A universal right to pain relief: balancing the risks in a vulnerable patient population

Worldwide, 15 million premature infants are born every year, according to a WHO report. With mortality risks reduced, neonatal research is focusing on improving quality of life and preventing long-term adverse outcomes in surviving preterm infants. Most of these infants require frequent essential painful procedures, and there is often an unspoken acceptance that this iatrogenic pain is unavoidable. Perhaps the discomfort of painful procedures is assumed to be fleeting and inconsequential; after all, many adults are familiar with the momentary pain of blood tests, and for most of us these events do not affect our wellbeing. However, this comparison might underestimate how traumatic these minor procedures are, for children and adults, when they are done repeatedly over weeks or months.[1,2]

In 2004, WHO declared pain management a human right.[3] Why, then, has it taken so long for the ethical importance of pain relief in infants to be recognised? 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,[4] and might alter brain structure and function, and later pain sensitivity.[5] Unique epistemic challenges associated with assessing pain intensity in non-verbal infants have hampered the development of adequate pain management. Neonatalogists have been highly reliant on analgesic drug doses extrapolated from paediatric and adult doses, and the ability to test analgesic efficacy has been constrained by the inherent ethical and practical challenges of performing drug trials in this vulnerable population.[6]

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 analgesic drugs into practice with good intentions, but without clear evidence of efficacy or safety.[7] Advances in understanding of the neurological processes underlying infant pain have led to the development of novel approaches to assess the effect of painful procedures on infant physiology and have provided new methods to comprehensively assess analgesic efficacy.[8] In *The Lancet*,[9] we report the results of the Procedural Pain in Premature Infants (Poppi) trial, which used multimodal endpoints to provide a holistic picture of the analgesic efficacy and safety of oral morphine in non-ventilated premature infants. We conclude that oral morphine at a dose of 100 µg/kg is not appropriate to treat pain evoked by screening for retinopathy of prematurity in these infants and that the trial establishes a rigorous new paradigm for testing future analgesics.

The Poppi trial[9] was terminated early after a recommendation by expert members of a data monitoring committee 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 than in the placebo group. Although researchers have a fundamental ethical requirement to monitor and report the safety of interventions, a 2017 review[10] of neonatal trials published in high-impact journals showed that 39% of trials did not report having a data monitoring committee and 79% did not report a valid stopping boundary, including several trials that were terminated early. Highlighting the potential harms of drugs in clinical trials seems unpopular; adverse effects are far too often inadequately assessed and under-reported. To establish the safety of an analgesic drug 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, it will be possible to draw balanced conclusions while safeguarding the interests of the participants, and progress will be made towards adequately addressing pain management in infants.

The Poppi trial[9] was stopped before conclusions could be drawn regarding the analgesic efficacy of oral morphine, because testing the efficacy would have required exposing infants to an unacceptable risk of adverse events. The level of adverse effects that should be accepted to provide effective analgesia for infants

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will be context dependent. In the Poppi trial,[9] morphine administration more than doubled the risk of apnoeas. Apnoeas occur frequently in premature infants, and are potentially life-threatening events associated with reduced cerebral oxygenation, reduced growth, and increased risk of severe retinopathy of prematurity and cognitive impairment in later life.[11] However, the potential occurrence of apnoeas and a requirement for increased respiratory support might be justified in the context of severe pain such as postoperative pain. In future analgesic trials in infants, might an increased risk of apnoeas be considered acceptable if evidence shows that 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 that the seriousness of the harms of painful procedures and drugs should not be trivialised simply because they form part of the current clinical landscape.

Morphine is often provided to infants receiving mechanical ventilation in the hope that it might provide comfort; this concept is based on an unsubstantiated expectation that continuous morphine infusions might provide analgesia, despite no convincing evidence.[12] Although the results of the Poppi trial[9] cannot directly inform conclusions on the efficacy of intravenous morphine, definitive proof of analgesic efficacy is long overdue and needs to be addressed. If morphine does not provide adequate analgesia for infants, then it should be established which analgesic drugs are effective in this population. Despite not providing proof of an effective analgesic for procedural pain in premature infants, we hope that the Poppi trial[9] has shown that clear stopping points, detailed physiological and clinical monitoring, and comprehensive multimodal assessment 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.

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