13<sup>a</sup>,33].

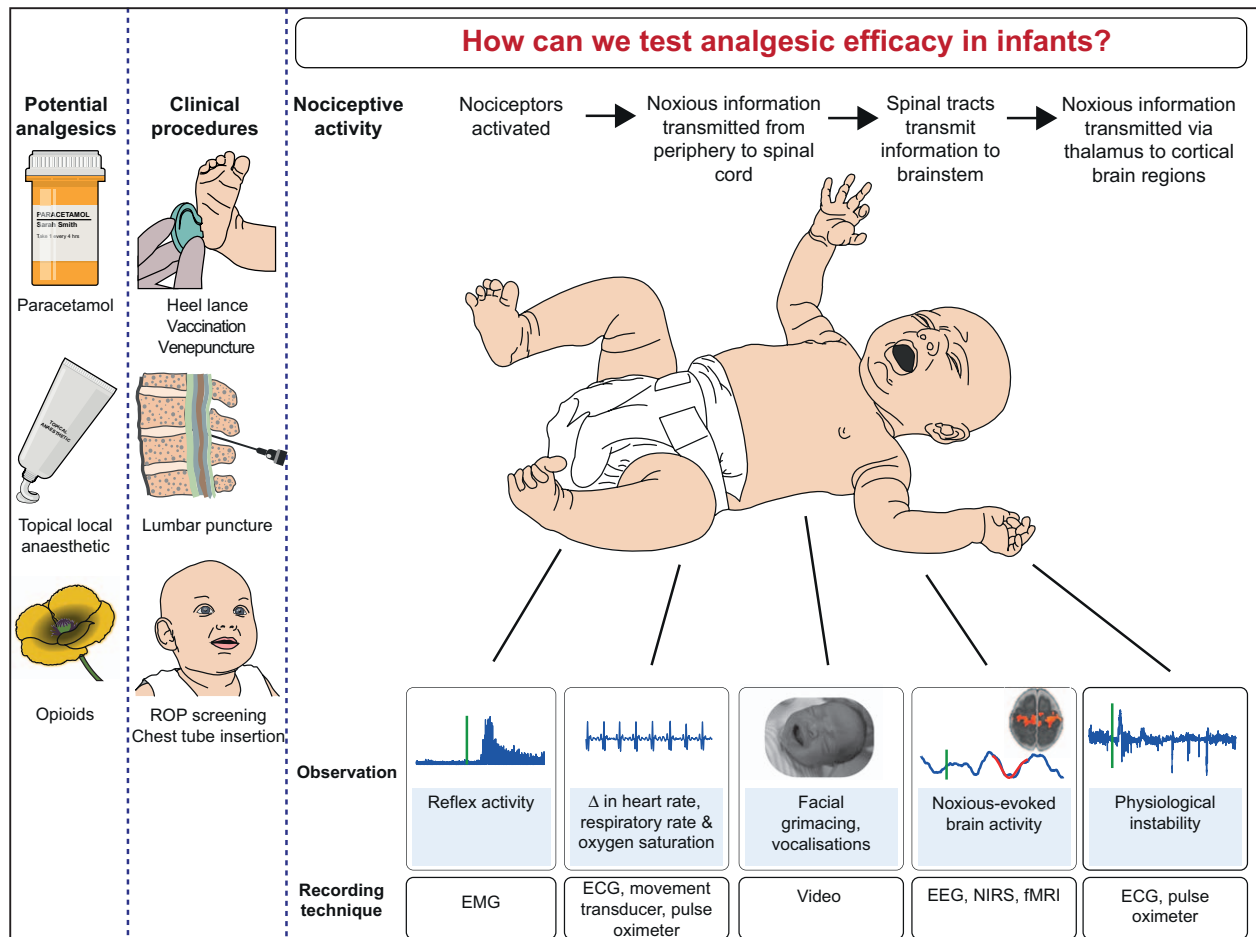
The efficacy of intravenous morphine has been studied using various behavioural pain scores across a variety of acute noxious procedures, including heel lancing [34,35], tracheal suctioning [28,33,36], elective intubation [37], and peripheral central venous cannulation [38]. Studies have yielded contradictory results, and differences in study methodologies, drug dosages, heterogeneity of outcome measures, and clinical procedures, as well as administration of ‘rescue’ opioid boluses to control groups, have made interpretation of the evidence challenging. Three large randomized placebo-controlled trials have tested the analgesic efficacy of intravenous morphine in the context of tracheal suctioning [28,33,36]. Although two of these studies appeared to demonstrate a significant reduction in a well validated pain score, the Premature Infant Pain Profile [28,33], results were not consistent across time points in one of the studies, and the statistically significant result did not equate to clinical significance [33]. A third study [36], found no significant effect of morphine infusion on three behavioural pain scores assessed before, during, and after endotracheal suctioning. This study, however, followed the principle of intention-to-treat and permitted the administration of open-label morphine at the discretion of attending physicians. In total, 40% of the placebo group received open-label morphine as the infants were considered to be ‘uncomfortable’ and requiring additional pain relief. The authors reported poor concordance between pain scores and acknowledged the potential lack of sensitivity and specificity of pain scoring methods. Meta-analysis unsurprisingly revealed significant heterogeneity, and failed to identify a significant effect of morphine [8].

Without sensitive and specific endpoints the analgesic efficacy of a drug cannot be appropriately evaluated. Can we really expect brief behavioural, physiological, or neurophysiological snapshots in isolation to provide compelling evidence to convince the neonatal community to administer an analgesic like morphine? Particularly in light of potential side-effects and long-term consequences [11], more detailed evidence of analgesic efficacy is clearly required. As pain elicits a wide spectrum of responses, a multimodal approach incorporating noxious-evoked brain and spinal activity, as well as behavioural and physiological measures, will provide a more complete understanding of infant pain (Fig. 1).

### THE MEASUREMENT OF NOXIOUS-EVOKED BRAIN ACTIVITY IN INFANTS

Noxious-evoked brain activity was first recorded in newborn infants approximately 10 years ago [39–41], and since then it has been shown to be graded with stimulus intensity [16], dependent on

gestational age [21,39,42,43], and is elicited across a network of brain regions which are similar to those activated in adults [17<sup>\*</sup>]. Although noxious-evoked brain activity, spinally mediated reflex withdrawal, and pain-related facial activity are relatively well correlated [16,44<sup>\*</sup>,45], noxious information can be transmitted to the cortex without producing observable behavioural changes [44<sup>\*</sup>,45]. Therefore, infants with low pain scores based on behavioural assessment alone may not be pain free [45]. Potential discordance between brain activity and various noxious-evoked patterns of physiology and behaviour was exemplified by a blinded randomized controlled trial investigating the analgesic efficacy of sucrose, a popular non-pharmacological analgesic [46]. Although a Cochrane review of 74 studies across a total of more than 7000 infants suggests that sucrose is effective for short procedures [27<sup>\*</sup>], noxious-evoked brain activity and reflex withdrawal to a heel lance are not altered by sucrose administration [46]. Measures of noxious-evoked brain and spinal cord activity appear more sensitive than facial expression change [16,47], and therefore lack of



**FIGURE 1.** Measuring analgesic efficacy in infants. EEG, electroencephalography; EMG, electromyography; fMRI, functional MRI; NIRS, near-infrared spectroscopy; ROP, retinopathy of prematurity.

sensitivity of the noxious-evoked brain activity is unlikely to be the cause of the discordance between these measures. Analgesics work by modulating nociceptive input to the brain and these results suggest that although sucrose may dampen behavioural signs of distress it may not provide analgesia, as it is not altering the noxious input transmitted to the brain.

This year an electroencephalography (EEG)-based template has been developed that can objectively quantify the magnitude of brain activity evoked by noxious stimulation [44<sup>■</sup>]. The validity of the template was tested across four independent samples of infants, ranging from 34 to 43 weeks' gestation. It robustly quantifies the nociceptive afferent brain activity, and allows direct comparison of noxious-evoked activity across different infant groups. Although the infant pain experience clearly cannot be solely represented by a brief pattern of electrical activity recorded at a single electrode site within 1 s of a noxious event, this method does provide sensitive quantification of noxious input reaching the brain. Importantly, it also provides a standardized approach for the measurement of analgesic efficacy, which can be used in clinical trials of analgesics [48,49<sup>■</sup>], and potentially in dose-finding studies. Topical application of tetracaine, a potent local anaesthetic, significantly reduces the magnitude of noxious-evoked brain activity quantified by the template [44<sup>■</sup>]. This is a critical demonstration that noxious-evoked brain activity is sensitive to analgesic modulation.

Similarly to morphine, behavioural pain score studies have provided inadequate evidence to establish the analgesic efficacy of topical local anaesthetics for needle-related pain in infants [9<sup>■</sup>]. Although multiple studies have demonstrated that topical local anaesthetics can reduce clinical pain scores [50–54,55<sup>■</sup>], there are numerous conflicting reports that challenge these observations across a range of clinical procedures, including heel lancing [56–60], venepuncture [61], and intramuscular injections [62,63]. In part these mixed results may be because of the heterogeneity across the study designs, such as the choice of local anaesthetic, length of application, pain assessment endpoints, age group of the infants, and low study participant number. Nevertheless, it is also plausible that the reported lack of analgesic efficacy may arise because the behavioural measures used to assess pain are not sensitive enough, and may be confounded by distress caused by non-noxious aspects of the procedures, such as the need to physically restrain the infant. Although all efforts should, of course, be made to limit infant distress as well as pain, the challenge of disambiguating these responses can

make it difficult to measure the antinociceptive properties of pharmacological analgesic agents. Using a multimodal approach in clinical trials of analgesics that includes measures of noxious-evoked brain activity may help address these challenges.

### **IS MORPHINE AN EFFECTIVE ANALGESIC FOR PROCEDURAL PAIN IN INFANTS?**

The Procedural Pain in Premature Infants (POPPI) trial is a recent example of a study where multi-dimensional measures could provide a better understanding of the effect of potent analgesic compounds [48,49<sup>■</sup>]. The POPPI trial is a blinded randomized controlled trial currently in progress, which aims to establish whether morphine provides effective analgesia for acute pain in prematurely born infants. Infants are randomized to receive oral morphine or placebo approximately 1 hour prior to an invasive eye examination for retinopathy of prematurity (ROP screening) coupled with a routine heel lance. Noxious-evoked changes in brain activity, spinal cord activity, heart rate, oxygen saturation, and behaviour are recorded during these painful procedures, as are longer term changes in physiological stability. In addition, drug safety is assessed for 24 hours after drug administration. If the results of the trial show that the administration of a single oral bolus dose of morphine prior to clinical heel lancing and ROP screening decreases noxious-evoked brain activity, reduces clinical pain scores, and prevents the physiological instability reported to occur in the 24 hour period after ROP screening, there would be a strong rationale for the use of morphine in clinical practice.

### **DEVELOPING BRAIN ACTIVITY MEASURES TO IMPROVE ANALGESIC DRUG DISCOVERY**

Although the EEG template [44<sup>■</sup>] provides an opportunity to quantify afferent nociceptive input and compare this activity across multiple studies, there are several inherent limitations currently associated with this technique. At present, it is only validated in a limited age range of infants, and has only been characterized in response to brief experimental noxious stimulation and clinical heel lance. Nevertheless, similar patterns of noxious-evoked activity have been recorded in response to vaccination [47], suggesting that the template could be developed to have more wide-reaching applicability. Importantly, this template is not a 'gold-standard' measure of brain activity. It does not preclude the



exploration of other features of noxious-evoked brain activity, such as analysis in the time-frequency domain [64<sup>\*</sup>] that will no doubt lead to further new insights. Integrating EEG responses with measures of haemodynamic activity using near-infrared spectroscopy (which can be done simultaneously at the cot side) [65] will also provide new understanding, for example, with regards to the development of neurovascular coupling [66]. Moreover, functional MRI (fMRI), which has been extensively used to understand the brain activity and connectivity underlying the sensory, cognitive, and emotional aspects of the adult pain experience [19,20], may provide important additional information in infants [17<sup>\*</sup>,18]. Machine learning techniques have been used to identify sensitive and specific fMRI neural signatures of pain in adults [67], and key potential applications include their use as surrogate biomarkers for drug discovery and for targeted analgesic treatments [67,68]. Given the inherent lack of infant language, characterizing the neural representation of noxious-evoked brain activity in the infant could be one of the most important applications for these techniques. There is so much that we can learn from the adult pain imaging literature, but also much that infant pain research can contribute to the understanding of the long-term development of adult pain. Identifying analgesics that can modulate noxious-evoked brain activity in infants is important, but furthering this work such that we know how analgesics impact brain activity across multiple brain regions is crucial if we are to understand mechanisms of action and improve analgesic efficacy.

## CONCLUSION

Pain is a complex sensory and emotional perception. Painful procedures trigger an array of responses across the body, which include reflexes, facial grimacing, changes in cortical activity, and disruption of physiological stability. Given the absolute requirement to quantify infant pain based on measurable changes in noxious-evoked activity, it is evident that infant pain cannot be interpreted by considering isolated measures; a composite assessment is required. An effective analgesic should ultimately reduce the transmission of noxious input to the brain and result in a reduction in observed behavioural distress and subsequent signs of physiological instability. It remains to be seen whether currently used analgesics can satisfy the conditions of this multimodal approach. Well designed clinical trials are urgently required to improve the provision of effective analgesia in this unique patient group.

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## Conflicts of interest

There are no conflicts of interest.

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