Human neonates and pain

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Summary

This paper deals with pain in human neonates, and explores its neurological development and its assessment. It also suggests ways of treating it.

Ten years ago pain treatment in neonates was of doubtful quality and effectiveness. The results of a questionnaire from the Paediatric Anaesthetists of Great Britain and Ireland in 1988 showed that, although 80% of the responders believed that newborns were able to perceive pain, only 11% administered an opioid for major surgery and only 27% used regional techniques (Purcell-Jones *et al*. 1988). During the last decade pain treatment in neonates has been improved by knowledge derived from studies on pain and stress. The results of a similar questionnaire distributed in 1995 showed that all responders agreed that even newborns are able to perceive pain; 91% of the anaesthetists prescribed opioids for major surgery and 88% used a local or regional nerve block (da Lima *et al*. 1996). However, some basic misconceptions about pain in the newborn infant still remain, including:

- the nervous system is immature and therefore neonates do not feel pain; and
- neonates are highly sensitive to the respiratory depression effects of opioids.

Neurological development of pain

Most of the knowledge of neurological development in humans is based on studies in rats. Spinal cord development from 30 weeks gestation to early postnatal life in humans is comparable with the perinatal period in rats. Pain perception is only possible when a functional pain pathway is present, including sensory neurons with afferent nerves to the dorsal horn cells, interneuronal spinal connections and connections to the higher centres. For the modulation and control of this system, local inhibitory circuits in the spinal cord and descending inhibitory pathways from the brainstem are necessary. In rats the C-fibre polymodal nociceptors, responding to high intensity stimuli of mechanical, thermal and chemical origin, are well-developed at birth. Although the connection between the C-fibres and dorsal horn cells is not mature before the second postnatal week, stimulation of the dorsal root by C-fibres results in a long-latency, long-lasting excitation. This is probably the result of a widespread depolarization of neighbouring spinal cord cells in response to a release of substance P. In newborn infants there is also a weak connection between the afferent nerve fibres and dorsal horn cells, but after a noxious stimulation, such as heel-lancing, they show the same long-lasting excitation. The great number of substance P receptors in the dorsal horns, which gradually diminish in the first two postnatal weeks, and the immaturity of the central inhibitory control systems of the newborn, are probably responsible for this exaggerated reaction.

The flexor reflex is a useful measure of nociceptive function in the central nervous system. In adults the cutaneous flexor reflex is correlated with sensory input and corresponds to pain perception. Similar thresholds

are documented in neonates, but at thresholds much lower than those in adults. The thresholds are even lower in pre-term neonates of less than 30 weeks. Repeated stimulation of the skin, especially in these young premature infants, results in a sensitization with generalized movements of all limbs. This hypersensitivity of the skin can be abolished by topical analgesia and is probably the result of a sensitization of the nociceptor and an altered level of excitability in the central cells of the dorsal horn. Although not much is known about the central projection of pain pathways, the functional maturity of the cortex can be demonstrated by electro-encephalography patterns, showing a day and night rhythm, and by the cerebral metabolism of glucose.

Thus, despite the immaturity of the nervous system, it has been demonstrated that the basic connections in pain pathways are formed before birth and that at 30 weeks of gestation a human fetus is able to perceive nociceptive stimuli. Later on, during the perinatal period, a number of endogenous pain control systems develop, which means that the nociceptive input becomes more regulated with increasing postnatal age (Fitzgerald 1993). From a bioevolutionary perspective, neonates should experience pain. At birth, the *in utero* protection disappears and pain will provide for adaptive responses to tissue damage and life-threatening events, just as in adults. In other words, 'pain is biologically meaningful' (Craig & Grunau 1993). There are no data available to show that neonatal nociceptive responses are experienced as pain similar to that experienced by older children and adults. However, the marked nociceptive activity clearly constitutes a physiological and perhaps even a psychological form of stress in premature or full-term neonates (Johnston 1993).

Physiological responses to painful stimuli have been well documented in neonates at various gestational ages. They are reflected in hormonal, metabolic, and cardiorespiratory changes similar to, but greater and shorter in duration than, those observed in adults (Anand *et al*. 1985, Anand 1986, Anand & Hickey 1987). Most attention has been given to the immediate response to an acute noxious stimulus, such as circumcision, heel-lancing or awake intubation. This short stimulus causes large fluctuations of transcutaneous pO2, increases in heart rate, arterial blood pressure and intracranial pressure (Anand 1993). Only a few studies have concentrated on the effects of longer-lasting tissue damage, such as major surgery. Surgery without sufficient analgesia results in the release of stress hormones, including catecholamines, corticosteroids, growth hormones and glucagon, which stimulate a cascade of metabolic changes. These can result in a breakdown of protein, fat and carbohydrate stores, leading to a catabolic state, negatively influencing the repair of the injured tissues. In a classic study, Anand *et al*. (1987) showed that preoperative suppression of stress responses by strong analgesics resulted in a decreased incidence of sepsis and metabolic acidosis, and in fewer post-operative deaths.

How can pain be assessed in human neonates?

Advances in medical technology have led to an increase in the number of premature low birth weight babies presenting for major surgery. In order to provide adequate pain relief it is important that an appropriate assessment of pain management in this particular group of infants is developed. In general, the best form of pain assessment is the self-report method but because neonates are not able to verbalize, their behaviour has to be observed in order to assess and measure pain. Physiological parameters are important and can be used as indicators of pain, but only in combination with behavioural observations. Behavioural aspects of acute pain, based on the gold standard of acute pain, heel-lancing, have been studied in detail and include crying, facial expression, and body movements.

Crying

Pain-induced crying differs in frequency and intensity from that due to anger or fear. But

recognition of cries elicited by pain is observer-dependent. Only experienced people, such as parents or paediatric nurses, can recognize the type of crying. Neonates given a pacifier to suck on during a painful procedure showed significantly less crying (Field & Goldson 1984).

Body movement and posture

The reflex withdrawal, and the variability of specific patterns of torso and limb activity, in terms of whether they are at rest, rigid, or thrashing, is influenced by pain. Full-term neonates react in a more active way than do pre-term infants.

Facial expression

A variety of emotional and subjective states can be observed in infants by the examination of the face. It is possible to divide the face into three regions that are largely independent of each other. The first region comprises the forehead and eyebrows; the second region the eyes, eyelids and bridge of the nose; and the third region the lower face, including the cheeks, mouth, lower nose and chin. There is a different response in facial activity between pre-term and full-term neonates. The upper facial activity (brow bulge) is an important indicator of pain in pre-term infants. Facial expressions in neonates are important because they represent a child's natural response to noxious events. However, the absence of a painful grimace does not necessarily mean that pain is not present.

Facial activity and crying are more specific in pain assessment in neonates than are physiological parameters. Pain elicits activity in the physiological systems, but its activation may also be a consequence of many other, perhaps non-noxious, events (Grunau *et al.* 1990). The Neonatal Facial Coding System (NFCS), a unidimensional behavioural scale developed by Grunau and Craig, looks promising, although it is not feasible for assessing pain in neonates in daily practice. A combination of behavioural and physiological measures may provide the best means of assessing pain in neonates. Four methods of pain scoring based on the psychometric properties and the clinical utility, are under review and are promising: the Comfort Scale (Ambuel *et al.* 1992), the Neonatal Infant Pain Scale (Lawrence *et al.* 1993), CRIES (Krechel & Bildner 1995) and the Premature Infant Pain Profile (Stevens *et al.* 1996). However, more studies are needed to develop the ideal bedside pain score which can distinguish pain from anxiety or agitation, and can discriminate between levels of pain. A postoperative study is nearly finished which will develop the ideal instrument for measuring ongoing pain in neonates, combining physiological parameters, hormonal and metabolic stress responses, with morphine pharmacokinetics and behavioural reactions (Bouwmeester *et al.* 1996).

How to treat pain in neonates

The effects of analgesia in neonates are different from those in older children and adults. The immaturity of their organs and physiological systems, and their metabolic and hormonal instability, make the neonate more vulnerable to stress from nociceptive inputs. Metabolic stability is more difficult to maintain due to:

(1) a relatively greater surface area, resulting in greater heat production;
(2) a larger brain to body weight ratio, with increased obligatory requirements for glucose;
(3) the need to maintain somatic growth;
(4) much smaller reserves of protein, carbohydrate and fat;
(5) metabolic adaptation to extra-uterine life and enteral nutrition; and
(6) the maturation of metabolic enzymes and other chemical mechanisms controlling these systems (Anand & Fitzgerald 1993).

This metabolic vulnerability is further substantiated by the relatively low thresholds to nociception.

In rats, low doses of morphine block the dorsal horn neuronal excitation in response to C-fibre input, and the conditioning of flexor reflexes by prolonged C-fibre stimulation can be prevented. Ten-fold higher doses of morphine are required once the reflex

withdrawal is established (Woolf & Wall 1986). Consequently, pain prevention is the best form of pain treatment.

These findings directly challenge the previous practice of providing minimal anaesthesia for neonates, based on concerns about the respiratory and haemodynamic side-effects of opioids. High-dose opioid anaesthesia appears to be well tolerated, even in critically ill infants, provided it is used in a carefully monitored setting by skilled anaesthesiologists (Yaster 1987, AHCPR 1992). Adequate analgesia significantly reduces surgical stress and postoperative morbidity. For analgesia during major surgery, including laparotomy and thoracotomy, a minimal dose of 10 μg/kg of fentanyl is administered and more if needed, depending on heart rate and blood pressure.

Regional analgesia is now widely used for infants and appears to be safe (Dalens 1989). Epidural analgesia can be administered caudally, as a single injection, or continuously via epidural catheters (Bösenberg *et al*. 1988). Whenever possible, in the Sophia Children's Hospital, we use a regional technique, preoperatively in combination with general anaesthesia, and postoperatively in combination with acetaminophen or morphine.

Young infants are susceptible to apnoea and respiratory depression when systemic opioids are used. Possible explanations for this phenomenon are the fast liver passage via the open ductus venosus and the immaturity of the liver, resulting in a longer elimination half-life of the opioid. Due to the greater permeability of the neonatal blood–brain barrier the concentration in the central nervous system of the more hydrophilic opioids, such as morphine, is higher in neonates than in adults. This does not mean that adequate management of pain in this age group is impossible or dangerous, but it requires special considerations and expertise. Consequently, major surgery in neonates and ex-premature babies should be done in a paediatric surgical centre. The clearance of opioids increases rapidly over the first few weeks of life and approaches adult levels by 1 to 2 months of age (Greeley & Bruijn 1998). Based on the literature and our own experience, children from the age of 3 months with continuous morphine infusion will be sent to the ward with a morphine protocol, including (besides the routine measurements of heart rate and blood pressure) hourly monitoring of the respiratory rate and a 3-hourly assessment of the pain score and the sedation score. The nurses in the ward are trained in the effective and safe administration of analgesia, which is essential for keeping this method of analgesia safe. Infants aged less than 3 months with continuous morphine are at a higher risk of respiratory depression and are sent to the intensive care unit. The loading dose of morphine in neonates is 0.05–0.1 mg/kg, followed by a continuous infusion of 10–15 μg/kg/h. After the age of 3 months the morphine doses are the same as in adults, a loading dose of 0.1–0.2 mg/kg, and a continuous infusion of 10–40 μg/kg/h. Rectal absorption of morphine is unpredictable and is no longer advisable in routine postoperative treatment.

The use of morphine may result in paradoxical hyperactivity or restlessness, especially in older infants. Under these conditions a change to fentanyl should be considered; doses of 1–4 μg/kg/h in neonates and 4–8 μg/kg/h in older children are recommended and these do not cause any adverse cardiovascular effects. The increase in pulmonary vascular resistance during endotracheal suction may be blunted by small intravenous amounts of fentanyl of 0.5–1.0 μg/kg or alfentanil 2.5–5.0 μg/kg.

For minor surgery, including herniotomy and the implantation of central lines, Acetaminophen on a fixed time basis will give sufficient analgesia. Acetaminophen is metabolized in the liver by sulfation and glucuronidation. A small fraction is oxidized by the cytochrome P-450 into a reactive metabolite. In neonates, glucuronidation is immature and most of the metabolism of Acetaminophen is done by sulfation. The production of cytochrome P-450 starts later in the neonatal period, which means that the neonate is protected against the toxic metabolites (Rumore & Blaiklock 1992). These data support the relative safety and analgesic efficacy of Acetaminophen in pre-term and term neonates. The absorption of Acet-

aminophen given rectally is delayed, so the first dose is given preoperatively, and repeated at fixed times. A minimal dose of 20 mg/kg rectally is needed to reach therapeutic plasma levels, with a frequency of 3–4/day (60–90 mg/kg/day). Acetaminophen combined with morphine gives an additive analgesia. In combination, lower doses of morphine are needed with, consequently, fewer side-effects.

EMLA has proven to be an effective local anaesthetic agent for venepuncture in infants and children. There are, however, only a few studies evaluating the efficacy and safety of EMLA in neonates. There was no analgesic effect when EMLA was used for heel-lancing, but EMLA was effective when used for circumcision and venepuncture. The application time ranged from 10–120 min; no adverse effects were found, specifically no pathologically increased methaemoglobin levels (Gourrier *et al*. 1995, Larsson *et al*. 1995). Based on these data we use EMLA in full-term neonates to produce analgesia for venepunctures; with an application time of 30 min and in a restricted amount of 2 g.

Pre-term and ex-pre-term infants

Pre-term and ex-pre-term infants of less than 6 months need special postoperative attention as they are more susceptible to develop postoperative apnoeic attacks, especially after the use of opioids or barbiturates. Major surgery can often be done with regional analgesia in combination with a light general anaesthesia. Independent of the kind of surgery, all pre-term infants of less than 45 weeks gestational age are sent to the intensive care unit. After major surgery those of gestational age of between 45 and 60 weeks are also sent to the intensive care unit, but after minor surgery they will be monitored for 2 h in the recovery room, and when no respiratory irregularities are observed, they are sent to the ward.

Conclusions

Immaturity in the newborn infant results in an inability to communicate about pain rather than an inability to experience it, and there is an urgent need for a study combining physiological data of stress responses and behavioural signs of neonates after major surgery in order to develop the ideal tool for pain assessment in this age group. Respiratory depression resulting from opioids can be controlled by judicious dosing and careful monitoring and so the decision to withhold such medication should be based on the same medical criteria used for older patients.

One of the major concerns for the future is the long time effect of pain experience in the neonatal phase of life. The brain is particularly vulnerable in an ever-increasing number of surviving prematurely-born infants and needs thorough evaluation using validated pain scores and application of new technologies such as somatosensory evoked potentials (SSEP) (McIntosh 1997, Anand 1998, Franck & Miaskowski 1998). An extremely interesting case in this field of science is that of twins who have experienced significant differences in painful neonatal procedures resulting from different amounts of illness in the immediate postnatal period (Grunau *et al*. 1994, Evrard 1997, McGregor *et al*. 1997, Grunau *et al*. 1998). Furthermore, the use of generally non-invasive techniques, such as salivary cortisol measurement, to evaluate the amount of stress looks promising (Gunnar *et al*. 1989, 1992).

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