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A DIFFERENT VIEW

No pain, neurodevelopmental gain: Time to avoid painful placebo injections in neonatal research

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1 | INTRODUCTION

> A research nurse is involved in an exciting randomised controlled trial using treatment X, which has been shown to improve lung function in a phase II study. Babies in the study either get an intramuscular injection of treatment X or a "sham" injection of normal saline. The nurse hesitates before giving the dose. They have done this a number of times before and each time the babies are upset despite sucrose. They wonder to themselves "is this the treatment? If it isn't, do I need to do this?"

Neonatology is a relatively new medical subspeciality with a number of unanswered questions of high clinical priority. The optimal care of both the preterm neonate and the term neonate who has suffered complications during birth has been advanced tremendously through the development and implementation of rigorous randomised controlled trials (RCTs) and meta-analyses including, famously, the logo of the Cochrane collaboration.[1,2]

The methodological purity of the properly conducted RCT is well documented. Proper blinding, controls and randomisation allow researchers to meet their ethical imperative to their participants that the research produces worthwhile and clinically useful results.

Here, we examine the ethical context in which research in neonates occurs, evidence around pain in preterm neonates and how recent placebo-controlled trials, while methodologically sound, may have inadvertently exposed the control group to harm.

2 | ETHICAL ISSUES IN NEONATAL RESEARCH

Neonatal research participants represent a particularly vulnerable group. They cannot consent or assent, and therefore their entry into a study is determined by their parent or guardian consenting for them. While this is obviously essential as a neonate has only just begun its journey to autonomous personhood, and neonates are an at-risk clinical population who require specific clinical studies to investigate conditions specific to them, and it creates an ethical dilemma for parents, guardians and investigators. How do we act in the 'best interests' of such study participants? Thankfully many parents and guardians enrol their children in such studies with the understanding that (a) the results will be impactful on the care of other infants in a similar situation and (b) their own child is not subject to excess harms with a principle of 'minimum risk' applied.

Clinical practices have also changed markedly over time with practices felt to be safe and in the best interest of the child being abandoned once it became clear that there was a significant burden for harm.[2] As new information becomes available on preterm

Abbreviations: RCTs, Randomised Controlled Trials.

neonatal physiology, it is important we assess how we ensure their care is both safe and ethical.

3 | PAIN AND SKIN BREAKAGES IN THE NEONATAL PERIOD

Until comparatively recently, it was not felt that neonates could feel pain with procedures taking place with minimal sedation and analgesia. This paradigm has since been turned on its head with the revelation that not only do neonates feel pain but also at lower gestational ages are likely to experience even non-noxious stimuli as painful.[3] Analgesia is now a cornerstone of the management of the preterm newborn with a focus on minimal skin breakages to maintain their skin integrity and wherever possible for adequate pharmacological or non-pharmacological sedation and pain relief before invasive procedures.[3]

With this evolving understanding of pain in preterm neonates, there has also been research demonstrating long-lasting consequences to repeated painful stimuli in preterm infants. Recent neuroimaging studies which have demonstrated that repetitive procedural pain is associated with reductions in thalamic volume loss in the territory of the somatosensory thalamus and is accompanied by disruptions in thalamo-cortical pathway maturation.[4] A study by the same research group demonstrated that neonates with fewer skin breaks had a significantly larger thalamic volume.[5]

Neurodevelopmentally, a systematic review demonstrated that neonatal pain-related stress is associated with alterations of both early and late developmental outcomes including delayed postnatal growth, high cortical activation, poor cognitive and motor development at 1 year.[6] Changes have been demonstrated to persist in children until at least 7 years old with changes in rhythmicity and cortical thickness shown.[6]

Beyond neurodevelopmental concerns, immaturity of the neonatal skin makes it vulnerable to chemical damage, microbial infections and accounts for a compromised general health.[7] Additionally, the use of invasive procedures, including injections, is associated with an increased risk of infections.[8]

4 | EXPOSURES TO PAINFUL STIMULI IN THE NEONATAL TRIAL LITERATURE

Given this evolving picture of neurodevelopmental deficits in neonates with excess or repeated painful stimuli, is it morally right that a control group in this population has repeated skin pricks in order to successfully mask a placebo drug?

A recent high impact study examining the role of subcutaneous erythropoietin in prevention of adverse neurodevelopmental outcomes in preterm infants used sham subcutaneous saline injections in their control cohort.[9] While in an older, more neurodevelopmentally mature cohort this may well have been appropriate, given what we now know is this ethically right? It is worth noting during the recruitment phase of this particular study the evidence surrounding neurodevelopmental impacts of painful stimuli was still incomplete. There are other intramuscular/subcutaneous interventions which have been trialled in the neonatal literature such as glucagon and vitamin A which utilised a similar approach with the aim of maintaining a high standard of evidence generation. Additionally, a recent trial examining the role of enteral insulin in feed intolerance infants in the placebo group had twice daily blood glucose tests on the first four study days representing up to 8 additional skin breakages for the purposes of the trial. It is worth noting that per inclusion criteria these infants would have been low risk for hyperinsulinemia/hypoglycaemia (Table 1).[10]

TABLE 1 Selection of trials published in the literature with additional skin breakages as part of their control group protocol

Authors and year	Intervention	Additional painful stimuli
Juul et al., 2020	Subcutaneous Erythropoietin/Saline	Up to 24 subcutaneous injections[9]
Mank et al., 2022	Enteral insulin	Up to 4–8 additional skin breakages[10]
Shenai et al., 1987	Intramuscular Vitamin A	14 injections in 28 days[11]

While placebo-controlled RCTs have uncovered the benefits and risks of clinical interventions such as antenatal steroids, intratracheal surfactant and nitric oxide in congenital diaphragmatic hernia there is plethora of high-quality neonatal evidence generated by non-placebo-controlled trials, for example therapeutic hypothermia in moderate-severe hypoxic ischaemic encephalopathy. Strong evidence for clinical practice can be elucidated from stringent trial design with blinding at time of statistical analysis and neurodevelopmental assessment as opposed to at time of treatment allocation. Provided stringent randomisation occurs and in the context of a placebo which is likely to cause harm, we believe the exposure of control groups to painful stimuli should be avoided.

5 | CONCLUSIONS

When considering how we perform research in our preterm participants, it is important that we appropriately balance the burden on ourselves as researchers to produce the highest quality evidence possible with the absolute minimum burden of risk on infants we include in our studies. While therapies and diagnostics that require intravenous or intramuscular access are a reality of clinical practice, in the context of trials skin breakages should be limited as much as possible.

There is a substantial body of evidence that suggests that painful stimuli in the preterm population predisposes to poor neurodevelopmental outcomes. While in the past it has been considered ethical to randomise preterm infants to groups receiving 'sham' injections of saline, we propose this practice should be reconsidered in the context of future trials.

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CONFLICTS OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

MT and AF developed the concept of this paper. MT, DOR and AF drafted the manuscript and all reviewed the manuscript prior to submission.

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