Pain control during retinopathy of prematurity screening: double-blind, randomised, placebo-controlled study

By late gestation, the fetus has developed the anatomic, neuro-physiological, and hormonal components necessary to perceive pain. Pain experienced in the neonatal period may have long-term effects. In this prospective, randomised, double-blind, placebo-controlled study of eighteen neonates the effect of morphine or paracetamol on pain experienced during retinopathy of prematurity screening was assessed by the Premature Infant Pain Profile.

Chikkanayakanahalli M. Manjunatha
MD, DCH, DNB, MRCP UK, FRCPCH
Consultant Neonatologist
cm.manjunatha@lanarkshire.scot.nhs.uk

Samuel E. Ibhanesebhor
BS, MBBS, MRCP, FWACP, FMCPaed, FRCPCH, FRCP, Consultant Neonatologist

Connie Rennix
RGN, RM, BSc(Hons) Neonatal Midwife

Hazel Fisher
BSc(Hons), MSc Clin Pharm, MRPharmS Paediatric Pharmacist

Rosemary Abara
MBBS, MRCP UK, FRCPCH Consultant Paediatrician and Neonatologist

Wishaw General Hospital, Lanarkshire

Keywords
premature infant pain profile (PIPP); retinopathy of prematurity; pain

Key points

1. Newborn infants have both the anatomic and physiological capacity to experience pain.
2. Pain experienced in the neonatal period may have long-term effects.
3. Neonates need measures to reduce pain during all common neonatal procedures including ROP screening.

Pain is defined as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage’. By late gestation, the fetus has developed the anatomic, neurophysiological, and hormonal components necessary to perceive pain. Newborn infants also have both the anatomic and physiological capacity to experience pain. Pain experienced in the neonatal period may have long-term effects. Neonates who were exposed to numerous painful and noxious stimuli between postconceptual weeks 28 and 32 showed different behavioural and physiological responses to pain compared with neonates of a similar postconceptual age who had not had such experiences. The World Health Organisation’s vision 2020 programme aims to have a world in which no one is needlessly blind and where those with unavoidable vision loss can achieve their full potential. Retinopathy of prematurity (ROP), a condition confined to the developing retinal vascular system of preterm babies, is one of the few largely preventable causes of childhood vision impairment. Thus, screening for ROP is an essential part of the care for this vulnerable group of infants. Due to the sequential nature of the progression of ROP, and in order to minimise the risk of visual loss by the proven benefits of laser therapy, standard practice now demands carefully timed retinal examinations of at-risk infants by an appropriately experienced ophthalmologist.

The procedure involves cycloplegia (paralysis of the ciliary muscles) and pupillary dilation. It also involves the separation of the eyelids with a retractor to provide a good view. Many of these babies require multiple examinations to monitor the course of their ROP so that appropriate measures can be taken.

Since very preterm infants may be exposed to several hundred painful procedures during their stay in the hospital, it is important that neonatal units develop strategies for appropriate pain relief during such procedures. A literature review did not identify any prior studies on the use of analgesics during ROP screening when this study was started.

The study

Aims
To ascertain if and to what extent neonates experience pain and discomfort during ROP screening and to compare the effect of paracetamol, oral morphine or placebo on the markers of pain in preterm infants.

Materials and methods
A double-blind randomised control study of three groups of infants given placebo, paracetamol, or oral morphine sulphate, was carried out. Prior approval from NHS Lanarkshire Research Ethics Committee was obtained. The study was conducted from 2003 to 2005 at Wishaw General Hospital, Lanarkshire.

Power and sample size
The sample size was calculated using MINITAB (Version 13). This calculation used an estimated standard deviation of 3.5 for PIPP scores (see reference 7), and was based on a difference in average pain score of 3 units using either analgesic compared to placebo.
Inclusion criteria
Babies who satisfied the criteria for ROP screening (≤31 weeks of gestation, or ≤1.5kg birth weight), were recruited into the study following written informed consent from parents/carers, at 34 weeks’ corrected gestational age or more.

Exclusion criteria
Babies, who were on morphine or paracetamol for other reasons, breast fed babies whose mothers were on methadone or other analgesics and babies with gastro-intestinal problems like ileostomy/colostomy were excluded.

Procedure
Neonates were randomised to receive a single oral dose of either morphine sulphate 200µg/kg, or paracetamol 20mg/kg, or placebo. Morphine, an opioid, administered for moderate to severe pain, has the advantages of analgesic potency without a ceiling effect, sedation, homodynamic stability, and reversibility of adverse effects.

Paracetamol (acetaminophen) is a non-opiate analgesic. The time to maximum serum concentration is 70 minutes. We used a single dose one hour prior to the ROP screening, as multiple doses in 28 to 32-week-old neonates would require an interval of more than eight hours to prevent progressively increasing serum concentration.

Blinded randomisation was done by picking up consecutive envelopes, providing a random allocation of patients to these groups. The pharmacy department at Wishaw General Hospital supplied the trial substances.

The babies received the trial substance (placebo or medication) one hour before the procedure. The physiological status of the baby was recorded prior to the procedure. The dose of each trial substance was dispensed as 10mL and administered as 2mL/kg/dose, one hour before the procedure.

Eligible babies received topical 2.5% phenylephrine hydrochloride and 0.5% cyclopentolate, one drop to each eye, 60 minutes and 45 minutes before the examination. Thereafter one drop of 0.5% proximetacaine local anaesthetic was instilled into each eye five minutes before the examination. The screening was carried out by the consultant ophthalmologist in all the babies.

Pain was assessed by the Premature Infant Pain Profile (PIPP) which includes facial actions (brow bulge, eyes squeezed shut, and nasolabial furrow) and physiological indicators (heart rate and oxygen saturation – SaO₂) in the context of gestational age and neonatal state. Pain was assessed by the Premature Infant Pain Profile (PIPP) (TABLE 1) which includes facial actions (brow bulge, eyes squeezed shut, and nasolabial furrow) and physiological indicators (heart rate and oxygen saturation – SaO₂) in the context of gestational age and neonatal state.

Results
Although the calculation of sample size indicated that we needed 63 babies in the study, we had recruited only 18 babies within the anticipated length of the trial. The study was stopped on advice by the Research and Development Department, NHS Lanarkshire in view of changes to research regulations of the Medicine and Health Regulatory Authority and the need to obtain new approval to continue the study.

The PIPP pain scores were compared at five minutes post procedure between the three groups using a Kruskall-Wallis test (TABLE 2 and FIGURE 1). The p-value of

<table>
<thead>
<tr>
<th>Process</th>
<th>Indicator</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>Gestational age</td>
<td>36 weeks and more</td>
<td>32-35 weeks and 6 days</td>
<td>28-31 weeks and 6 days</td>
<td>Less than 28 weeks</td>
<td></td>
</tr>
<tr>
<td>Observe infant for 15 seconds</td>
<td>Behavioural state</td>
<td>Active/awake</td>
<td>Eyes open, facial movements</td>
<td>Quiet/awake</td>
<td>Eyes open, facial movements</td>
<td>Active/sleep</td>
</tr>
<tr>
<td>Observe baseline saturation and heart rate for 30 seconds</td>
<td>Heart rate max</td>
<td>0-4 beats/min increase</td>
<td>5-14 beats/min increase</td>
<td>15-24 beats/min increase</td>
<td>&gt;25 beats/min increase</td>
<td></td>
</tr>
<tr>
<td>Observe infant for 30 seconds</td>
<td>Saturation minimum</td>
<td>0-2.4% decrease</td>
<td>2.5-4.9% decrease</td>
<td>5-7.4% decrease</td>
<td>7.5% or more decrease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brow bulge</td>
<td>None</td>
<td>0-9% of time</td>
<td>Minimum 10-39% of time</td>
<td>Moderate 40-69% of time</td>
<td>Maximum 70% of time or more</td>
</tr>
<tr>
<td></td>
<td>Eye squeeze</td>
<td>None</td>
<td>0-9% of time</td>
<td>Minimum 10-39% of time</td>
<td>Moderate 40-69% of time</td>
<td>Maximum 70% of time or more</td>
</tr>
<tr>
<td></td>
<td>Naso-labial furrow</td>
<td>None</td>
<td>0-9% of time</td>
<td>Minimum 10-39% of time</td>
<td>Moderate 40-69% of time</td>
<td>Maximum 70% of time or more</td>
</tr>
</tbody>
</table>

TABLE 1 Infant pain profile (PIPP).
Infant PIPP score

<table>
<thead>
<tr>
<th>Time of observation</th>
<th>Solution</th>
<th>n</th>
<th>n*</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Median</th>
<th>Maximum</th>
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<tr>
<td>5 mins prior</td>
<td>Morphine</td>
<td>6</td>
<td>0</td>
<td>3.667</td>
<td>0.516</td>
<td>3.000</td>
<td>4.000</td>
<td>4.000</td>
</tr>
<tr>
<td></td>
<td>Paracetamol</td>
<td>6</td>
<td>0</td>
<td>5.000</td>
<td>2.970</td>
<td>3.000</td>
<td>4.000</td>
<td>11.00</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>0</td>
<td>3.500</td>
<td>0.837</td>
<td>3.000</td>
<td>3.000</td>
<td>5.000</td>
</tr>
<tr>
<td>5 mins post</td>
<td>Morphine</td>
<td>6</td>
<td>0</td>
<td>3.500</td>
<td>1.517</td>
<td>1.000</td>
<td>3.500</td>
<td>5.000</td>
</tr>
<tr>
<td></td>
<td>Paracetamol</td>
<td>5</td>
<td>1</td>
<td>4.600</td>
<td>1.517</td>
<td>3.000</td>
<td>4.000</td>
<td>7.000</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>0</td>
<td>6.167</td>
<td>2.229</td>
<td>4.000</td>
<td>5.000</td>
<td>9.000</td>
</tr>
<tr>
<td>30 mins post</td>
<td>Morphine</td>
<td>4</td>
<td>2</td>
<td>5.500</td>
<td>2.380</td>
<td>3.000</td>
<td>5.500</td>
<td>8.000</td>
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<tr>
<td></td>
<td>Paracetamol</td>
<td>6</td>
<td>0</td>
<td>4.333</td>
<td>0.816</td>
<td>4.000</td>
<td>4.000</td>
<td>6.000</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>4</td>
<td>2</td>
<td>3.750</td>
<td>0.500</td>
<td>3.000</td>
<td>4.000</td>
<td>4.000</td>
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<tr>
<td>1 hour post</td>
<td>Morphine</td>
<td>6</td>
<td>0</td>
<td>4.333</td>
<td>2.338</td>
<td>1.000</td>
<td>4.500</td>
<td>8.000</td>
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<td>6</td>
<td>0</td>
<td>4.500</td>
<td>1.049</td>
<td>3.000</td>
<td>4.500</td>
<td>6.000</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>0</td>
<td>4.333</td>
<td>0.816</td>
<td>3.000</td>
<td>4.500</td>
<td>5.000</td>
</tr>
<tr>
<td>2 hours post</td>
<td>Morphine</td>
<td>6</td>
<td>0</td>
<td>4.667</td>
<td>1.506</td>
<td>3.000</td>
<td>4.000</td>
<td>7.000</td>
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<tr>
<td></td>
<td>Paracetamol</td>
<td>5</td>
<td>1</td>
<td>6.200</td>
<td>1.924</td>
<td>4.000</td>
<td>6.000</td>
<td>9.000</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>0</td>
<td>4.000</td>
<td>1.265</td>
<td>3.000</td>
<td>3.500</td>
<td>6.000</td>
</tr>
<tr>
<td>3 hours post</td>
<td>Morphine</td>
<td>6</td>
<td>0</td>
<td>4.670</td>
<td>2.500</td>
<td>2.000</td>
<td>4.000</td>
<td>9.000</td>
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<tr>
<td></td>
<td>Paracetamol</td>
<td>6</td>
<td>0</td>
<td>4.833</td>
<td>1.835</td>
<td>3.000</td>
<td>4.500</td>
<td>7.000</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>5</td>
<td>1</td>
<td>3.600</td>
<td>0.894</td>
<td>3.000</td>
<td>3.000</td>
<td>5.000</td>
</tr>
</tbody>
</table>

TABLE 2 PIPP scores over time. n* = number excluded.

Boxplot of pain score five minutes post ROP screening.

0.083 was suggestive of a trend towards a higher PIPP score in the placebo group.
The babies who received morphine tended to experience less pain. However, this difference did not reach statistical significance.

Discussion

In the recent past, interest in pain in infants hospitalised in NICU has increased dramatically. A survey conducted to look at the pain relief during common neonatal procedures in the UK showed that analgesia was commonly used for elective intubations, the commonest agent used being morphine, followed by fentanyl. Analgesia was also used in 11% of neonatal units for intravenous cannulation and 10% of units for heel pricks. The analgesia most commonly used for cannulation was sucrose or dextrose. The wider use of sucrose and topical anaesthetics seems likely to be the most effective way to improve the situation. Our study looked at one of the common neonatal procedures which may produce significant pain in the neonates.

Anecdotally clinicians believe that neonates who undergo ROP screening, experience pain, and in some cases have cardiorespiratory collapse following the procedure. Since we completed this study, the RCPCH/RcOphth guideline for the screening and treatment of retinopathy of prematurity has been published and this addresses the provision of pain relief during screening. As well as pharmacological intervention, measures like swaddling are also used during the ROP screening in many units to provide comfort to the babies.

A recent study by Kleberg et al looked at the efficacy of a Newborn Individualised Developmental Care and Assessment Program (NIDCAP) – based intervention to reduce pain during ROP screening. Although there was no reduction in pain response there was faster recovery of salvery cortisol levels following NIDCAP intervention. Another recent study showed that indirect ophthalmoscopy without specula causes significantly less stress to infants than screening with lid specula and scleral indentation.

The results from the present study are based on the available data. It was not possible to perform the PIPP scoring during the procedure itself as the eyes were kept open by retractors (PIPP scoring includes brow bulge, eyes squeezed shut and naso labial furrow). Our study shows a trend for neonates without any analgesia (placebo group) to experience more pain, particularly shortly after the ROP screening (p value 0.083). The babies who received morphine tended to experience the least pain, however, this did not reach statistical significance. This may be due to the small sample size but also perhaps due to the inadequacy of morphine to provide adequate analgesia for acute pain caused by invasive procedures, as recently reported. The use of paracetamol did not appear to...
affect the degree of pain experienced by the neonates who underwent ROP screening. Larger trials, possibly with a combination of analgesics are required to explore how a definite and satisfactory degree of analgesia can be achieved during ROP screening. Neonates need measures to reduce pain during all common neonatal procedures including ROP.

Acknowledgements
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References