Microcirculation – a tool for the study of pain in neonates and infants?

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Abstract

The relationship between pain and the newborn's microcirculation has been a poorly understood field of research. Introduction of orthogonal polarization spectral (OPS) imaging and sidestream dark field (SDF) imaging to clinical medicine has opened a new field of monitoring and target treatment in various neonatal diseases and states. The non-invasiveness and safety of these bedside technologies make them very favorable in bringing us closer to a better understanding of the impact of pain on the newborn's microcirculation. Early and long term impact of neonatal/infant pain syndrome, current tools of pain assessment in neonates and infants as well as infant microcirculation will be discussed.

Key words: microcirculation, pain, neonates, orthogonal polarization spectral (OPS), sidestream dark field (SDF)

Introduction

Pain is defined by the International Association of Pain as unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage. Pain is always subjective (1). This definition faces two obstacles in neonates and infants. Firstly, emotional experiences require subjective expression. This is impossible in the usual sense in the preverbal neonate when even the individual behavioural cues are nonspecific (e.g. cry of hunger, discomfort, pain). Secondly, if this experience is based on previous "actual or potential" tissue damage, from where has the newborn gained the experience and how long does she or he have to gather it before it is subjectively pain. No surprise till the 1980's scientists assumed that neonates and infants were unable to feel pain and, even if they could feel pain,

this was not considered important because they would not remember it anyway (2). The reason for this old view that neonates do not feel pain included inadequate myelination, immature receptors, modified transmission in immature nerve tissue, higher plasma concentrations of B-endorphins and increased permeability of the blood brain barrier (24). In reality, pain pathways are myelinated in the fetus during the second and third trimesters and are completely myelinated by 30 to 37 weeks of gestation. Moreover uncompleted myelinated or unmyelinated fibers are still able to carry pain stimuli. Incomplete myelination only results in slower transmission (3).

In 1987 Anand and Hickey proved that the anatomical requirements for pain are in place prior to birth (3). Anand and Craig disputed that pain is a learned phenomenon maintaining that it is an inherent quality of life itself and expressed by all viable living

organisms and while it is influenced by life's events it does not require prior experience in the first instance (4). This led to a further clarification in 2001, when the following statement was added to the prior definition: „the inability to communicate in no way negates the possibility that an individual is experiencing pain and is in need of appropriate pain relieving treatment", highlighting the importance of pain assessment and intervention in all populations, including infants and neonates (5).

Further evidence suggested that infants not only experience pain, they experience it more acutely than adults (6-8). Neural pathways for afferent/ascending pain transmission are present in even the smallest preterm infant (4, 9). However, the immaturity of the central nervous system (CNS) as a whole makes them unable to modulate and ill equipped to cope with their pain experience through internal or external mechanisms (11). Fitzgerald et al. (12) studied developmental changes in the threshold for the flexor withdrawal reflex, because it closely corresponds with the pain threshold and is exquisitely sensitive to inhibition by opioids and other analgesics. Flexor reflex thresholds were directly related with increasing gestational age, with significantly lower thresholds in preterm neonates as compared to term neonates. In addition to mechanical stimuli (12), pain thresholds measured by thermal stimuli were also decreased in neonatal rat pups as compared to older rats (13). Repeated stimulation and local tissue injury were associated with prolonged periods of sensory hypersensitivity in neonatal rat pups or preterm neonates (12, 14), and these changes were abolished by topical analgesia (15). The early and abundant expression of putative neurotransmitters mediating nociception, and delayed expression of descending inhibitory neurotransmitters (16, 17, 18) further indicate an increased excitability in the dorsal horn of the premature spinal cord. An increased magnitude of hormonal, metabolic or cardiovascular responses to surgical operations in preterm and term neonates (19, 20), and higher plasma concentrations of analgesics and anesthetics required to produce clinical signs of anesthesia in neonates as compared to older age groups (21-23), also indirectly support the concept of increased pain sensitivity. In 2000, Anand et al. suggested that the preterm infant may have increased sensitivity to pain compared with older children and adults because of a lack of neurotransmitters in the descending tract. This suggests that inhibitory mechanisms may be lacking (25).

A recently published report from the Royal College of Obstetricians and Gynecologists (2010) concluded that the human fetus is not able to feel pain at 24 weeks and is in an unconscious state while in the womb. The report highlighted that, after 24 weeks gestation, there is continuing development and elaboration of intracortical networks. It also indicated that, when the newborn preterm neonate is exposed to noxious stimuli, the cortical responses necessary to experience pain, are produced (26).

Epidemiology

Even the healthiest neonate will face painful experiences during the first hours or days of life. The intramuscular vitamin K injection and the third-day screening test are unavoidable painful stimuli that occur during the first week. Neonates who are small for gestational age and infants born to diabetic mothers undergo heel lancing to monitor their blood glucose concentrations.

Newborns routinely undergo painful invasive procedures, even after uncomplicated birth. For obvious reasons, these invasive procedures that cause pain or distress are more frequently performed on infants admitted to the neonatal intensive care unit (NICU). For sick babies, multiple studies have documented a high frequency of invasive procedures during neonatal intensive care, particularly in preterm neonates (27,28). The most frequent procedures performed in NICUs are heel sticks, endotra-

cheal suctions, and venous and arterial punctures (28, 29).

Notwithstanding an increased awareness among clinicians regarding neonatal pain, management of procedural pain in neonates is not yet optimal. A prospective, multicenter study, conducted in a large geographically defined population, documented the epidemiology and management of neonatal painful and stressful procedures in neonates admitted to ICUs (29). This study demonstrated that neonates undergo numerous painful and stressful procedures during the first 14 days of intensive care, that the frequency of painful procedures does not markedly decrease during the ICU stay, that some common procedures require four or more attempts to be terminated in almost a fifth of neonates, and that many of the documented painful procedures were not accompanied by analgesia. The mean number of painful and painful plus stressful procedures per day were 12 and 16, respectively; some neonates experiencing as many as 62 procedures per day (29). Of all painful procedures, 2.1% were performed with specific preprocedural pharmacological-only therapy, 18.2% with nonpharmacological-only interventions, 20.8% with pharmacological, nonpharmacological or both types of therapy and 79.2% without specific analgesia; 34.2% were performed while the neonate was receiving concurrent analgesic or anesthetic infusions for other reasons. Prematurity, category of procedure, parental presence, surgery, daytime and day of procedure after the first day of admission were associated with greater use of specific pre-procedural analgesia, whereas mechanical ventilation, non-invasive ventilation and administration of nonspecific concurrent analgesia were associated with lower use of specific pre-procedural analgesia (29). To assess how frequently analgesics were used for invasive procedures, Simons et al (30) prospectively recorded all painful procedures and analgesic therapy used during the first 14 days of NICU admission in 151 neonates. Each neonate was subjected to a mean of 14 procedures per day. Whereas many procedures (26 of 31 listed) were estimated to be painful, <35% of neonates per study day received preventive analgesic therapy, and 39.7% of the neonates did not receive any analgesic therapy in the NICU.

Some congenital or neonatal conditions such as limb amputation, birth lesions of the brachial plexus, and medullary lesion, can also lead to neuropathic pain that is difficult to assess in the neonate (31).

Early and long term impact of neonatal/infant pain syndrome

Noxious influences may be episodic and related to specific procedures (procedural pain), or may be more chronic in nature. Systematic laboratory and clinical studies of neonatal pain have demonstrated that 1. neonates exhibit a physiological increased sensitivity to pain, 2. preterm neonates develop prolonged hyperalgesia after acute painful stimuli, leading to established or chronic pain, 3. there is a possibility that the acute physiological responses to painful stimuli may cause or extend early intraventricular hemorrhage (IVH) or ischemia leading to periventricular leukomalacia (PVL) and there are possible associations between the neurobehavioral and developmental sequelae resulting from premature birth and the exposure to repetitive painful experiences during neonatal intensive care (4, 32).

Early neurological injury to the newborn is related to the acute episodic pain. Following exposure to painful stimuli, physiologic responses are expressed as acute increases in heart rate, blood pressure, heart rate variability, intracranial pressure and decreased arterial oxygen saturation. These physiologic responses, due to their magnitude and rapidity, may cause reperfusion injury and venous congestion leading to IVH and/or PVL. In ventilated neonates, the diaphragmatic splinting associated with acute pain leads to substantial changes in intrathoracic pressure, reflected in clinically significant alterations

in intracranial blood volume and cerebral blood flow. Vagal responses following invasive procedures such as feeding tube insertion, tracheal suctioning or heel sticks lead to substantial changes in cerebral blood flow and oxygen delivery. It has been demonstrated that the occurrence of such events in the 4 days after birth is associated with the sonographic findings predicting later neurodevelopmental sequelae. Thus, physiologic responses to venipuncture, endotracheal suctioning, nursing procedures and mechanical ventilation may enhance the vulnerability of preterm neonates to stress-related complications. Hemorrhage occurs within the first 24 h after birth in more than half of all preterm neonates who will ever develop IVH, and more than 95% of all events occur at less than 5 days of age. The acute physiologic effects of pain and stress and the temporal association of early IVH with the multiple painful procedures required just after birth demonstrate a role for pain/stress in the causality of early neurologic injury. Behavioral and physiologic responses to repetitive pain may lead to an extension of the early IVH caused by perinatal factors, or directly contribute to the hypoxia, hypercarbia, acidosis, hyperglycemia, ventilator dissynchrony and pneumothoraces, all of which have been correlated with late IVH or the extension of early IVH (33).

Possible long term effects of early exposure to neonatal pain can be seen even in neonates who did not develop IVH or PVL and who are assessed as neurologically intact in later childhood, they may show abnormal behavior as a result of their exposure to repetitive pain. Both singular (e.g. circumcision) and repetitive (e.g. heel lances) painful procedures may have long-term consequences in full-term or prematurely born neonates (34-37)

Preterm neonates born at 28 weeks and exposed to routine NICU care for 4 weeks (32 weeks post-conception) were compared with neonates who were born at 32nd week of gestation. Both groups were assessed during a heel stick procedure. The preterm neonates who had experienced 4 weeks of NICU therapy manifested decreased behavioral responses and increased cardiovascular responses to pain of a heel stick as compared with neonates born at 32nd week. These responses were strongly correlated with the number of invasive procedures experienced since birth, rather than other clinical factors such as age, Apgar score, birth weight, severity of illness. In another study, neonates who underwent unanesthetized circumcision manifested changes in their behavior for prolonged periods of time and an increased behavioral responsiveness to the pain of vaccination at 4–5 months of age. In addition, stressful conditions at birth were similarly associated with increased salivary cortisol responses to vaccination at 4 and 6 months of age. These data suggest that early environmental programming of the hormonal and the behavioral stress responses may persist during later infancy (33).

Recently, Walker et al. (38) showed a generalized decreased sensitivity to all thermal modalities but not in mechanical sensitivity in 43 children at 11 years of age recruited from the UK EPICure cohort (born at < 26 weeks' gestation in 1995) compared with 43 full-term controls. This suggests centrally mediated alterations in the modulation of C-fiber nociceptive pathways, which may have an impact on the child's response to future pain or surgery.

Relatively few studies have assessed long-term effects of early surgery on pain sensitivity later in life (39). Peters et al. (40, 41) found that infants who had undergone surgery within the first 3 months of life in combination with adequate analgesia demonstrated higher sensitivity to subsequent surgery in the same dermatome. These infants needed more intraoperative fentanyl, had higher pain scores, had greater norepinephrine plasma concentrations, and needed more morphine than did infants with no prior surgery. Developmental alterations in spinal and supraspinal processing were the proposed mechanisms for this higher sensitivity (40, 41). Neonates suffering from uni-

lateral hydronephrosis three months after pyeloplasty demonstrated greater tenderness to mechanical stimuli both in the area of incision and on the unaffected contralateral side of the body than age-matched controls (40, 41). Most interesting was the fact that hyperalgesia did not differ between infants who were treated conservatively or by surgical intervention, suggesting that the visceral nociception might be responsible for the long-term effects. Fitzgerald and colleagues (42, 43) showed that this localized hyperalgesia might even persist for 8 to 10 years after abdominal or thoracic surgery in early infancy, both on the ipsilateral and contralateral side.

Current literature suggests that repeated noxious stimuli can lead to chronic neuropathic states so that normally innocuous stimuli can produce pain (44). Therefore, minimizing and managing neonatal pain is required to promote normal growth and development and to reduce any potential long-term sequelae. Thus the crucial and most important step must be adequate assessment.

Current tools of pain assessment in neonates and infants

Infant pain assessment is challenging because infants are unable to verbalize the presence and intensity of their pain. Further, the younger preterm infant may have diminished responsiveness due to nervous system and musculoskeletal immaturity (45), which makes most of the current neonatal pain scales, that depend on facial expression and musculoskeletal movements more challenging. The main goal of pain assessment is to identify an infant's potentially painful condition, quantify the pain level, and predict the need for an intervention (46).

Pain can be assessed by unidimensional or multidimensional approaches (46). Most available pediatric pain scales are multi-dimensional, including both behavioral (facial expression, crying, gross motor movement, changes in behavioral state, and functioning) and physiologic indicators (heart rate, blood pressure, etc.). Even though these two dimensions do not much correlate yet, when they exist together in a single infant pain scale, makes the assessment more efficient (46).

Despite the availability of over 40 pain assessment tools, there is still no consensus on the best method for measuring and treating pain in newborns. One group of commonly used infant pain scales, depends on procedural pain as the main pain stimulus, can be used for term and preterm neonates and depends on a combination of increased heart rate, brow bulging, eye squeezing, tongue protrusion, crying, breathing patterns, state of arousal. This group of pain scales includes the Premature Infant Pain Profile (47), Neonatal Facial Coding Scale (48), and the Neonatal Infant Pain Scale (49). The CRIES score (50) depends on prolonged postoperative pain as the pain stimuli and used indicators such, crying, requirement of increased oxygenation administration, increased vital signs, facial expressions and sleepiness.

In situations associated with persistent pain or discomfort, an attempt should be made to assess its intensity and the effectiveness of analgesic treatment using a validated measure for pain assessment such as the Echelle Douleur Inconfort Nouveau-né (EDIN) (51) or the Neonatal Pain Agitation and Sedation Scale (52).

These latter scales have been developed for prolonged pain in neonates; however, construct validity has not yet been established for the EDIN. A recent study (53) showed that EDIN scores were positively associated with gestational age, and that postnatal age, sepsis, and presence of respiratory support also influenced the EDIN score.

Neonatal pain should always be assessed systematically. Pain assessment should be performed every 4–6 hours or as indicated by the pain scores or clinical condition. It's recommended to choose a multidimensional scale that includes contextual, behavioral, and physiologic indicators.

The infant microcirculation

Physiological alterations during pain have been studied mostly at the macrohemodynamic level. Alterations are manifested as acute increases in heart rate, blood pressure, heart rate variability, increase in intracranial pressure and decreased arterial oxygen saturations (54, 55). Tousiquant-Laflamme et al. studied the relationship between pain and the heart rate. In their experiments they showed that pain could elicit a rise in heart rate up to 11%. They also showed that the relationship between heart rate response and pain was gender related, i.e. it was only found in male subjects. Therefore, heart rate should not be used for pain evaluation in female subjects (56).

In newborns studies have shown that pain produces many physiological changes and all invasive procedures lead to undesirable stress responses. Lagercrantz et al. (57), determined plasma catecholamines in arterial blood from infants in a neonatal ward before and after various management procedures. Special care led to a 60% increase in plasma noradrenaline levels, whereas the adrenaline concentrations were not significantly affected. Stevens and Johnston (58) looked at the physiological response to painful stimuli in preterm infants. The study involved 124 preterm infants with gestational ages 32-34 weeks. They analyzed heart rate, oxygen saturation, and intracranial pressure during heel stick and heel squeeze tests. Significant increases in heart rate and intracranial pressure and significant decreases in oxygen saturation were found between baseline and heel-stick phases and between baseline and heel-squeeze phases.

The microcirculation is influenced by the increased sympathetic tone produced as a response to painful stimuli. Several studies have reported changes in microcirculation in subjects with long-standing neck and shoulder myalgia. Oxygenation and blood flow are the two commonly investigated parameters (59). Larsson et al. (60) showed that subjects with trapezius myalgia had impaired muscle blood flow in the painful side during static contraction at different levels, compared to controls. Cagine et al. (59) investigated oxygen saturation and blood flow in different parts of the trapezius muscle in office workers with and without trapezius myalgia during a standardized computer task lasting 60 minutes. They showed a significant decrease in oxygen saturation and blood flow, thus highlighting the effect of stress on muscle microcirculation during work load. Groeneweg et al. (61) suggested that endothelial dysfunction was the mediator of the impaired microcirculation during the chronic stage of complex regional pain syndrome (CRPS).They did so by examining the distribution of endothelial nitric oxide synthase (eNOS) and endothelin-1(ET-1) relative to vascular density represented by the endothelial marker CD31-immunoreactivity in the skin tissue of patients with chronic CRPS (64). Codere et al. (62) suggested that in at least a subset of CRPS patients, the fundamental cause of the abnormal pain sensations is ischemia and inflammation due to microvascular pathology in deep tissues, leading to a combination of inflammatory and neuropathic pain processes. Quattrini et al. (63) investigated the cutaneous microcirculation of the foot by laser Doppler flowmetry, in patients suffering from painful diabetic neuropathy. They found a significant impairment in vasoreactivity and flow in subjects suffering from painful diabetic neuropathy.

The relationship between pain and the newborn's microcirculation is a field that gains less or no focus from researchers. Most of the studies investigating the newborn's microcirculation focuses on the critically ill newborn (64, 65). They aim at utilizing the microcirculation in optimizing the newborns conditions in neonatal intensive care units. Genzel-Boroviczny et al. (66) used orthogonal polarization spectral imaging (OPS), to study the effect of blood transfusion on the microcirculation in anemic infants. They found a significant increase in functional capillary density 2 h after transfusion with an

additional significant rise after 24 h (66). Interestingly, conventional monitoring methods did not show any changes after transfusion (66). Top et al. (67) also utilized OPS to show that inhaled nitric oxide improved the systemic microcirculation in children with hypoxemic respiratory failure.

Studies from the early 1990's used videophotometric microscopy or laser Doppler to evaluate RBC velocity in the nailfold capillaries of the thumb (68,69). The introduction of OPS and SDF imaging to clinical medicine has opened a new field of monitoring and target treatment in various neonatal diseases and states. Many factors make these two bedside technologies very favourable, but most of all is their safety. The light emitting probe of the OPS and SDF create adequate images of the microcirculation, just by placing them on infants skin (66) or the buccal mucosa (64), making it a safe and non-invasive tool.

Conclusion

The management of infant pain is important not only to provide comfort but also to prevent both immediate and long-lasting consequences that are harmful to the child's overall health. Repeated painful procedures may result in decreased pain thresholds and hypersensitivity to pain. Immediate harmful effects of pain include physiologic instability and increased incidence of serious complications such as intraventricular hemorrhage. Painful stressors may lead to sleep disturbances, feeding problems, and inability to self-regulate. Long-term effects of pain may include altered pain perception, chronic pain syndromes, and somatic complaints (70).

The overall pain response results in increased heart rates and respiratory rates, increased blood pressure, decreased oxygen saturation, and release of adrenal stress hormones. These physiological changes along with others play an essential role as part of the multidimensional assessment tools designed for infant pain syndromes.

To date, there have been eight studies published on the use of OPS/SDF in children (64), none of them focusing on pain. The non-invasiveness and safety of these bedside technologies make them very favorable in bringing us closer to a better understanding of the impact of pain on the newborn's microcirculation. This has motivated us to design a study on the relationship of pain and the microcirculation in newborns using the SDF technology. Results will be published in 2013. We believe that microcirculation should play a role in the multidimensional assessment tools for infant pain.

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