Editorial Commentary

Parental participation in neonatal heel lance pain management

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Introduction

Soon after birth infants may undergo medical procedures necessary for their wellbeing. Some of these may be painful. One such is collection of a small blood sample by heel lance skin laceration, often called a heel prick. The desire to minimize pain is important. The use of various non-pharmacological approaches for babies is desirable. These can involve the soothing effect of skin-to-skin contact such as massage and the use of swaddling. However, the mechanisms responsible for the analgesic effect of these interventions are not well understood.

This article discusses the findings and implications of a recent British study by Hauck *et al.* to test whether gentle leg stroking ameliorated the expected pain induced by heel lance (a noxious stimulus) as compared with standard care in neonates (i.e., babies aged 0–4 weeks) (1). It then went on to discuss neural mechanisms involved in pain in neonates.

Pilot studies

The authors cite two independent pilot studies that found when a trained researcher stroked the skin of babies with a calibrated brush at approximately 3 cm per second before the heel lance, there was an approximately 40% reduction in activity of brain regions that respond to noxious stimuli (2,3). Hauck *et al.* wanted to test whether a similar intervention, but instead that involved parents stroking their neonate, would have the same effect.

How the parental stroking study was conducted

The authors conducted a multicentre, randomized, two-arm, parallel, controlled, superiority trial—the Parental Touch Trial (Petal)—in which parents stroked their baby for 10 seconds at a speed of approximately 3 cm per second, which was regarded as optimal for activation of C-tactile nerve fibres. The latter are unmyelinated slow conducting afferent fibres present in skin with hair (4,5). These fibers encode the affective dimensions of touch (4). The optimum response of C-fibers is achieved by gentle touch in a caressing motion. The optimal range of gentle touch that C-fibers respond to is 1–10 cm/s at skin temperature (6). It is known that adults perceive stroking at this speed as pleasant (6-9). Based on self-report, skin stroking is able to decrease pain and diminish clinically determined brain activity (7-9). In infants, such stroking has a calming effect based on its ability to slow heart rate (10-12). Since watching a painful procedure could cause anxiety and distress to parents (13), parental anxiety was evaluated as a secondary outcome.

Two centres were involved—the John Radcliff Hospital in Oxford and the Royal Devon and Exeter Hospital. Selection criteria included birth at ≥35 weeks of gestational age, being less than 8 days old at the time of the intervention and needing to have a heel lance for blood collection and testing. Neonates with adverse clinical conditions,

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neurodevelopmental impairments, any who had been administered with analgesics or sedatives in the 24 hours preceding the study or born to a mother with a history of mood-altering substances use were excluded.

The study recruited 112 neonates. These underwent rigorous 1:1 randomization into two equal groups—intervention and control—that were matched for gestational age at birth, postnatal age at study, sex, demographic similarity, and primary reason for blood collection. The primary outcome involved noxious-evoked brain activity measured by a noxious-neurodynamic response function (n-NRF) in which a fix-shaped waveform was fitted to each neonate's electroencephalogram (EEG) record. n-NRF was measured 400–700 milliseconds after stimulation.

In the intervention group, the parental tactile stimulation was applied before the heel lance procedure and in the control groups, the same stimulation was applied at least 30 seconds after the heel lance procedure. Blood collection took place at least 30 seconds after the heel lance. The slight delay was to ensure blood collection did not affect the Premature Infant Pain Profile-Revised (PIPP-R) (14) score. Vital signs were measured continuously from half an hour prior to the procedure to half an hour after by electrocardiogram and pulse oximetry. Neonatal EEG recording at 8 standard sites on the scalp began 10 minutes before and ended 10 minutes after the heel lance. Comfort measures such as swaddling and non-nutritive suckling were offered to all neonates.

Before the heel lance, a sham heel lance using the back of the blade was applied to determine the neonate's response to a non-noxious intervention. Video recordings were made of the baby's facial expressions in order to categorize the behavioral state of the baby throughout. The start and end of the parental stroking were time-locked to the recordings of vital signs by automated or manual means. The time of the sham and heel lance were identified in the video recordings by a researcher activating an LED light. The primary outcome measure was magnitude of noxious-evoked brain activity. There were also several secondary outcome measures: PIPP-R score, development of tachycardia, and score for parental anxiety. The pain score range spanned 0–21, where 0= no pain, 1–6= mild pain, 7–12= moderate pain, greater than 12= severe pain. Tachycardia from heel lance was heart rate ≥160 beats per minute at any time during the 30 seconds after heel lancing compared with <160 beats per minute in the 15 second baseline period. Parent anxiety score, measured with the State-Trait Anxiety Indicator-Subscale (STAI-S), which ranges from a low of 20 to a maximum of 80 (high anxiety), with mean score in working adults being 35, compared with approximately 50 for parents of neonates admitted to a neonatal intensive care unit (NICU).

The mean age of the neonates who participated was 38.6 weeks (range, 37.2–40.3 weeks), 61% were male and 35% female, 81% were white, median weight at birth was 3.30 kg (range, 2.77–3.77 kg), median number of prior painful procedures was 4. The reasons for having a blood test were bilirubin assay to test for jaundice (48% of neonates), infection marker analysis to test for sepsis management (29%), blood spot screening (7%), glucose monitoring (5%), and 10% for other reasons such as urea and hemoglobin measurement. Parent stroking proportion was mothers 65% and fathers 35%. There were 56 neonates in each study group. Non-adherence to the protocol, such as parental stroking more than 45 seconds before the heel lance, included 5 neonates from the primary outcome, 7 from the secondary (PIPP-R) outcome, and 8 from the secondary tachycardia outcome.

What the trial found

The primary outcome (n-NRF) did not differ significantly between the intervention and control groups: 0.85±0.70 arbitrary units and 0.91±0.76 arbitrary units, respectively. The mean time between stoking commencement and heel lance was 16.9 seconds (range, 11.6–33.0 seconds). As for the secondary outcomes, none differed significantly between intervention and control: PIPP-R 8.08±3.17 *vs.* 7.20±3.56, tachycardia frequency 21% *vs.* 15%, parental anxiety STAI-S 33.8±12.2 *vs.* 30.1±9.87.

Why parent stroking failed to replicate mechanical device

These results were at odds with the results of the pilot investigations in which the protocol was the same as in the parental stroke randomized controlled trial (RCT) except for the use of a mechanical calibrated brush for stimulation rather than a parent's hand to apply gentle touch, which had an extra benefit of being applied at skin temperature when C-tactile fibers respond optimally. The advantage of the stimulation applied by researchers in the pilot studies was the precision obtained in the timing of the stimulus immediately before the heel lance. Parents could not achieve such a degree of accuracy. Moreover, in the Petal trial, there was a 16.9 (range, 11.6–33.0) second gap between the parent stroking and the heel lance in the intervention group. This was deemed important as delaying the time from C-fiber stimulation and the noxious heel lance stimulus by as little as 5 seconds is known to reduce the efficacy of the intended analgesic intervention (8).

The authors of the study surmised that it might have been better if they had allowed the parents to stroke their baby for longer, i.e., throughout the heel lancing and blood collection. In further self-criticism of the protocol used Hauck *et al.* pointed out that because the parents were watching a computer animation displaying the speed and direction of the strokes, this inadvertently created an unnatural set of circumstances, unlike the more probable natural intuitive means by which parents comfort their babies. Because the parents' movements when complying with the protocol become more mechanical and oriented on the task at hand, there was a potential for failing to achieve the normal parent-to-infant bonding. These two factors may have contributed to less natural touch, so risking the baby becoming aroused and failing to optimize the desired pain relief mediated by C-fibers. Previous studies showed benefits when parents stroked their baby for a few minutes (12). However, there is no evidence that stroking for the few seconds stipulated in the Petal trial would soothe a baby. During interactions with infants, parents intuitively stroke their babies at speeds optimal for C-tactile nerve stimulation (12,15). Although the trial failed to reject the null hypothesis, the authors suggested that the study did highlight the importance of involving parents in provision of care for their babies during procedures that may be painful. The parents reported that being able to do as they did resulted in them feeling "reassuring" and "useful".

The way forward

Hauck *et al.* called for further studies on mechanisms and optimization so that improvements in information on administration of various non-pharmaceutical means of analgesia leading to the development of better guidelines for their use. Besides parental stroking, they mention the use of other effective means of providing skin-to-skin contact, such as "kangaroo care" which, like marsupial behavior, involves ventral maternal-infant contact (16), and safe pacifiers such as sucrose (17), and oral stimulation by non-nutritive sucking by the baby on a pacifier (18).

Neurological aspects of pain perception

The nociceptive system is a sensory component to the peripheral and central nervous systems. Pain activates nociceptors in skin, leading to transmission of signals via the peripheral nervous system to the dorsal horn in the spinal cord from where they are transmitted to the central nervous system (19). The areas of the brain associated with pain are: medial prefrontal cortex (mPFC), which represents the affective aspect of pain, dorsolateral prefrontal cortex (DLPFC) involved in localizing painful stimuli, orbitofrontal cortex (a link between painful area discrimination, memory and emotion), anterior cingulate cortex, which is part of the "pain matrix" that consistently responds to painful stimuli, and which also includes the thalamus and insula.

The nociceptive system involves the sensory component to the peripheral and central nervous systems. Brain regions having pain-related sensory and affective components are active in the neonatal period and infancy, so dispelling the misconception prior to 1980 that neonates do not experience pain (20). A review found evidence that despite the immature nervous systems of neonates, neonates not only experience pain, but are hypersensitive to it (20). It has been suggested, moreover, that the pain experience in infancy could conceivably resemble the experience of pain in adults (21). Administration of noxious stimuli to infants activates 18 of the 20 adult brain regions activated during pain (21).

The developing nociceptive system shows development-related plasticity and this can be influenced by painful medical procedures such as those that take place in an NICU (22,23). A study in Germany found that amongst children aged 11–16 years, those who had been treated in an NICU and who were born pre-term, a moderate 30 seconds heat stimulus (but not exposure to comfortable warmth) caused the activation of the thalamus, anterior cingulate cortex, cerebellum, basal ganglia, and periaqueductal gray regions of the brain (22). Amongst children who had been born full-term and had been treated in an NICU, activation of the primary somatosensory cortex, anterior cingulate cortex, and insula was seen, but there was no response in any of these regions in children born full term and not treated in an NICU. In a Canadian study, procedural pain experienced by preterm infants was associated with reduced white matter and subcortical gray matter at 40 weeks of age (24). A study in London, of children aged 9–12 years who had undergone cardiac surgery as infants found that they were less sensitive to touch and were only able to detect uncomfortable heat when temperature on the thoracic scar region was raised substantially (25).

In any study of changes in brain activity in response to painful interventions in NICUs, a confounding factor can be the influence of anesthesia if it is used. Depending on the study design to exclude this possibility, the outcomes ascribed to pain, may include or be solely due to the effect of general anesthesia on nociceptive regions of the brain (26). For heel lance, in particular during the Petal trial by Hauck *et al.* (1), anesthesia was not used.

Painful procedures to which neonates are subjected

In addition to heel lancing, various other painful procedures are often performed in NICUs. These include tracheal intubation, tracheal suctioning, insertion of catheters, placement of chest tubes, lumbar puncture, and subcutaneous or intramuscular injections. Neonates can experience 300 or more painful procedures during their hospital stay (20). These tend to be underestimated and under-treated. It is noteworthy that neural development extends from the embryonic period right through to adolescence (27). Moreover, nociceptive pathways are functional in the perinatal and neonatal periods, as evident from physiological and behavioral responses (28). In preterm and term neonates neurophysiological recordings and neuroimaging can quantify the responses to noxious stimuli of nociceptive pathways, such as occur during surgical procedures in NICUs.

Since the neonatal nervous system is immature, sensory processing within the spinal cord exhibits lower thresholds for excitation and sensitization, potentially resulting in tissue-damaging inputs to the brain (29). Moreover, in the neonatal period, both peripheral and central sensory connections exhibit plasticity. Such early damage may result in prolonged structural and functional alterations in pain pathways, and these can persist into adulthood (29). As pointed out earlier and in the latter review, neonates may actually be hypersensitive to painful stimuli.

Assessment of pain in neonates

In neonates, pain can be assessed by rating changes in facial expression, percent cry duration, and visual analogue scale pain rating. An RCT was conducted to investigate interventions to reduce pain amongst 200 neonates of 26–36 weeks gestational age requiring heel-prick for bedside glucose assessment (30). All premature neonates were given expressed breast milk during the procedure. Using the Sheffe's test, the study found that PIPP score (on recorded videos) was 33% lower in the study's Kangaroo mother care group (P<0.001) and 26% lower in the study's Kangaroo mother care with music therapy group (P=0.001) as compared to the control group PIPP score. But it did not differ significantly between the control group and music therapy alone group. These data complement the heel-stroking data of Hauck *et al.* Another systematic review of non-pharmacological pain management in neonates found no effect (31).

A review described the vital importance of pain assessment of preterm and term neonates in NICUs because of the prevalence of procedural and postoperative pain (32). Of over 40 tools available, 2 have been validated in premature infants. Importantly, the latter review also pointed out that preterm neonates do not display pain behaviors and physiological indicators as reliably and specifically as full-term infants.

Findings on non-pharmacological interventions generally

A recent systematic review compiled the findings on kangaroo-mother care, breastfeeding, oral sucrose and non-nutritive sucking on pain during heel lance in neonates as assessed by PIPP, heart rate, and oxygen saturation (33). None were statistically significant in reducing neonatal pain (5% higher, 2% lower, and 12% lower, respectively). There was, however, a small contribution to reduction in pain score and to faster stabilization of vital signs. An extensive Cochrane review in 2023 of RCTs of non-pharmacological management of procedural pain in infancy, involving 138 studies, found non-nutritive sucking, facilitated tucking, and swaddling may reduce pain behaviours in neonates born preterm, while non-nutritive sucking may reduce pain behaviours in full-term neonates. Despite a large body of evidence, no interventions showed promise in reducing pain behaviours in older infants (34). This Cochrane review found that most analyses were of very low or low certainty grades of evidence, with none based on high-quality evidence.

Consequences of pain in neonates

Painful experiences could have long-term sequelae, such as on growth (35). brain and somatosensory development (24,36-38) and subsequent behavior (37). Short-term consequences include tolerance, withdrawal, and ventilator dependency, whereas the long-term consequences are not well known (36,39). The low tactile threshold of preterm infants coupled with unstable immature physiological systems can increase their vulnerability to the effects of repeated invasive procedures on allostatic load (39).

Brain-oriented approaches may become available in the future. Meanwhile, neonatal pain assessment tools must be taught, implemented, and their use optimized for consistent, reproducible, safe, and effective treatment.

Is neonatal pain remembered in the short term?

In an attempt to determine whether neonates remember pain, a classic study in *The Lancet* by Taddio *et al.* of neonatal male circumcision (NMC) performed without anesthesia found that pain response indicators—percentage facial action, percent cry duration, and visual analogue scale pain rating (each scored by a research assistant from videotaped recordings)—during subsequent routine vaccination at age 4–6 months were higher than in demographically-matched uncircumcised boys (40). The findings suggested that memory of pain affected subsequent pain perception and response to pain. A subsequent double-blind RCT by Taddio *et al.* found that use of local anesthetic (topical EMLA cream applied 60–80 minutes prior to NMC) resulted in significantly lower pain scores during subsequent vaccination (41). It would be interesting to perform a study like this, comparing neonates who had heel lance with those who did not, to see whether there was a greater response in the heel lance group than the control. As well, this should be done for heel lance with *vs.* heel lance without local anesthesia (such as EMLA, or the more recent LMX4 cream).

Although the pain experienced by the mother while giving birth is well appreciated, rarely mentioned is the potential pain from the mechanical pressure on the neonate as it travels through the vaginal canal during birth. Resilience mechanisms in mother and baby during parturition should be applied to dampen the pain. Newborns delivered vaginally show higher pain expression than those delivered by cesarean section (42). It would be interesting to perform studies of various painful procedures comparing neonates delivered vaginally *vs.* neonates delivered by cesarean section.

Does neonatal pain have long-term consequences?

Pain during NICU procedures can influence neurodevelopment as well as somatosensory and emotional aspects of the pain response at older ages, especially in those born preterm or very preterm (43). The latter review found that this includes tissue-breaking procedures such as heel lance and neonatal surgery. Data are available on long-term effects of NMC performed in hospital and family medicine settings. A longitudinal study of NMC in a New Zealand birth cohort comparing NMC intervention *vs.* no intervention in an era when local anesthetic was not used examined participants annually from age 1 to age 16 years for cognitive ability, namely, IQ at age 8–9 years, and scholastic ability at age 13 years (44). The study found no statistical difference between each group. In a US study, survey data on the idiopathic personality trait known as alexithymia (characterized by difficulty identifying and describing an individual's own, or other peoples' emotions, social attachment, and interpersonal relations) also found no statistical difference between men of contrasting NMC status (45).

Although there have been no studies in adults who had received a heel lance as neonates, there are data for 21 socio-affective processing traits or behaviors amongst 408 US men who had received NMC *vs.* 211 who had not (46). The study concluded those who had received NMC had higher levels of avoidance and anxiety, perceived stress, and emotional instability, but no difference in empathy and trust, stating "*The psychological differences that we found … are not sufficiently severe in themselves to be suggestive of pathology*". Critics corrected the data for multiple testing using a Holm-Bonferroni method and found that only sociosexual desire (18% higher), dyadic sexual libido/drive (7% higher), and stress (14% higher) remained significant among men who had received NMC (45). Contrary to their expectations that empathy would be lower in the NMC group because of the known association of painful NICU procedures with lower volume of brain structures associated with empathic processing (47,48), namely subcortical gray matter and white matter in frontal and parietal regions (24,49), the study found no difference in empathy.

Conclusions

A recent RCT found parental stroking for 10 seconds, at a speed optimal for activation of C-tactile nerve fibers, delivered 10 seconds before heel lance of neonates for blood collection did not affect activity of brain centers that respond to pain, nor did stroking counter tachycardia seen in some neonates. The authors, Hauck *et al.*, suggested that the study should be repeated after modifications such as allowing intuitive dynamic tactile parental stroking rather than stroking guided by a video and allowing stroking continuously for the entire period leading up to the heel lance event, rather than being guided by a timer alerting the parent to start or stop stroking. The present review draws attention to related issues, such as other painful procedures performed in NICUs, assessment of pain in neonates, undertreatment, non-pharmacological approaches to pain reduction, as well as short- and long-term consequences of pain in neonates.

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