Managing neonatal pain while rationalising the use of morphine using a structured systematic approach

A structured, systematic approach to assess and manage ongoing pain in preterm ventilated infants in a tertiary neonatal unit was successfully implemented. In order to assess efficacy of the pain management project, a retrospective observational study analysing data pre- and post-implementation was performed. The study enabled development of practical guidance for optimising the use of morphine in this group of infants.

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Key points

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1. It is possible to implement a system for assessment and management of ongoing pain.
2. Ventilated infants can be assessed using the N-PASS pain assessment tool.
3. With a proper pain assessment tool in place, the possible side effects associated with pharmacological analgesia can be avoided.

Pain management is an important, but often overlooked, aspect of neonatal care. A consequence of the increased survival rate of extremely preterm infants is a rise in the number of painful procedures that they endure. One study showed that neonates experience an average of 10 painful procedures per day of hospitalisation, with a range of 0-51 procedures[1]. The pathways responsible for conducting pain signals to the brain are developed by 20 weeks' gestation, but the inhibitory pathways do not mature until the last trimester of pregnancy[2-4]. This may increase the pain sensitivity of infants born prematurely and make them more susceptible to pain[1,5-11]. Untreated pain can adversely affect both the short-term and long-term outcomes of infants[8,12-20].

Although there is plenty of literature on the management of acute pain, there is much less for the management of ongoing pain, for example when infants are ventilated. Not only are there ethical considerations for infants suffering pain, there is evidence to support adequate analgesia in reducing long-term morbidity, as it is suggested that pain suffered during the neonatal period is associated with adverse behavioural and neuro-developmental outcomes[12,20]. Accurate recognition of pain in a neonate can ensure more appropriate use of analgesics therefore reducing morbidity, mortality and limiting potential side effects.

Infants rely entirely on their caregivers for assessment and management of their pain. Current methods of assessing neonatal pain include behavioural cues and physiological markers (eg heart rate, oxygen saturations). Many neonatal units do not have a pain assessment protocol; according to a survey conducted in 2005, less than 20% of the neonatal units in the UK have a pain assessment protocol[21]. Moreover there are few validated pain-assessment tools suitable for evaluating pain in infants who are ventilated or experiencing long-term pain.

Management of pain in preterm infants remains controversial. Both pharmacological and non-pharmacological (eg developmental care strategies) tools of pain control are currently in use in neonatal units. Even though pain relief is provided after surgery, daily routine procedures are still carried out without any form of pain control[22-27]. Generally there does not appear to be any consensus among clinicians with regard to the best means of managing pain in neonates. A lot of anxiety still exists with regard to the use of drugs like opiates in neonates, mainly arising from fear about their side effects and uncertainty about long-term effects on neurodevelopmental outcomes. More recently, attention has focused on individualised developmental care programmes to help with the evaluation and management of pain and discomfort[28-29]. Striking a balance between effective pain relief and avoidance of serious adverse effects from analgesics is a major challenge for caregivers[30]. Among the drugs used for pain relief, morphine is one of the most commonly used medicines in all age groups.

Aim and methodology

This study was prompted by a general concern in the authors' tertiary neonatal

unit about the routine use of morphine for managing pain and discomfort in ventilated preterm infants without the use of a pain-assessment tool, possibly leading to an increased use of inotropes. The aim of the project was to rationalise the use of morphine as an analgesic in ventilated preterm infants by instituting a validated pain assessment scoring system without compromising the mortality and morbidity in this group of infants.

A structured and systematic approach to management of pain in very low birthweight (VLBW, <1,500 grams) ventilated preterm infants called PMP (pain management project) was introduced in the neonatal unit. Its implementation was approved by the local guidelines group and education sessions on using the tool were implemented for all nursing and medical staff, with refreshers at the start of every shift and at every medical induction. Nursing documentation of N-PASS (neonatal pain, agitation and sedation scale scores) was audited following this training period to ensure assessment was robust.

In order to see the effect of PMP, a retrospective observational study was carried out in which pain management practices and interventions were reviewed before and after the introduction of PMP. Medical records of ventilated preterm infants with a birth weight <1,500g born six months before (June to December 2004) the introduction of PMP (Group 1, n=35) and six months after (June to December 2005) introduction (Group 2, n=35) were reviewed retrospectively. Infants who received any muscle relaxants and those with missing data were excluded from the analysis. The local research and development committee approved the study. Data collection included:

- infant demographics (birth weight, gestational age and gender)
- morphine use (infusion and bolus)
- duration of ventilation
- inotrope use in the first 14 days of life
- cranial ultrasound findings (normal or ≥ grade 2 haemorrhage based on Papile classification[31]) and mortality.

Pain management project (PMP)

The authors' neonatal unit has an established individualised developmental care programme derived from the Newborn Individualised Developmental Care and Assessment Program (NIDCAP). Ventilated infants were assessed using N-PASS (**TABLE 1**) every four hours. N-PASS was selected as the assessment tool because it is the only tool that measures ongoing, as well as acute pain and sedation, and is adjusted for gestational age.

If any of the infants scored >4 on the scale, a systematic comfort check and/or a medical check (**TABLE 2**) was carried out. The nurse looking after the infant at that time carried out the comfort check. All points were checked and changes implemented if problems were identified. A thorough medical check was performed if the comfort check did not identify any iatrogenic cause leading to pain or discomfort in the infant. If any problems were identified, an attempt to resolve them was made and use of analgesia was reviewed. For infants scoring less than 0 on N-PASS, analgesia was reduced. The dose of analgesia was increased (or started) if the N-PASS score was >4 with normal comfort and medical checks on at least two occasions, four hours apart.

Results

The mean gestational age and birthweight comparison between Groups 1 and 2 can

Assessment criteria	Sedation		Normal	Pain/agitation	
	-2	-1	0	1	2
Crying irritability	No cry with painful stimuli	Moans or cries minimally with painful stimuli	Appropriate crying Not irritable	Irritable or crying at intervals Consolable	High pitched or silent-continuous cry Inconsolable
Behaviour state	No arousal to any stimuli No spontaneous movements	Arouses minimally to stimuli Little spontaneous movement	Appropriate for gestational age	Restless, squirming Awakens frequently	Arching, kicking Constantly awake or arouses minimally/no movement (not sedated)
Facial expression	Mouth is lax No expression	Minimal expression with stimuli	Relaxed Appropriate	Any pain expression intermittent	Any pain expression continual
Extremities tone	No grasp reflex Flaccid tone	Weak grasp reflex ↓ muscle tone	Relaxed hands and feet Normal tone	Intermittent clenched toes, fists, or finger splay Body not tense	Continual clenched toes, fists, or finger splay Body is tense
Vital signs (BP, HR, RR, SaO_2)	No variability with stimuli Hypoventilation or apnoea	<10% variability from baseline with stimuli	Within baseline or normal for gestational age	↑ 10-20% from baseline SaO_2 76-85% with stimulation – quick ↑	↑ >20% from baseline SaO_2 ≤75% with stimulation – slow ↑ Out of synchrony with ventilator

TABLE 1 Neonatal pain, agitation and sedation scale scores (N-PASS), taken from Hummel and Puchalski[38]. Key: BP = blood pressure, HR = heart rate, RR = respiratory rate, SaO_2 = oxygen saturation.
Starting score (weighting score for prematurity): <28 weeks' gestation/corrected age = +3; 28-31 weeks' gestation/corrected age = +2; 32-35 weeks' gestation/corrected age = +1.

Comfort check	Medical check
Wet/soiled nappy/bedding	Airway: obstructed ETT/dislodged ETT
Position (eg twisted/trapped limb/retracted shoulders)	Airway compromised by head position
Baby struggling to change position	Airway blocked by large nasal prongs
Noise: excessive background or peak noise	Abnormal movements: seizures
Noise: from high CPAP pressure (needs medical review)	Breathing: irregular, inadequate MAP
Light: direct light in face, flickering, frequent variations	Breathing: pneumothorax
Bedding: rough, lumpy	Breathing: grunting/fast, needs more assistance
Lack of supportive boundaries	Circulation: poor, due to sepsis, shock
Movements too restricted	Cold or hypothermic baby
Baby naked	Digestion: reflux
Many sleep interruptions	Digestion: NEC
Abrupt handling	Digestion: perianal/nappy rash
Hunger	Dislodged NG tube
Response to soothing strategies (eg soothing voice): grasping, still holding, bracing, sucking	Distended abdomen: gaseous
	Drug withdrawal, neonatal abstinence
	Drug: rapid withdrawal of morphine
	Temperature: hyperthermic baby
	Trauma: IV extravasation
	Trauma at birth following forceps/ventouse delivery
	Trauma: ischaemic injury to extremities/ fingers/toes
	Trauma: fractures

TABLE 2 An example of the comfort and medical checks – the potential causes of discomfort to be excluded/addressed (not applicable to every baby). Key: CPAP = continuous positive airway pressure, ETT = endotracheal tube, MAP = mean airway pressure, NEC = necrotising enterocolitis, NG = nasogastric, IV = intravenous.

be seen in **TABLE 3**.

Morphine was used less frequently ($p<0.001$) in infants assessed by N-PASS, ie after the introduction of PMP. This was independent of birth weight and gestational age. The likelihood of infants who were assessed by N-PASS receiving morphine was 0.122 of that of infants who were not. It was noted that the post PMP group were generally bigger babies, although even when taking this into account the overall impact of implementing PMP was still significant for reducing morphine use.

It was also observed that the infants who received morphine were more likely to receive inotropes (number needed to treat = 6, number needed to harm = 3). Twenty-seven out of 35 babies needed inotropes when morphine was used, compared to five out of 35 babies when no morphine was used ($p=0.001$) (**TABLE 3**). For those who did not receive morphine, the likelihood of having inotropes was 0.045 of that of infants who did receive morphine.

Although the babies in Group 2 weighed more, the median duration of ventilation was significantly longer in the pre-PMP group (96 vs 40 hours, $p=0.04$) and there were no significant differences in mortality and length of hospital stay between the two groups. There were also no significant differences in cranial ultrasound findings (**TABLE 3**). The lack of any statistical difference in mortality and cranial ultrasound findings may be due to small sample size.

Discussion

Infants on the neonatal unit are often exposed to a considerable amount of noxious and painful stimuli. Based on various physiological and behavioural indicators, more than 40 different pain assessment scores are in use worldwide[32]. Many use similar criteria, although no gold standard exists. There are fewer scales for evaluating ongoing pain, the most commonly cited being the French EDIN (Échelle Douleur Inconfort Nouveau-Né, neonatal pain and discomfort scale)[33] and N-PASS[34]. N-PASS has the advantage in that it can be used to assess the degree of sedation as well as agitation and applies to both term and preterm infants. There is emerging evidence to suggest that N-PASS is also a reliable tool for assessing acute pain in infants at 0-30 days and 23-40 weeks' gestation[13]. However both the EDIN and N-PASS scales have unproven construct validity for pain[32].

N-PASS uses the physiological indicators of heart rate, respiratory rate, blood pressure and oxygen saturation as well as behavioural cues of crying, irritability, behavioural state and tone of extremities (**TABLE 1**). Studies have validated the use of N-PASS as a reliable assessment tool for neonatal pain and sedation, comparing the score with the premature infant pain profile (PIPP)[13,34]. The main advantage of this score,and the reason for its selection as the assessment tool for this study, is that it is the only tool to measure ongoing and acute pain and sedation, with a score adjusted for gestational age.

In this study, a threshold of >4 on two occasions, four hours apart, was set as the cut-off to increase the analgesia, as most of the ventilated babies were under 28 weeks' gestation and therefore would have started with an initial score of +3 (<28 weeks at birth) or +2 (between 28 and 31 weeks' gestation at birth).

N-PASS is a useful tool in assessing infant behaviour but requires staff training so that discomfort can be identified early. It is paramount that all staff involved in the care of the neonates have regular training to ensure a robust standardised approach to pain assessment. Before introducing the scoring system on the neonatal unit, all staff underwent training on the use of the N-PASS score.

For many years morphine has been used as one of the first line drugs to control pain in adults. It is often used on neonatal units

	Group 1, prior to N-PASS (n=35)	Group 2, following introduction of N-PASS (n=35)	P value
Ventilated babies	35	35	NS
Male	16	17	NS
Female	19	18	NS
Mean gestation (range)	26.2 weeks (24-29 weeks)	26.8 weeks (23-29 weeks)	0.257
Mean birthweight (range}	870g (460-1,035g)	980g (520-1,500g)	0.816
Number of babies receiving morphine	29	6	0.001
Mean duration of morphine (SEM)	87.8 hours (14.6)	73 hours (14.2)	
Number of babies receiving inotropes	22	10	0.001
Median duration of ventilation (25th quartile-75th quartile)	96 hours (40.5-189)	40 hours (12-114)	0.04
Normal cranial ultrasound on Day 1	17	20	NS
Grade 2 and above	8	5	NS
Normal cranial ultrasound at discharge	14	18	NS
Outcome Discharged home/transfer	27	33	NS
Death	8	2	NS

TABLE 3 The different outcome parameters between Groups 1 and 2. Key: SEM = standard error of the mean, NS = not significant.

for moderate to severe pain when babies are unwell and needing invasive and intensive support. This is important as there is evidence that adequate pain control can improve clinical outcomes after surgery and decrease mortality[28]. In many neonatal units morphine is routinely prescribed when babies are ventilated in order to provide relative comfort while intubated, as was practised on the local unit prior to the introduction of PMP. However, along with its obvious beneficial effects of pain relief and sedation, morphine can also cause significant side effects. Acute side effects of morphine include:

- respiratory depression
- hypotension
- bradycardia
- seizures
- constipation due to reduced gastrointestinal mobility
- urinary retention[35].

Debate continues over the use of morphine in neonates, stemming from anxieties about its short-term side effects and uncertainty about long-term neurodevelopmental outcomes. Long-term use in neonates can lead to dependence. Two large randomised controlled trials have looked at the use of intravenous morphine as a potential means of reducing poor neurologic outcome in preterm neonates receiving mechanical ventilation. One recent study showed that morphine has no apparent analgesic effect and does not alter the neurological outcome[35]. In another study, morphine use reduced pain scores slightly but did not improve neurological outcomes[36]. In the study presented here, there is suggestion of a short-term benefit of reducing the use of morphine, however long-term benefits were not seen.

Systematic checking for cause of discomfort is obviously a sensible strategy to prevent the injudicious use of medication. Successfully reducing medication depends on how skilled staff are at identifying what makes an infant comfortable and ensuring that the whole care giving approach is individualised to maximise an infant's comfort by protecting it from environmental stressors. All staff in the unit had some training in the implementation of individualised developmental care strategies. Systematic checking ensures that medication is not just prescribed on the basis of signs presented, but also that the source of pain is identified and treated correctly. Since the introduction of PMP, the staff have become confident in accurately identifying infants that need any form of pain relief.

The observation that morphine was used statistically less often in infants assessed by N-PASS, suggests that adequate assessment allowed rationalisation of the use of opiate analgesia. The number of infants who received morphine after the introduction of PMP was lower when compared to pre-introduction of PMP. The reduction in the use of morphine reduced the median duration of ventilation and did not seem to have any adverse effects on duration of stay in the hospital, abnormal cranial ultrasound scans and mortality.

The primary aim of developing an effective, structured and practical way of assessing pain and rationalising the use of morphine in ventilated preterm infants was achieved, although there remain some limitations to this study. There is a possibility that in this study pain may have been underscored. In addition it is possible that staff were biased towards underscoring, as they were clearly aware that the purpose of scoring was not just to ensure comfort but also to reduce medication. There is also a risk that if decisions about pain management are dependent on rigid routine pain scoring at set intervals, infants could endure many hours of pain without adequate treatment, which might have been given had intuitive observations been followed. It should also be pointed out that the sedation part of the scale also covers behaviours that indicate conditions in which pain may still be a related factor, such as sepsis. The fact that an infant does not show behavioural signs of pain does not necessarily indicate that the baby is not experiencing pain or discomfort. In a study comparing behavioural response to a painful stimulus with cortical activity measured with infra-red spectroscopy, facial expression was most closely associated with the cortical response, however some infants responded inconsistently and sometimes failed to show a change in facial expression[37].

Group 2 infants were ventilated for

shorter periods, given less inotropes and less morphine. It could be argued that this group of babies was simply less sick in the first place however, there were no clinically significant differences between the two groups implying that the use of less morphine and less inotropes was related to pain management awareness, which has now become a part of care for all ventilated babies on the unit.

Conclusion

It is possible to implement a pain management strategy without compromising the care of VLBW ventilated infants. Using non-pharmacological strategies and systematic elimination of possible sources of discomfort, it is possible to rationalise the use of opiates in the preterm population.

The success of this project was dependent on multidisciplinary team involvement to facilitate understanding of infant behavioural cues and use of appropriate comfort measures, however replicating these results will depend on ongoing training and assessment of staff involved in the care of these vulnerable infants. Further studies to look at the longer-term implications of rationalising morphine use are indicated.

Hopefully this article will encourage other neonatal units to consider and implement pain management as an important aspect of neonatal care. The use of pain assessments during vulnerable periods of life in order to minimise the use of analgesic drugs should be considered as an advance in neonatal care.

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