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EDITORIAL

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'First, do no harm' – the use of analgesia or placebo as control for babies in painful clinical trials

The belief that babies could not feel pain nor needed pain relief prevailed not that long ago. It has been only three decades since the coinciding release of Anand's (1) seminal work which demonstrated that untreated pain in neonates leads to adverse effects and the media awareness campaign led by Jill Lawson after the death of her preterm son, Jeffrey, following surgical ligation of his patent ductus arteriosis without the benefit of any anaesthesia. The combination of these two events created a 'perfect storm' that led to a surge in attention to neonatal pain. Since that time, contributions to our understanding of the impact of early neonatal injury through animal models (2) as well as the biology of pain processes (3) have been made. In numerous human studies, there is now an accumulation of knowledge on the measurement and management of neonatal pain (4,5) and the immediate and long-term consequences of untreated repetitive pain-related stress including alteration in later perception of pain, cognition, executive functioning, brain development and behaviour (6,7). While many unanswered questions remain, we have had many successes. One achievement is that we have demonstrated strong evidence supporting effective ways to reduce procedural related behavioural pain response in newborns.

Yet despite the known associated adverse outcomes, procedural pain exposure in neonates is largely undermanaged and under-prioritised. High exposure to ubiquitous pain remains an everyday reality for infants requiring neonatal care. A recent systematic review conducted by Cruz and colleagues (8) including six studies reporting daily pain exposure over the first 14 days of age during NICU hospitalisation reported a range of 7.5–17 exposures per day. Bellieni and Johnston (9) in reporting the incidence of no treatment or placebo control for babies, provide a compelling picture that researchers have perpetuated the lack of provision of effective treatment by failing to provide standard of care to newborns enrolled in neonatal clinical pain trials. Previously published consensus statements and clinical guidelines report that over the past 2 ½ years, 32 of the 46 studies (70%) reporting on interventions to reduce pain associated with common neonatal procedures included a no treatment or placebo control group, thus exposing newborns to unnecessary harm. These findings were consistent with Harrison (10) who reported that 89% (111/125) of the studies examining the effectiveness of sweet-tasting solutions to reduce pain associated with commonly performed neonatal procedures included a no treatment or placebo control group.

The debate that these authors raise is, should researchers knowingly withhold an established effective treatment when conducting clinical trials in newborns? According to the Declaration of Helsinki and the review provided by Bellieni and Johnston (9), the answer would be no. So, why then, if the answer was this apparent, have almost three quarters of all the recent neonatal studies still been conducted in this manner? Bellieni and Johnston (9) identify numerous reasons why this may not be the case for neonatal research trials: the continued lack of awareness of the impact of untreated neonatal pain, lack of an infant's ability to consent or provide assent and lack of parental understanding of what effective treatments could be available to be able to provide an truly informed consent. Additionally, they describe the academic pressures that many researchers face to publish a positive trial with a large effect, and the benefits of requiring fewer associated resources due to the need for less participants when effect size are anticipated to be large when comparing novel interventions to a no treatment group. Beyond the actual conduct of the studies, Bellieni and Johnston (9) suggest that journal editors play a significant role in ensuring the ethical conduct of neonatal pain trials by not publishing results of studies with no treatment or placebo control groups. I would also argue that in addition to the editors, reviewers have a duty to acknowledge the unethical conduct of these studies and consider recommending a do not accept.

So, is there ever a time that the inclusion of a placebo or no treatment arm would be considered ethical? I would say, a cautious yes. As Bellieni and Johnston (9) point out, a no treatment control would be acceptable if there was no known effective intervention associated with the procedure being studied, as in the case of neonatal eye examinations for the diagnosis of retinopathy of prematurity. While it is true that we do not yet have a known effective intervention to reduce the pain associated with this procedure, I would contend that

it would still be unethical to simply include an absolute no treatment arm (i.e. an uncovered infant lying supine alone in a cot or incubator) without any form of comfort. A minimum standardised protocol should still be employed for the control group ensuring at least a minimum level of known comforting strategies such as positioning supports, swaddling or non-nutritive sucking to minimise stress and provide some regulatory support to the infant.

Bellieni and Johnston (9) also raise the concern related to the perceived acceptability of usual versus standard care as an acceptable control group. Proponents of usual care often refer to the TCPS (2014) Tri Council Policy Statement: Ethical Conduct for Research Involving Humans Proportionate risk which states that 'probability of harm is no more than one would encounter in daily life' to justify the ethical use of usual care in clinical trials as well as the conduct of naturalistic observation studies. As Bellieni and Johnston (9) point out, *two wrongs do not make a right*. One could argue that there is ample opportunity to observe the natural processes of pain even when best standards for pain are being followed. This is especially true given that our current treatments remain only moderately effective and that pain response in newborn is extremely variable (11). Lack of translation of research findings to clinicians, researchers and parents regarding effective pain relief for neonatal procedures is also at the very core of the problem. Lack of knowledge of current evidence may contribute to the issue of usual versus standard care and lack of awareness regarding clinical equipoise. Similar concerns regarding wide variations in the use of opioids, sedatives-hypnotics or general anaesthetics were recently reported from a large prospective cohort study by Carbajal et al., which included almost 7000 neonates admitted to one of 243 European NICUs during their initial month of hospitalisation (12).

Lastly, while it is imperative that we continue to attempt to better understand the newborn's experience of pain, subjecting newborns to untreated pain may not be the only way to provide answers to these questions. Continued emphasis should be placed on the creation of novel animal models simulating the neonatal context. Additionally, the utilisation of a nontissue damaging acute experimental stimuli such as the PinPrick MRC system described by Hartley and colleagues (13) holds excellent promise to help us better understand these questions.

In summary, regardless of our discipline I believe that the words 'First, do no harm' is a fundamental philosophy taught to all of us. We need to ask ourselves, why is it that this value does not equate to ensuring that our tiniest of patients are spared from needless suffering? It would certainly be unlikely that we would conduct such a trial examining a novel approach to treat diabetes using a no treatment control group. Alternatively, it would be expected that one would conduct a comparison, equivalence or noninferiority trial to determine whether one treatment is more or as effective as evidence based treatments. While no treatment control trials should be limited, this in no way means that studies related to effective neonatal pain care should be halted. Rather, future studies should focus on the most effective treatment associated with each procedure alone and in combination with other treatments, differences in responses across gestational age, the sustained effectiveness of these interventions over time, and the impact of their use on longer term outcomes. Studies examining ways to combine and balance these treatments with analgesics and sedatives to achieve optimal pain relief with less prolonged exposure to medications is also important. Lastly, to ensure that every baby receives optimal care, the importance of studies examining ways to improve uptake of effective pain relieving interventions into clinical care cannot be over emphasised.

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