Oral morphine analgesia for preventing pain during invasive procedures in non-ventilated premature infants in hospital: the Poppi RCT

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Scientific summary

The Poppi RCT

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Scientific summary

Background

Although infant pain is recognised to have immediate and long-term consequences, it is still undertreated, and few trials have been conducted to test whether or not pharmacological analgesics are effective in this population. Consequently, comfort measures (such as non-nutritive sucking and swaddling) are often recommended as an alternative to pharmacological analgesia. Given that an infant requiring intensive care will experience an average of 12 painful procedures per day, and the youngest and sickest infants may experience 50 procedures per day, it is imperative to identify analgesics that are effective in this population.

The aim of this study was to test whether or not morphine can provide effective pain relief for procedural pain in prematurely born infants. Although morphine is a potent analgesic that provides effective pain relief in adults, efficacy in infants is less clear. Morphine is one of the most frequently prescribed analgesics in neonatal practice. There is evidence to suggest that intravenous morphine provides sedation in ventilated infants, and some research suggests that it may provide effective analgesia for acute painful procedures, such as chest drain insertion and central line placement. However, differences in study designs and dosing, heterogeneity of outcome measures and the administration of 'rescue' boluses have made interpretation of the evidence challenging. A recent Cochrane review (Dempsey E, McCreery K. Local anaesthetic eye drops for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity. *Cochrane Database Syst Rev* 2011;**9**:CD007645) concluded that there is insufficient evidence to recommend the routine clinical use of morphine in ventilated infants and, to date, analgesic efficacy for procedural pain in clinically stable non-ventilated infants has not been investigated. In this study, well-validated clinical pain assessment tools were used to test whether or not morphine provides analgesia during a painful eye examination (retinopathy of prematurity screening) and during a clinical heel lance. Multiple modalities were used to quantify analgesic efficacy, which included changes in clinical pain scores, noxious-evoked brain activity and reflex withdrawal activity. As retinopathy of prematurity screening can cause physiological instability in the immediate 24 hours after the procedure, whether or not the provision of morphine analgesia leads to an improvement in physiological stability after the examination was also tested. A comprehensive approach was used to assess changes in oxygen saturation, respiratory rate, heart rate and ventilation requirement in the 24 hours before and after the clinical procedures. In addition to standard clinical pain assessment (which primarily relies on changes in infant facial expression and autonomic activity), electrophysiological techniques were used to examine the effects of morphine on the underlying brain and spinal cord activity evoked by the painful procedures.

Objectives

The primary objective of the PrOcedural Pain in Premature Infants (Poppi) trial was to investigate the analgesic efficacy of oral morphine using a well-validated clinical pain score following retinopathy of prematurity screening. However, given the development of objective, validated neurophysiological measures of pain in infants, the trial also provided an opportunity to gain a mechanistic insight into how morphine affects nociceptive brain and spinal cord activity in this population.

Design

The Poppi study was a single-centre, double-blind, placebo-controlled randomised clinical trial.

Setting

The John Radcliffe Hospital, Oxford University Hospitals NHS Trust, was chosen as the most suitable site for this trial.

Participants

Inclusion criteria

Infants were considered eligible for the trial if they met the following inclusion criteria:

- were inpatients on the neonatal unit at the John Radcliffe Hospital, Oxford
- were born at < 32 weeks' gestation or at a birthweight of < 1501 g
- at the time of the study, were 34–42 weeks' gestational age
- required a clinical heel lance and retinopathy of prematurity screening on the same test occasion
- their parents/guardians had given written informed consent for inclusion in the trial
- a senior clinician considered inclusion in trial to be medically appropriate for them.

Exclusion criteria

Infants were considered ineligible for the trial if they met any of the following exclusion criteria:

- had an intraventricular haemorrhage > grade II
- had short-bowel syndrome
- were receiving nil by mouth because of documented gut pathology
- had received opiates in the last 72 hours
- had received other analgesics or sedatives in the last 24 hours
- had a previously documented episode of morphine sensitivity
- had congenital malformation or a genetic condition known to affect neurological development
- were born to mothers who regularly used opiates during pregnancy or while breastfeeding or while expressing breast milk.

Interventions

In the Poppi trial, 31 non-ventilated infants of 34-42 weeks gestational age were randomised to receive either 100 µg/kg of oral morphine or placebo solution prior to retinopathy of prematurity screening and clinical heel lancing (15 infants received morphine, 15 infants received placebo, and one infant was withdrawn before receiving treatment).

Main outcome measures

There were two co-primary outcomes: Premature Infant Pain Profile-Revised score (a higher score implies more nociceptive processing) during the 30-second period after retinopathy of prematurity screening, and the magnitude of noxious-evoked brain activity (a higher activity implies more nociceptive processing) following the heel lance. Physiological stability and safety were secondary outcomes.

Results

The study showed that administration of 100 µg/kg oral morphine in non-ventilated premature infants has profound respiratory adverse effects without suggestion of analgesic efficacy. Three of the 15 infants who received morphine had apnoeas requiring resuscitation with non-invasive positive-pressure ventilation

in the 24 hours after drug administration, compared with 0 of the 15 infants in the placebo arm [difference in proportion 0.2, 80% confidence interval (adjusted to allow for planned multiple analyses) 0.05 to 1.00; $p = 0.085$]. There was no significant difference between the trial arms for either primary outcome (Premature Infant Pain Profile-Revised score following retinopathy of prematurity screening mean score ± standard deviation – morphine: 11.1 ± 3.2; Premature Infant Pain Profile-Revised score following retinopathy of prematurity screening mean score ± standard deviation – placebo: 10.5 ± 3.4; mean difference in Premature Infant Pain Profile-Revised score following retinopathy of prematurity screening score 0.5, 95% confidence interval –2.0 to 3.0, $p = 0.66$; noxious-evoked brain activity following heel lancing median – morphine: 0.99, interquartile range 0.40–1.56; noxious-evoked brain activity following heel lancing median activity – placebo: 0.75, interquartile range 0.33–1.22; and median difference in noxious-evoked brain activity following heel lancing 0.25, 95% confidence interval –0.16 to 0.80, $p = 0.25$).

The trial was therefore stopped early by an independent committee reviewing the safety and conduct of the trial and we do not recommend the use of oral morphine at this dose in non-ventilated premature infants for retinopathy of prematurity screening. Difficulties in measuring infant pain are widely recognised. The methodology used in this trial to measure both analgesic efficacy and side effects of a pharmacological intervention sets new standards for the conduct of clinical trials of analgesics in infants.

Limitations

The trial lacked power for the primary outcome measures because of early cessation. However, there was a trend across modalities favouring placebo, suggesting that it was unlikely that a clinically significant analgesic benefit would have been detected in the original proposed sample of 156 infants.

Conclusions

The administration of 100µg/kg of oral morphine to non-ventilated premature infants has the potential for harm without analgesic benefit. Oral morphine is not recommended for retinopathy of prematurity screening, and caution is strongly advised if this is being considering for other acute painful procedures in non-ventilated premature infants.

Future work

Further clinical trials are essential to ascertain effective pain management for retinopathy of prematurity screening. Using multimodal measures with detailed physiological recordings provides a rigorous approach to assess analgesic efficacy and adverse effects, leading to greater mechanistic understanding of the drug effects. This is essential in future clinical trials of analgesics in infants.

Patient and public involvement

The research team worked closely with an on-site charity during the trial design, conduct, oversight and dissemination.

Trial registration

The trial was registered with the International Standard Randomised Controlled Trial Number (ISRCTN) registry as ISRCTN82342359. In addition, the trial was registered with the European Clinical Trials Database as number 2014-003237-25.

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