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## **A universal right to pain relief – balancing the risks in a vulnerable patient population**

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Fifteen million premature infants are born every year worldwide<sup>1</sup>. With mortality risks reduced, the neonatal community is focussing its research efforts on improving quality of life and the prevention of long-term adverse outcomes in surviving infants. Most of these infants require frequent essential painful procedures and there is often an unspoken acceptance that this iatrogenic pain is unavoidable. Perhaps it is easy to assume that the discomfort of painful procedures is relatively fleeting and inconsequential; after all, adults are familiar with the momentary pain of blood tests, and for most of us these events do not impact on our overall well-being. This comparison, however, underestimates how traumatic these minor procedures may be, even for children or adults, when experienced repeatedly over weeks to months.<sup>2,3</sup>

In 2004 the World Health Organisation declared pain management a human right.<sup>4</sup> Why, then, has it taken so long to recognise the ethical importance of pain relief in infants? Despite no conscious memory of events, infants should have as much right to analgesia as children and adults, perhaps more so given that these events occur at a time of heightened sensitivity and rapid neurodevelopment,<sup>5</sup> and may alter brain structure and function, and later pain sensitivity.<sup>6</sup> Unique epistemic challenges associated with assessing pain intensity in non-verbal infants have hampered the development of adequate pain management. Until recently we have been highly reliant on analgesic drug doses extrapolated from paediatric and adult doses, and our ability to test analgesic efficacy has been constrained by the inherent ethical and practical challenges of performing drug trials in this vulnerable population.<sup>7</sup>

Infants have a right to receive analgesics that are both effective and safe during essential clinical procedures. This right is underpinned by the physician's ethical duty to carefully balance the principles of beneficence and non-maleficence. The neonatal community has often been guilty of hastily introducing drugs into practice with good intentions, but without clear evidence of efficacy or safety.<sup>8</sup> Advances in our understanding of the neurological processes underlying infant pain have led to the development of novel approaches to assess the impact of painful procedures on infant physiology and have provided new methods to comprehensively assess analgesic efficacy.<sup>9</sup> In the *Lancet*, we report the results of the Poppi (Procedural Pain in Premature Infants) trial, which employed multimodal endpoints to provide a holistic picture of both the analgesic efficacy and safety of oral morphine in non-ventilated premature infants. We conclude that oral morphine at a dose of 100µg/kg is not appropriate to treat pain evoked by retinopathy of prematurity (ROP) screening in these infants and that the trial establishes a rigorous new paradigm for testing future analgesics.

The Poppi trial was terminated early following a recommendation by expert members of a Data Monitoring Committee (DMC) that the potential for harm outweighed the potential for benefit. This decision was predicated upon a predefined stopping boundary and planned interim analysis, which showed the rate of respiratory intervention was unacceptably higher in the morphine-treated infants. Although researchers have a fundamental ethical requirement to monitor and report the safety of interventions, a recent review of neonatal trials published in high impact journals revealed that 39% of trials did not report having a DMC and 79% failed to report a valid stopping boundary, including several trials that were terminated prematurely.<sup>10</sup> There seems to be a natural aversion to highlighting the potential harms of drugs in clinical trials; they are far too often inadequately assessed and under-reported. To determine the safety of an analgesic requires substantive proof of the absence of harms. When adverse events are rigorously assessed and clearly reported in tandem with benefits in all neonatal clinical trials, we will be able to draw balanced conclusions whilst safeguarding the interests of the participants, and progress will be made towards adequately addressing infants' right to pain management.

The Poppi trial was stopped before conclusions could be drawn regarding the analgesic efficacy of oral morphine as testing this would have required exposing infants to an unacceptable risk of adverse events. What level of adverse effects are we prepared to accept to provide effective analgesia for infants? This will be context-dependent. In the Poppi trial, morphine administration more than doubled the incidence of apnoeas. Apnoeas are frequently experienced by premature infants, and are potentially life-threatening events associated with reduced cerebral oxygenation, reduced growth, and increased risk of severe ROP and cognitive impairment in later life.<sup>11</sup> However, the potential occurrence of apnoeas and a requirement for increased respiratory support may be justified in the context of severe pain, for example post-operatively. In future analgesic trials in infants, might an increased risk of apnoeas be considered acceptable if there is evidence the intervention is providing effective analgesia and limiting other negative pain-related consequences? This is a challenging question, which requires consideration and consensus, but we believe it is imperative not to trivialise the seriousness of the harms of painful procedures and drugs simply because they form part of the current clinical landscape.

Morphine is frequently provided to infants receiving mechanical ventilation in the hope that it may provide 'comfort'; this is based upon an unsubstantiated expectation that continuous morphine infusions may perhaps provide analgesia, despite a lack of convincing evidence.<sup>12</sup> Although the results of the Poppi Trial cannot directly inform conclusions on the efficacy of intravenous morphine, definitive proof of analgesic efficacy is long overdue and urgently needs to be addressed. If morphine does not provide adequate analgesia for infants then we need to discover which analgesic drugs are effective in this population. Despite failing to provide proof of an effective analgesic for procedural pain in premature infants, we hope that the Poppi trial has demonstrated that clear stopping points, detailed physiological and clinical monitoring, and comprehensive multimodal evaluation of analgesic efficacy can provide a path forward for future research addressing this fundamental problem in neonatal care. It is time to address the right to analgesia of the youngest and arguably most vulnerable members of our society with evidence-based treatments.

### **Contributions**

The idea for the manuscript arose from discussions between all authors surrounding the Poppi trial. FM, AS and RS wrote the first draft. All authors critically reviewed the manuscript and agreed on the final version submitted.

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