

How Should We Manage Pain in Ventilated Neonates?

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Key Words

Pain · Newborn infant · Artificial respiration · Analgesia · Stress · Opiate alkaloid · Benzodiazepines · Muscle relaxant

Abstract

Newborn babies, even if extremely preterm, show responses to pain. The major stress responses seen with surgical pain are associated with serious adverse medical outcomes. There is an ethical imperative to consider pain relief in babies, despite the fact that they cannot verbalise their experience. Ventilator support, and accompanying treatments are described as distressing in adults, and are associated with an endocrine stress response in babies. Opiates have been shown to reduce physiological instability in sick newborn babies. Despite this, they have not been shown to reduce morbidity when given by infusion in ventilated infants, and in view of their serious side effects probably should not be used routinely in this way. It is logical and may be appropriate to give opiates peri-operatively and in babies likely to have severe pain (either from an underlying disease process such as necrotising enterocolitis, or during certain procedures). It is now accepted practice to use a potent analgesic/sedative for elective intubation and as cover for the treatment of retinopathy of prematurity. Topical anaesthetic creams reduce the pain response when used in anticipation of phlebotomy or vascular cannulation. Intra-oral sucrose is effective cover for procedures associated with mild to moderate distress, but its role in preterm infants is uncertain. Nursing interventions to reduce environmental stress, although commonly used, have not consistently been shown to be of benefit.

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Introduction

The last 20 years have seen an increased interest in, and some change in attitude to, pain in the newborn. We have come a long way from the days when it seemed justified not to give analgesia to babies undergoing surgery [1]. The response to acute noxious stimuli has now been well studied in neonates. It is clear that the stress related to such stimuli can be reproducibly measured in the form of behavioural, physiological and endocrine changes. There is no doubt that these responses are present in the most preterm infants in our care. It has been demonstrated that the dramatic stress responses seen during surgery lead to serious adverse medical outcomes which can be reduced by the provision of opiate analgesia [2]. Such evidence has put to rest attitudes that pain did not matter because it was not consciously remembered, and that concern about the serious side effects of potent analgesics should lead to their avoidance. In addition, there is now evidence that there is a biological memory for pain, which when encountered in late gestation enhances later pain response [3], and in early gestation seems to dampen it [4]. Could the cumulative effect of neonatal stress in part explain the behavioural difficulties more commonly encountered in ex-preterm children [4]?

When we consider babies who are mechanically ventilated in neonatal intensive care, we need to ask ourselves several questions:

- 1 Is ventilation itself painful or distressing?
- 2 What is the natural history of ventilation in neonates?

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- 3 Are there other noxious influences in neonatal intensive care units (NICUs)?
- 4 Are there effective treatments for pain and stress for babies receiving neonatal intensive care?
- 5 Is there more benefit than harm in using pain management techniques?

Is Ventilation Itself Painful or Distressing?

'Pain' and 'distress' are terms used for the perception by a conscious individual of the effects of certain noxious stimuli. We infer that babies experience these sensations because noxious stimuli produce reproducible behavioural responses which suggest this. We believe that pain and distress should be avoided in babies because (a) they are likely to be associated with an excessive stress response which may be harmful and (b) it would be inhumane to ignore them.

Inevitably, when there are questions about pain in specific situations, we tend to refer to the experience of verbally competent older subjects who are able to report it. In one study, around half of those adults who remembered their ICU experience thought that ventilator dependence was stressful (about 50% of respondents had no memory of these events). It is, of course, difficult to know how much of this is the effect of the adult's awareness of the implications of being in ICU and the associated anxiety [5].

Ill preterm infants have very high cortisol levels, sometimes even higher than those seen after surgery, presumably reflecting the stress relating to illness and to the environment [6]. There is an association between high stress hormone levels and increased mortality [7], although the link may be with illness severity [8]. In one study, the perceived need for sedation based on a sedation score correlated with the severity of respiratory distress [9]. The level of stress appears to be affected by the mode of ventilation [10].

What Is the Natural History of Ventilation in Neonates?

Twenty-seven percent of all infants admitted to NICUs undergo mechanical ventilation [11] and most of those born at less than 28 weeks' gestation need to be ventilated [12]. The pattern of ventilation has changed in neonatal units in the last 10 years. In the authors' unit, although the proportion of babies requiring some ventilatory support has not changed significantly (around 28% of all

admissions), the duration of ventilation has decreased markedly, so that the number of days of ventilation given to babies of less than 30 weeks' gestation has declined from a median of 7 days in 1995–2000 to a median of 2 days in 2004 [unpubl. data]. This is in keeping with published data [13] and is presumably explained by the more universal use of antenatal steroids and early surfactant, and the more aggressive use of nasal continuous positive airway pressure. Such a trend means that caution has to be used in applying the results of studies of pain management carried out in an earlier period.

Are There Other Noxious Influences in NICUs?

Babies who are ventilated in intensive care units undergo many procedures which are remembered as distressing in adults. One of the commonest of these is endotracheal suction. In the study quoted above [6], for those who remembered their stay in intensive care this was one of the most stressful experiences recollected. The other common procedures carried out on ventilated babies include nasal suction, heel prick, insertion and removal of intravenous cannulae, and insertion and removal of nasogastric tubes [14]. Aspects of the wider environment of neonatal intensive care may have adverse consequences, partly by causing stress. This includes bright ambient lighting, noise, physical exposure and repeated handling.

Are There Effective Treatments for Pain and Stress for Babies Receiving Neonatal Intensive Care?

A number of different approaches have been taken to the management of pain in ventilated babies.

Stress during Ventilation

Opiate Cover

Opiates are potent analgesics which have been shown to have an effect on stress responses and when used in surgery improve important medical outcomes [15].

Opiates have been shown to reduce physiological instability in the newborn in several ways. Studies have variously demonstrated that with opiates there is less hypoxaemia [16, 17], less blood pressure fluctuation [17], less behavioural and hormonal stress response [9, 18] and increased ventilator synchrony [19].

A number of studies have looked at the practice of providing opiate analgesia during ventilation. A meta-analysis published in 2005 which included 13 studies on 1,505 infants showed no difference in overall mortality, duration of ventilation or neurodevelopmental outcomes. It concluded that there was insufficient evidence to recommend the routine use of opiates in ventilated neonates. It should be noted that these trials differed in the indications for use of opiates, the type and dose of opiate used, the duration of treatment and the outcomes looked at.

The approach to pain and stress in NICUs has often been to infuse an opiate with the knowledge of its potent analgesic effects and also with the hope that its sedative effect will be beneficial. This is the approach used in intensive care units caring for older subjects in which the ability of opiates to produce amnesia is also valued.

Several studies have shown improvements in endocrine stress responses, behavioural scores and physiological stability, and although they reported little difference in major clinical outcomes, they were almost certainly not sufficiently powered for this [18, 20–22].

It had been hoped that as a result of physiological stabilisation pre-emptive opiate cover during intensive care would create similar improvements in outcome to those seen with surgical analgesia. Dyke et al. [19] in a double-blind RCT of morphine infusion in infants 29–36 weeks' gestation requiring ventilation for RDS found a reduction in duration of supplemental oxygen therapy.

In a pilot double-blind randomised controlled trial of morphine, midazolam and placebo, Anand et al. [23] showed a reduction in the proportion of babies with poor neurological outcome (a combined adverse outcome of death and major abnormality on cranial ultrasound) with morphine treatment.

The definitive trial which followed on from this [24] is the largest single study so far of opiate treatment during assisted ventilation. Eight hundred and ninety-eight preterm infants were randomised to morphine or placebo infusion in 16 centres in USA and Europe, but there was no overall difference in the incidence of poor neurological outcome. A similarly designed trial recruiting 150 neonates in the Netherlands [25] also failed to show any effect of morphine on this outcome.

In the only long-term follow-up study of babies given opiate analgesia, MacGregor et al. [26] reported the combined outcome of babies recruited to two randomised controlled trials. Both trials recruited preterm infants less than 34 weeks' gestation, in one randomising babies to receive morphine, pancuronium or a combination and the other morphine or placebo. With 62 of 95 infants re-

ceiving morphine, no effect of morphine on cognitive, motor or behavioural outcome could be identified at age 5–6 years.

Sedation and Paralysis

It is plausible that sedation might alleviate distress by reducing the amount of time that the baby is awake and by reducing struggling related to awareness of a noxious environment. The latter effect might, in addition, reduce adverse respiratory and other outcomes by reducing undesirable infant interaction with ventilator breaths [27]. This may be the mechanism by which muscle relaxants appear to reduce the risk of intraventricular haemorrhage and air leak [28].

Opiates have been studied specifically in the context of the struggling infant or compared with other sedatives or with muscle relaxants whose most plausible benefit would be to suppress the baby's own breathing.

Benzodiazepines produce effective sedation [29, 30]. Morphine given to preterm infants struggling against the ventilator reduced stress hormone levels [31], but its sedative effect has not been proven in this group [23].

Non-Pharmacological Techniques

A number of interventions are now commonly used to reduce the environmental stress experienced by babies undergoing intensive care, although there is conflicting evidence about the clinical benefit of these interventions. These include containment and reduction of light and noise levels. 'Sensorial saturation', a technique involving visual, tactile and auditory stimulation at the same time as giving intra-oral glucose appears to reduce some of the behavioural and physiological responses to heel prick [32]. There is some evidence that an individualised package of care incorporating these techniques, with care procedures tailored to behavioural cues given by the baby (Newborn Individualised Developmental Care and Assessment Program or NIDCAP) can improve short-term respiratory, and long-term behavioural and developmental outcome [33].

Procedural Cover

Invasive procedures are carried out frequently in sick preterm infants [14], and they may pose a greater threat to a baby's physiological stability and to clinical outcome than the more constant features of the baby's environment. Procedural pain accentuates the stress response to subsequent stimuli, whether normally noxious or not

[34]. The evidence base for procedural analgesia in the newborn has been well reviewed [35].

In the past we have assumed that once a ventilated baby was on a morphine infusion this provided sufficient analgesic cover for most needs. There is evidence that this is not true even for heel pricks [36].

One of the commonest procedures performed in ventilated babies is endotracheal suction. A study done by Saarenmaa et al. [37] showed that alfentanil reduced pain scores and adrenaline levels in response to the procedure.

Laryngoscopy and intubation are associated with major physiological disruptions including hypoxia and bradycardia, hypertension and increased intracranial pressure. These changes are suppressed by the use of pre-medication which also increases the success rate of non-emergency intubation [38]. Many regimens involve a combination of a muscle relaxant and an opiate, but it is not clear which combination is best.

Treatment for retinopathy of prematurity is likely to be acutely painful and also may cause vagal bradycardia precipitated by eyeball pressure. Laser therapy is usually done with analgesia and sedation or general anaesthesia in a ventilated infant. One case report suggested that nasal instillation of ketamine and midazolam was effective [39] and a recent study showed that cardiorespiratory stability can be equally well maintained with a morphine infusion as with general anaesthesia [40]. The current authors believe that neuromuscular paralysis is helpful to the ophthalmologist for the duration of the procedure and pre-emptive atropine treatment should also be considered.

Local anaesthetic gels containing lignocaine-prilocaine or amethocaine decrease the pain response to venepuncture [41–43]. However, there appears to be no benefit when used for heel prick or for central venous catheterisation [44, 45]. Spring-loaded lances might reduce the pain of heel prick [43, 46]. Local infiltration with lignocaine is often used for the insertion of chest drains, but this has not been subjected to formal assessment. The evidence for the benefit of lignocaine infiltration for lumbar puncture is conflicting [33].

Oral (as opposed to intra-gastric) sucrose solution effectively reduces pain behaviour in term and preterm infants, and this can be achieved by 0.1 ml of 24% sucrose [47]. Although sucrose is the most widely tested, glucose and mother's milk appear to have a similar effect.

Is There More Benefit Than Harm in Using Pain Management Techniques?

Neonatology has had to learn repeatedly about the price to be paid for introducing inadequately tested treatments [47]. It is thus important that we study the evidence base very carefully before embarking on population-based guidelines of pain management.

Systemic treatment with potent drugs needs particular care in the newborn because pharmacokinetics and pharmacodynamics depend on many factors including gestation, clinical condition and genetics. Adverse effects from opiates appear additionally to relate to cumulative dose, infusion time of bolus doses and interacting medications. Benzodiazepines, in particular, when given with opiates increase the risk of respiratory depression and hypotension [48].

The use of opiates as routine cover for ventilation has become more widespread with the realisation of the importance of pain in the newborn. Several adverse effects have to be considered when deciding on pre-emptive opiate cover for ventilation.

- 1 The respiratory depressant effects of opiates might increase the level of ventilation needed and its duration [18]. This might be particularly important with the move to minimise ventilator therapy even in extremely preterm infants with relatively poor respiratory drive. The place of routine analgesia during assisted ventilation needs to be reassessed in this context.
- 2 In the largest study to date of opiates in ventilated preterm infants, the NEOPAIN study [24], the morphine infusion rate varied with gestation (babies receiving 10, 20 or 30 $\mu\text{g}/\text{kg}/\text{h}$). Clinicians were given the option of giving additional bolus doses of morphine for procedural cover and also if there was a clinical suspicion that the baby was distressed. Morphine infusion was associated with hypotension, and this was more likely when bolus doses were given [49]. There was a higher risk of poor neurological outcome in infants of 27–29 weeks' gestation (who received 20 $\mu\text{g}/\text{kg}/\text{h}$) and in those with previous hypotension who received additional doses of morphine. It is possible that both hypotension and brain injury resulted from the accumulation of opiate in some babies.
- 3 The need for muscle relaxants has diminished considerably with the reduced severity and duration of respiratory disease in preterm infants. Their use cannot be justified except for a limited period in babies with respiratory failure who are requiring high levels of ventilatory support.

- 4 Morphine delays the attainment of full enteral feeds, presumably by slowing gut motility, and may thus increase the risk of complications related to the use of venous lines and parenteral nutrition [50]. The synthetic opiates, of which fentanyl is the most frequently used, have less histaminic and gut effects. Saarenmaa et al. [21] found that gastrointestinal motility (assessed by the size of gastric residuals and stool frequency) was less impaired with fentanyl than with morphine.
- 5 Fentanyl and its derivatives, if given as a rapid bolus, may produce chest wall rigidity through effects on stimulatory pathways in the spinal cord [51].
- 6 Morphine may cause bronchospasm because of its histaminic effects in children predisposed to this and should perhaps be avoided in infants with chronic lung disease.
- 7 Tolerance to opiate drugs is a very real phenomenon, and the resulting withdrawal syndrome after prolonged use causes troublesome symptoms [52]. Tolerance and withdrawal are particularly difficult to diagnose in preterm infants. Naloxone is avoided in preterm infants in the authors' institution because of the possibility of acute withdrawal associated with a surge of catecholamines and changes in cardiovascular homeostasis [53]. This is the explanation given for pulmonary oedema and fits when opiate antagonists are given to adults with opiate addiction [54].
- 8 There is a considerable body of evidence that opiates can have important effects on the immature organism. Children of opiate-dependent mothers are more likely to have later deficits in cognition and performance [55]. In animal models opiate exposure in pregnancy causes alteration in the structure of the adult brain with effects on behaviour [56] and adrenal atrophy with decreased adrenal function [57].

In the absence of evidence of benefit the apparent increase in the incidence of periventricular leucomalacia associated with midazolam in one study [23] should be taken seriously.

There are still uncertainties about the best clinical application of other treatments. For oral sucrose the optimum dose and the effectiveness and safety of repeated doses are unknown. Subgroup analysis of one study of suggested poorer neurobehavioural outcome in preterm infants who had repeated doses [57]. There are obvious difficulties in the context of a busy neonatal unit in planning the site and timing of venepuncture to allow the preparatory application of local anaesthetic cream.

What Should We Do Now?

The currently available evidence leaves considerable uncertainty about the best approach to many areas of pain management in the newborn.

Careful thought should always be given to the need to handle or intervene in the care of sick babies in NICUs. Procedures which may not be thought of as painful can cause considerable stress including X-ray and ultrasound examinations, and weighing. The use of indwelling arterial lines and central venous catheters can reduce the need for repeated stabs to obtain blood gases and for venous cannulation. However, these techniques are associated with complications and the balance of risk to benefit needs to be considered on an individual basis. Whilst measures to make the environment of care kinder for babies is now considered part of good neonatal nursing practice, neonatologists should be wary about embracing expensive packages of care such as NIDCAP which a Cochrane review found had little proven benefit [58].

In relation to routine analgesic or sedative cover for ventilation some would react to the absence of evidence of benefit by arguing that the ethical imperative to act humanely should be adopted. The authors would argue that the ethically appropriate approach is not to give analgesia or sedation routinely to ventilated babies until there is more information available about the balance of risk to benefits. We also believe that it would still be ethical to carry out placebo-controlled trials in this area [59]. There is currently no good cotside measure for chronic pain or distress to allow the rational prescribing of analgesics in this group. More work is needed to clarify the most appropriate drug and dosing regimen for different groups of babies and to develop better measures of chronic pain and distress.

Sedation with an opiate and/or neuromuscular paralysis are reasonable therapeutic choices in the very few babies who in the modern era develop severe respiratory failure and in whom the need for a high level of ventilator support in the face of a struggling baby puts the baby at risk of air leak. An attempt should be made to discover and correct the reason why a ventilated baby is unsettled before making an assumption that it is appropriate to sedate the baby (fig. 1).

Following surgery babies should be given good doses of opiate by infusion with respiratory and circulatory support if needed. For some very invasive procedures whose associated stress might be comparable to that encountered during surgery the empirical use of opiate analgesic treatment is generally considered appropriate, al-

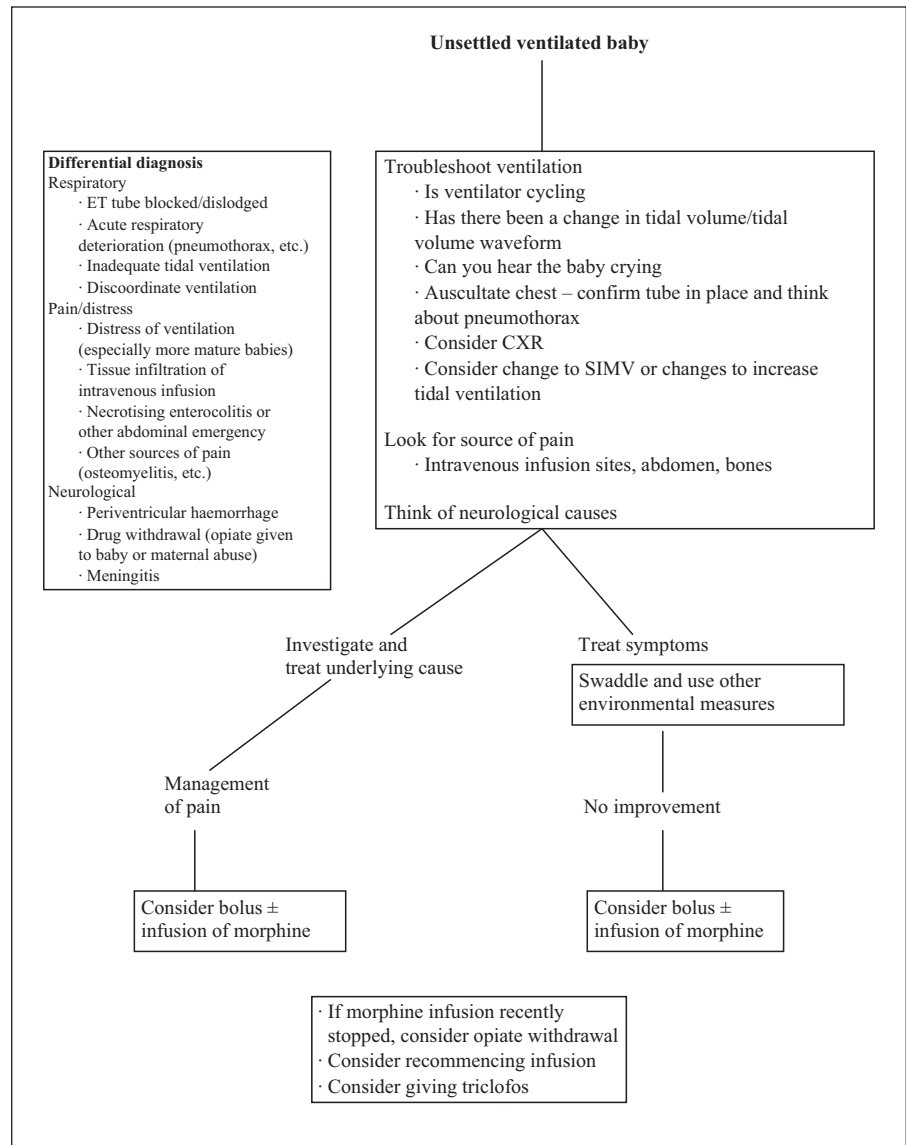


Fig. 1. An approach to the unsettled ventilated baby. CXR = Chest X-ray; SIMV = synchronized intermittent mandatory ventilation.

though it is likely that we will never have good quality proof of its benefit. Premedication for non-urgent intubation is now considered good clinical practice, although there is continuing uncertainty about the optimal drug regimen. Laser treatment for retinopathy of prematurity probably requires opiate analgesic cover with or without a full general anaesthetic. In situations where withholding or withdrawal of life-prolonging care is planned, opiate drugs with their potent analgesic effect in all age groups and ‘feel good’ effect in treated adults, should be used without concern about the respiratory depressant or other side effects [60].

Morphine is probably still the most widely used opiate drug. Fentanyl with its lesser histaminic effects may be preferable when opiates are needed in babies with chronic lung disease. Fentanyl also has the effect of reducing pulmonary vascular resistance and may thus be the opiate of choice in infants with persistent pulmonary hypertension and during ECMO and after cardiac surgery [61].

Oral sucrose should be given for procedures involving mild to moderate distress in term infants including heel pricks and attempts at vascular access. Although oral sucrose appears to be effective in preterm infants for vene-

puncture [62] and retinopathy screening [63], more work needs to be done to clarify the effect of repeated doses on long-term outcome.

Although neonatologists are as a group more aware of the existence and importance of pain in newborn babies, outside the area of peri-operative pain, it is not simple to

define a group in which there is clear evidence of the benefit of therapy. Whilst continuing to be humane practitioners we also need to be cautious about embracing potent therapies with good intent but a poor scientific basis. More research is needed particularly about the long-term effects of treatment with opiate analgesics.

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