

REVIEW

Neil McIntosh

Pain in the newborn, a possible new starting point

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Pain is not only a subjective experience, it is, particularly in children, an emotional issue. The formation of the International Association for the Study of Pain (IASP) in 1973 injected some standards and objectivity into the subject which allowed investigators around the world to probe both the underlying scientific basis of pain and nociception (nociception being the noxious sensation *per se* with no regard to the emotional experience). At the same time therapeutic strategies for different clinical problems have been evaluated, putting pain management on a scientifically secure and more individually effective basis. Self report has been the ‘gold standard’ of pain measurement but even in co-operative adults this has inherent weaknesses/biases related to the person and their situation (both the feelings and the reporting of pain are context sensitive). In some clinical areas, subject report is clearly impossible e.g. the psychogeriatric population, the mentally retarded and in preverbal children. However, even in these groups, there are usually behavioural responses to acute pain that are reasonably interpretable by their caregivers.

Key words Pain · Newborn · Stress**The newborn**

Newborn infants, especially when preterm, are particularly vulnerable and dependent on caregivers interpreting their needs, and yet at this time their repertoire of responses is limited and even more so if they are unwell [35]. All newborns meet painful experiences shortly after birth, if not before and during the delivery [18]. Intra-

muscular vitamin K and the Guthrie test are almost invariable as painful stimuli during the 1st week of life and immunisations are given over the first few months at regular intervals. Some newborns, such as those requiring intensive care may receive a multitude of such small yet obviously painful stimuli [39, 41, 51] and a further subgroup may need operative procedures with painful postoperative courses. Thankfully the days are now past when the assumption was that the newborn was incapable of feeling pain and that even if they did, it was not important as they would not remember it. All paediatricians would now accept (as would all parents) that the newborn infant feels pain acutely and that their responses are comparatively uniform – attempted withdrawal from the painful stimulus, generalised writhing and facial action and crying.

Pain definition and the newborn

The IASP defined pain as a sensory and emotional experience based on actual or potential tissue damage or described in terms of such damage [48]. Such a definition has two problems when considering the newborn infant. Firstly, emotional experiences require subjective expression. This is impossible in the usual sense in the preverbal neonate when even the individual behavioural cues are non specific (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”? Anand and Craig [2] dispute that pain in this way 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 [2]. This accords more clearly with the observations of both the neonatologist and the mother who see no difference between the infants reactions to first and subsequent painful stimuli.

N. McIntosh (✉)
University of Edinburgh, Department of Child Life and Health,
20, Sylvan Place, Edinburgh EH9 1UW, UK,
Tel.: 0131 536 0801, Fax: 0131 536 0821

Further difficulties arise with the separation of acute from chronic pain (the latter being defined as of 3 or more months duration [60] or pain persisting beyond the usual time period required for healing [45]). Also the separation of pain from distress – pain being a hurtful (emotional) experience and stress a harmful (non emotional) experience. In practice the classification of pain as acute, chronic, recurrent or cancer related as discussed by McGrath [45] is not too helpful for the neonatologist who recognises that there is a practical management difference between acute procedural and operative pain, pain associated with meningitis or osteomyelitis and the distress caused by ventilatory manoeuvres. Such classic definitions as given above and their respective attributes, may have advanced the study of pain and may be reasonable for individuals able to describe and relate their own feelings but they do not help management in groups who are unable to give such subjective description of their distress. Possibly more useful is the division of pain by time epochs [68] where the immediate pain (of the heel prick or surgeons knife) lasts for seconds or minutes, the resulting ‘medium term pain’ lasting for hours or days, and the longer term pain (do we see this in the neonate) lasting for weeks or years.

A pragmatic approach to pain in the newborn

Some insults received by newborn infants have to be regarded, both from the point of view of the infants response and as dictated by logic, as painful. Thus the infant undergoing circumcision shows responses, behavioural [23, 42, 54, 55, 70], humeral [23, 63, 65, 70, 71] and physiological [11, 31, 44, 53, 55, 72], that indicate severe and acute distress. In the absence of their ability to describe their feelings are we unable to say that this is pain? There are other obviously painful insults – the operation, the postoperative course, the heel prick to obtain blood etc. One can divide these insults into the acute relatively short lived event – the operation, the circumcision, the heel prick – and the more subacute longer lasting such as a post operative course. The acute event has a primarily neurological basis with sensory receptors and sensory nerves being directly involved [7] whereas with subacute and chronic pain there is often an inflammatory cytochemical or paracrine basis initiating or continuing the sensorineural phenomenon [13]. Chronic persisting pain – defined as more than 3 months duration [49] is effectively impossible in the neonatal period – which is defined as lasting for only 28 days. However, inflammatory pain associated with certain neonatal illnesses such as necrotising enterocolitis, meningitis and osteomyelitis, may more resemble a severe chronic pain than an acute or subacute episode.

At the other end of the scale we can view certain stimuli as being pleasurable for infants. Feeding would logically be in this group as might be the rhythm of the nursery rhyme or the mothers song. Some types of

massage might also be regarded as pleasurable though there is some data that both vocal attention seeking [10] and massage [46] may not always be benign. Somewhere between the benign pleasurable and the painful experience comes the distressing, where from our own experience we would not believe pain to be likely but would accept discomfort as the description. Such stimuli might include tracheal aspiration via an endotracheal tube (acute distress) and ventilation for both acute and chronic respiratory problems of the newborn (chronic distress).

Measurement problems associated with pain in the newborn

Acute

If pain is going to be scientifically evaluated it has to be measured. Once it can be measured the painfulness of procedures can be quantified and the effectiveness of interventions assessed. As previously discussed, in older age groups great reliance is placed on verbal communication for this measurement and even quite young children can indicate verbally [45], or with the help of visual analogue scales [52, 66] and the ‘poker chip’ game, [30, 67] how severe their pain is, thus allowing assessment of any intervention designed to improve the situation. It has taken a long time to gather data quantifying distress in the preverbal newborn infant, but it is now accepted that three broad areas of measurement can be used:

1. Behaviour patterns: when a painful intervention is performed on an infant, a number of behavioural responses can be guaranteed. There will be generalized writhing with a tendency to withdraw from the area subjected to pain – these body movements can be quantified [16]. There is a marked change in the facial expression – a feature which Grunau and Craig [21] have quantified by video analysis and found to be remarkably accurate at predicting the degree of stress. The baby will also usually cry, both questionnaires given to parents [74] and spectrographic analysis [56] would indicate that the quality of the cry is related to the degree of stress and pain.
2. Neurochemical secretions: adults respond to noxious stimuli by releasing a large range of neurochemicals into the circulation. The catecholamine and cortisol responses are classically associated with pain and stress, but many other hormones are also released, e.g. renin [12], vasopressin [36], and beta-endorphins [18, 32, 37, 59]. It is now accepted that newborn infants have the same neurohumeral responses when subjected to such painful stimuli as venepunctures [12] and circumcision [23, 63, 65, 70, 71] as adults.
3. Physiology: there are a number of recognised physiological consequences to acute pain in infants. Increase in heart rate is almost instantaneous and is therefore unlikely to be related to the secretion of

catecholamines but more due to a neurogenic mechanism. The heart rate change is frequently accompanied by change in the respiratory rate and the blood gas contents [47]. There is palmar sweating in the term baby and infant [26].

Chronic

Sadly, at the moment we have no way of quantifying chronic pain or distress in the newborn. It is possible that urinary neurochemical excretions will differ in the stressed and unstressed infant, but such measures will only be of use on a research basis, possibly becoming the gold standard with which to compare physiological measures. Several researchers [24, 25] suggest that heart rate variability is reduced in chronic distress but whether this is specifically pain related has not been identified. The use of non linear analytic techniques (chaos) [19] may be useful in delineating this problem in the future and has the potential benefit for on line measurement and display.

Management problems with regards to pain in the newborn

Sensitisation

Not only has hyperalgesia been convincingly demonstrated in the newborn and preterm infant but so also has the neurological phenomenon of sensitisation [4, 14, 15]. Before 32–34 weeks gestation a small and repetitive stimulus leads to an increasing and uncontrolled response, while beyond this gestation the same stimulus results in habituation. Following a painful stimulus (for example a heel stick) the immature infant may, for a period of time, display massive and apparently distressing responses to quite minor and usually innocuous stimulation. Thus care given to the newborn must attempt to reduce both the initial sensitisation and also the later distress that may be triggered. Some have considered the batching of care procedures to allow important time out (rest periods) for the newborn [6, 39, 41, 51, 62] but simple procedures such as nappy changing and massage may be distressing when they are performed within a short time of a heel prick or venepuncture. This phenomenon of wind up is well recognised in the experimental animal model [9, 57].

Analgesia in the newborn

Do analgesics work in the newborn as they do in older individuals? There are many theoretical reasons why they shouldn't. Better analgesia might be predicted from: (1) a reduced plasma albumin with therefore more free, active circulating drug or; (2) the greater permeability of the blood brain barrier in the infant, particu-

larly preterm; or (3) the slower elimination ($> t_{1/2}$) resulting from immature hepatic metabolism or immature renal excretion. This might though be offset by; (1) the larger volume of distribution (particularly in the preterm) resulting in a lower peak drug level; or (2) reduced receptor numbers. How these factors balance in the individual infant must vary considerably and this complexity may be reflected in the widely discrepant pharmacokinetic data there is available (see review by Hartley and Levene [27]). The newborn rat (usually considered to be approximately neurologically equivalent to the 24–26 week gestation newborn) is 40 times less sensitive to morphine than the 14-day-old rat [75]. The development of analgesia to opiates (related to mu receptor development) is to some extent separated from the development of sedation (more related to kappa receptors) [73]. Published data on opiates in the newborn have used widely discrepant doses and whereas some have maintained that the newborn manifest opiate sensitivity, others suggest there may be resistance. Such 'resistance' could be due to poor receptor development as seems to be in the newborn rat, but it could also be related to inadequate circulating levels or the fact that there is poor metabolic conversion to the better analgesic, morphine 6 glucuronide (see review by Hartley and Levene [27]). If opiates do not work in the newborn as well as in the adult, should we assume that other analgesics do?

Pharmacological end points

If receptor development in the newborn (particularly when preterm) is poor, what blood level of analgesic should be aimed for, and will significant side-effects occur before effective analgesic levels are reached? Way et al. [69] in 1965 suggested that the respiratory centre of the newborn was particularly sensitive to opiate analgesia and this led to a conservative approach for their use in neonatal intensive care. This study has not been confirmed more recently [8, 38] and some sources would suggest insensitivity as sometimes high doses of opiates are required to synchronise a neonates breathing activity with that of the ventilator [28]. Koren et al. [38] suggested that seizures seen in neonates on opiate infusions were due to excessive doses but these infants received no higher doses than others described. The conclusion could be that this was an idiosyncratic response. Do signs of opiate withdrawal imply that a successful analgesic level was reached? Moorse et al. using recommended doses of morphine in the preterm newborn showed withdrawal after as little as 48–72 h of use [50] in infants where the blood levels did not exceed the normally accepted therapeutic range.

Clinical end points

The objectives of pain assessment in the newborn infant are, as in the older child, firstly to detect its presence and

extent, secondly to estimate its effects in the individual infant and thirdly to observe the effectiveness of any measures designed to offset it. The development of a measure of pain which can be used to estimate the success of analgesic manoeuvres in the newborn infant is particularly difficult. The facial appearances that even the preterm infant demonstrates following an acutely painful insult are now well accepted [21, 22, 35, 58], but one does not expect such facial appearances to remain for hours following such an insult even though the infant, like the older child or adult, is still in pain. Gross restlessness or agitation can occur with pain [17, 20] but the restlessness that some display in these subsequent hours is not universal and some remain particularly still and quiet unless disturbed when they may display significant agitation and redisplay their painful facial appearances. Both analgesics and sedatives may cause behavioural change at this time though presumably not in each case by analgesic action. Distinguishing irritable, restless behaviour due to pain from agitation from other causes (e.g. respiratory insufficiency) is one of the most difficult and challenging tasks of infant pain management [20, 29]. Attia et al. [5] have devised a postoperative comfort score attempting to measure post-operative pain and the effectiveness of narcotic administration, and the 'pain assessment inventory for neonates' (PAIN) has been developed for acute pain [34]. Recently Stevens et al. [64] have developed the premature infant pain profile (PIPP) which can be used to assess distress during acutely painful or distressing procedures whereas the COMFORT scale is more useful for chronic pain situations though it has not been specifically validated in the neonate [1].

Future development of a pain and sedation score

To develop satisfactory pain management in the newborn we must examine/develop some standardised and pragmatic situations and observe them scientifically (physiologically, neurochemically and behaviourally) both with and without analgesia and sedation. The paradigm of the heel prick and the circumcision have already been used in this way but other common situations need to be evaluated. Distinctions between stressful and painful stimuli may be meaningless in the newborn period or infancy. We need to develop more widely accepted end points of behaviour and physiology that can be used in real time by staff (possibly automatically aquired and on line to the infant monitors) and these need to take account of maturity. We also need to develop micromethods for the neurochemicals involved in pain and stress that ethically allow repeated measurement – it may then be possible to use these as a gold standard reference for research. The magnitude of the problem is large compared to the size of the infants and the repertoire of their responses but data indicating metabolic stress reviewed by Schmeling and Coran [61] and increased mortality when the subject is ignored would predicate its importance [3].

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