

# Influence of gestational age on the EDIN score: an observational study

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Accepted 12 May 2008  
Published Online First  
22 May 2008

## ABSTRACT

**Background and aim:** Hospitalised neonates, particularly if preterm, may be exposed to prolonged pain. At present the only validated scale to assess prolonged pain in preterms is the EDIN (Echelle Douleur Inconfort Nouveau-Né) scale. Gestational age has been shown to influence the response of infants to acute pain but its potential effect in the setting of prolonged pain has not been investigated. The aim of the present study was to evaluate whether neonatal maturity as expressed by gestational age and/or postnatal age influences their expression of prolonged pain.

**Methods:** In a 1 year period, 84 neonates (gestational age 25–41 weeks), referred to the authors' neonatal intensive care unit were evaluated using the EDIN scale two to three times a day (1571 scores). The EDIN scores were categorised as indicative (>6) or not indicative ( $\leq 6$ ) of pain. Gestational age and postnatal age were included in a logistic regression analysis along with some painful situations and analgesic treatment to identify the impact on the EDIN scores.

**Results:** Logistic regression analysis showed that the EDIN scores were positively associated with gestational age (odds ratio 1.166; 95% CI 1.123 to 1.211). Postnatal age, sepsis and presence of respiratory support also influenced the EDIN score.

**Conclusions:** Gestational age influences expression of prolonged pain. Content validity of the EDIN scale could be improved by adding categories for gestational age and attributing higher basal scores to less mature newborns.

Historically, all newborns, particularly preterm newborns, have been viewed as incapable of pain perception because of an immature central nervous system.<sup>1</sup> There is now sufficient evidence to suggest that even fetuses are capable of nociception by 20–24 weeks of gestation.<sup>2</sup> Pain is a complex, multidimensional phenomenon that is most often expressed subjectively; in preverbal patients, such as newborns, who cannot self-report pain, pain must be inferred through the observation of physiological and behavioural indicators. Detection of pain is particularly important in the setting of neonatal intensive care units (NICUs), where newborns are often hospitalised for several weeks and are subjected to multiple tissue-damaging noxious stimuli as part of diagnostic and therapeutic procedures.<sup>3,4</sup> Pain scales have been developed with the aim of objectively detecting and quantifying pain expression, with scales for acute, procedural pain and for chronic, prolonged pain. However, it has been hypothesised that indicators of pain can be modified by factors internal and external to the individual.

## What is already known on this topic

- ▶ Pain expression does not always equate to pain perception in newborns.
- ▶ Expression of acute pain is influenced by gestational age.

## What this study adds

- ▶ Gestational age influences the expression of prolonged pain as well as the expression of acute pain.

Gestational age and postnatal age,<sup>5–8</sup> illness severity,<sup>9</sup> behavioural state<sup>9</sup> and previous pain experiences<sup>10,11</sup> have all been shown to influence the expression of acute pain. For this reason, gestational age and behavioural state have been used as indicators of pain in a validated scale for the detection of acute pain in newborns.<sup>12</sup> The effects of potential influencing factors on the expression of chronic pain have not yet been investigated. The EDIN (Echelle Douleur Inconfort Nouveau-né) scale<sup>13</sup> is presently the only validated scale to assess chronic pain in term and preterm neonates, and also in those on mechanical ventilation.

The aim of the present study was to evaluate whether neonatal maturity expressed as gestational age and/or postnatal age influences the EDIN score.

## PATIENTS AND METHODS

This study was conducted in a tertiary care NICU where pain is routinely assessed on a daily basis by trained nurses using validated algometric scales. All nurses and neonatologists attend a theoretical and practical course given by two experienced neonatologists, one physiotherapist and one nurse, for basic knowledge of neonatal care and pain detection. With regard to pain detection, the EDIN scale was chosen for the measurement of chronic pain. The EDIN is a unidimensional scale made up of five behavioural indicators: facial expressions, body movements, quality of sleep, quality of contact with nurses or sociability and consolability.<sup>13</sup> A total score >6 is considered indicative of pain. The nurses, at the end of an 8-h observation period, calculate the EDIN score while performing their

usual work. In addition, our NICU has a set of guidelines for the management of pain in newborns.<sup>14</sup>

Between January 2006 and January 2007, all the 84 newborns referred to our NICU were evaluated by the EDIN scale, giving a total of 1571 scores. The number of EDIN scores obtained for each patient was also recorded. The scores were divided into two groups according to whether they were  $\leq 6$  or  $>6$ . The reasons for referral were: prematurity (58 infants), sepsis (4 infants), malformations (4 infants), asphyxia (4 infants) and respiratory distress (14 infants). Newborns on mechanical ventilation for more than 24 h were routinely treated with fentanyl at a dosage ranging from 0.5  $\mu\text{g}/\text{kg}/\text{h}$  to 2  $\mu\text{g}/\text{kg}/\text{h}$ .

We reviewed the medical records of all the newborns and recorded the EDIN pain scores. For each EDIN score, the following data were also recorded at the same time: number of total previous painful procedures (including heel pricks, venous or arterial punctures, endotracheal intubations, catheter insertions), presence of sepsis and previous surgical operation, type of ventilator support (mechanical ventilation, nasal continuous positive airway pressure (nCPAP), nasal cannula, no respiratory support), fentanyl treatment, concomitant treatment with ibuprofen or indometacin for patent ductus arteriosus closure.

This study and data release were approved by the local ethics committee, and all parents/legal guardians of the babies studied gave informed written consent for data analysis and data publication.

## STATISTICAL ANALYSIS

We entered the data into a specific Excel database and conducted the analysis using SPSS version 13.0 for Windows. The two groups of newborns with EDIN scores  $>6$  or  $\leq 6$  were compared for continuous variables (number of previous painful procedures) using one-way analysis of variance and for categorical variables (fentanyl treatment, surgery, sepsis, type of respiratory support, ibuprofen/indometacin administration) using  $\chi^2$  tests. Variables significantly influencing the presence of pain in the univariate analyses were included as independent variables in a logistic regression analysis model (backward elimination) together with gestational age and postnatal age in order to identify the individual impact of gestational age and postnatal age on the newborn's ability to express pain. The model also included, as independent variable, the number of EDIN scores per newborn in order to account for the within-child variability. To estimate EDIN values at different gestational ages, we devised three categories of gestational age: 25–31, 32–37 and  $>37$  weeks. For the same purpose, the following

**Table 1** Data on 84 newborns referred to the neonatal intensive care unit (NICU) in a 12-month period

|   |  |
|---|--|
| Boys/girls  | 47/37                                    |
| Gestational age (weeks), median (range)           | 30 (25 <sup>+1</sup> –41 <sup>+2</sup> ) |
| Birth weight (g), median (range)                  | 1768 (550–3940)                          |
| NICU length of stay (days), median (range)        | 6 (1–106)                                |
| No. of painful procedures/newborn, median (range) | 9 (0–47)                                 |
| Sepsis, n (%)                                     | 17 (20)                                  |
| Surgical procedures,* n (%)                       | 6 (7)                                    |
| Mechanical ventilation, n (%)                     | 18 (21)                                  |
| Nasal continuous positive airway pressure, n (%)  | 55 (65)                                  |
| Opioid treatment, n (%)                           | 16 (19)                                  |
| Ibuprofen/indometacin n (%)                       | 20 (24)                                  |

\*Surgical correction of gastric malrotation in 1 newborn, ventriculoperitoneal shunt positioning for tetra ventricular hydrocephalus in 1 newborn, surgical correction of a hypoplastic aortic arch in 1 newborn, Broviac catheter placement in 1 newborn, and surgical correction of myelomeningocele in 2 infants.

categories for postnatal age were created: 0–30, 31–60, 61–90, 91–120 and  $>120$  days. Comparisons among groups were performed using the Kruskal–Wallis test. All hypotheses were tested using two-sided tests at the 0.05 level of significance.

## RESULTS

Neonatal data are shown in table 1. A total of 194 EDIN scores were  $>6$ , indicating prolonged pain. EDIN scores  $>6$  were more frequently detected after surgery (odds ratio (OR) 2.0, 95% CI 1.3 to 3.1;  $p = 0.002$ ), in presence of sepsis (OR 2.8, 95% CI 1.8 to 4.3,  $p < 0.001$ ), when a nasal cannula was being used (OR 3.5, 95% CI 2.2 to 5.6,  $p < 0.001$ ) and when the infant was not receiving fentanyl (OR 1.8, 95% CI 1.3 to 2.5,  $p = 0.001$ ). Neither ibuprofen/indometacin administration nor the number of previous painful procedures were associated with EDIN scores  $>6$ . When surgery, presence of sepsis, presence of respiratory support, fentanyl treatment and number of EDIN score/newborn were introduced in a logistic regression analysis model together with gestational age and postnatal age, only gestational age, postnatal age, sepsis and presence of respiratory support were considered significant predictors of the EDIN score. Fentanyl treatment did not show a significant independent effect. ORs and 95% CIs are reported in table 2.

When we categorised the infants by gestational age into three groups (25–31, 32–37 and  $>37$  weeks), we found a significant increase in the EDIN scores ( $p < 0.001$ ) from the lower to the higher gestational age groups. The upper quartile for the EDIN score was 3 at 25–31 weeks' gestational age, 4 at 32–37 weeks' gestational age and 5 at  $>37$  weeks' gestational age. Therefore, an increase of about 1 point in the EDIN score may be expected with increase in gestational age, based on the three groups in this study. Moreover, the EDIN scores increased significantly from 0 to 60 days postnatal age ( $p < 0.001$ ) and from 61 to  $>120$  days postnatal age ( $p = 0.002$ ). Newborns who had a nasal cannula and were on nCPAP, but not those who were on mechanical ventilation, had significant higher EDIN scores than newborns without any respiratory support (Kruskal–Wallis test,  $p < 0.001$ ,  $p = 0.002$ , and  $p > 0.05$ , respectively).

## DISCUSSION

Algometric scales have been developed with the aim of helping caregivers to identify and objectivise pain signals in preverbal patients. However, especially in preterm, compromised neonates the expression of pain may not necessarily equate the experience of pain.<sup>15</sup> Preterm, young critically ill newborns referred to the NICU may be too weak or too tired to express pain vigorously. Moreover, these preterm newborns are often unable to cry due to an endotracheal tube or are restrained/positioned in such a way as to preclude body movements. Therefore, preterm neonates may be at higher risk for the consequences of unrelieved pain than term and older neonates if

**Table 2** Multiple logistic regression analysis

| Independent variables                            | OR (95% CI)            | p Value  |
|--|------------------------|----------|
| Gestational age (weeks)                          | 1.166 (1.123 to 1.211) | $<0.001$ |
| Postnatal age (days)                             | 1.007 (1.003 to 1.012) | 0.002    |
| Sepsis   | 3.741 (2.296 to 6.096) | $<0.001$ |
| Ventilatory support (MV*, nCPAP†, nasal cannula) | 2.106 (1.448 to 3.062) | $<0.001$ |
| Number of EDIN scores/newborn (n)                | 0.998 (0.990 to 1.005) | 0.575    |
| Surgery  | 1.002 (0.605 to 1.660) | 0.993    |
| Fentanyl   | 1.142 (0.731 to 1.783) | 0.559    |

\*MV, mechanical ventilation; †nCPAP, nasal continuous positive airway pressure.

they are not accurately assessed. For the above mentioned reasons, Stevens *et al*,<sup>12</sup> when developing and validating a scale for the detection of acute pain, attributed higher pain scores to infants of lesser gestational age and to those who were not awake and alert. However, the potential effects of gestational age and/or postnatal age in a situation of prolonged pain have not been established. Debillon *et al*<sup>13</sup> developed and validated a useful scale for the measurement of prolonged pain in newborns, also preterm or mechanically ventilated, based only on behavioural indicators. However, the authors suggested that further studies would be useful to investigate the potential influencing role of internal or external factors on the EDIN score. In the present study we investigated, in a homogeneous setting of neonatal pain and distress management, whether gestational age and postnatal age affect pain expression as detected by the EDIN score.

First, we performed univariate analysis to evaluate the correlation between EDIN scores (categorized as  $>6$  or  $\leq 6$ , respectively) and several painful procedures or analgesic treatment. Presence of respiratory support, surgery, sepsis, opioid treatment but not ibuprofen/indometacin treatment or number of previous painful procedures significantly affected the risk of having an EDIN score  $>6$ . Previous pain experience has been explored as a factor influencing pain expression in newborns. The number of previous painful procedures has been shown to dampen the response to subsequent acute pain. Our data do not confirm this observation concerning prolonged pain. In our NICU, all critically ill newborns who undergo mechanical ventilation are treated by continuous fentanyl infusion; moreover, before performing minor invasive procedures (heel prick, venous and arterial sampling) oral sucrose is routinely given unless contraindicated. Pain control in our population may have avoided the dampened pain response due to uncontrolled pain reported in previous studies. Moreover, each newborn in our study underwent a mean of 10 painful procedures: the impact on the EDIN score of a higher number of painful procedures needs to be investigated.

Variables increasing significantly the risk of having an EDIN score  $>6$  at the univariate analysis were included in a logistic regression analysis, together with number of EDIN scores per newborn, gestational age and postnatal age, in order to detect whether these last two factors could independently influence EDIN scores. Fentanyl treatment, which was associated with a lower risk of having an EDIN score  $>6$  in the univariate analysis, also had no significant effect when introduced in the logistic regression analysis. The possible explanation for this result is that fentanyl treatment was not an independent variable as fentanyl was given only to mechanically ventilated newborns and to those who underwent surgical treatment. Therefore, the effect of fentanyl treatment could have been obscured by the effects of the surgery or by the type of respiratory support.

The most important determinant of the EDIN score in our population of preterm and term newborns was gestational age (OR per 1 week increase in gestational age: 1.166, 95% CI 1.123 to 1.211,  $p < 0.001$ ). The increase in the EDIN score with increase in gestational age can be interpreted in two ways. First, it may indicate a reduced ability to feel pain at lower gestational age. This hypothesis has been largely refuted in the past two decades and it has been extensively demonstrated that newborns, even if preterm, have anatomical and functional maturity for pain perception. The second and more reliable explanation is that less mature newborns have a reduced ability to express pain. Craig *et al* reported marked changes in pain response

across the age range of prematurity, with the most premature infants showing the lowest activity.<sup>6</sup> Johnston *et al*, who compared the response to heel stick in the same infants across 8 weeks of development, found that infants demonstrated increasingly more behavioural responses as they matured.<sup>5</sup> Also, Xia *et al* found that preterm infant pain behaviours (particularly facial activity and limb movements) increased with increasing gestational age.<sup>7</sup> All these studies referred to acute pain; to our knowledge this is the first study demonstrating an influence of gestational age on the expression of prolonged pain. This finding suggests that the EDIN score could be improved by adding categories for gestational age and attributing higher basal scores to less mature newborns in order to better detect prolonged pain in newborns less able to respond vigorously to chronic/prolonged pain. On the basis of our data a basal score of 2, 1 and 0 could be attributed to newborns of gestational age 25–32 weeks, 33–37 weeks and  $>37$  weeks, respectively. Comparison of construct validity, inter-rater reliability and internal consistency of the EDIN scale applied with or without categories for gestational age could be useful in confirming our hypothesis. Our results were obtained on a mixed population of newborns, with only a few newborns in the postoperative period. Further studies in a more selected population undergoing chronic pain could be useful.

Another factor influencing the EDIN score in our population of newborns was postnatal age. EDIN scores increased significantly about every 2 months of age so that the effect of postnatal age over EDIN in the neonatal period may be considered negligible. Type of respiratory support, sepsis and surgical treatment also affected the EDIN score in our population. EDIN scores in newborns with a nasal cannula and on nCPAP, but not EDIN scores in newborns on mechanical ventilation, were significantly higher than EDIN scores in newborns without any respiratory support. A possible explanation of this result is that all mechanical ventilated newborns, but not those with a nasal cannula or on nCPAP, receive routine opioid treatment in our unit. In addition, sepsis, which is not routinely treated with analgesics in our unit, and that is clearly a source of distress, correlated with a higher risk of having an EDIN score  $>6$  (OR 3.74, 95% CI 2.30 to 6.10,  $p < 0.001$ ).

## CONCLUSIONS

It was already well known that gestational age influenced the expression of acute pain in newborns; now it seems that gestational age also influences the expression of prolonged pain. In the present study the EDIN scores were influenced by gestational age; the EDIN scores were lowest in the least mature gestational age neonates and highest in the most mature.

Therefore, creating categories for gestational age may improve the content validity of the EDIN scale.

**Competing interests:** None.

**Ethics approval:** This study and data release were approved by the local ethics committee.

**Patient consent:** All parents or legal guardians of the babies studied gave informed written consent for data analysis and data publication.

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### Calling European Paediatric Research Networks

The European Medicines Agency (EMA) is fully committed to facilitating a “virtual” European Network through linking all existing national and European networks, investigators and centres with specific expertise in the performance of paediatric studies. This commitment is grounded in the Paediatric Regulation EC No 1901/2006, as amended (Article 44), which has the objectives:

- ▶ to ensure that medicinal products used to treat children are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population
- ▶ to improve the information available on the use of medicinal products in the various paediatric populations
- ▶ to achieve the above without subjecting the paediatric population to unnecessary clinical trials

Clinical trials in the paediatric population require specific expertise, specific methodology and, in some cases, specific facilities. They should be performed by appropriately trained investigators.

The EMA European Network aims are:

- ▶ to identify, coordinate and link together existing networks, existing national and community initiatives and study centres in order to build the necessary competences at community level
- ▶ to ensure efficient, timely communication and exchange of information between networks
- ▶ to be a source of information and expertise for health professionals
- ▶ to provide a forum for scientific discussion related to paediatric clinical trials with all stakeholders, where necessary
- ▶ to take account of community and third country data
- ▶ to help facilitate cooperation
- ▶ to avoid unnecessary duplication of studies

This network will:

- ▶ provide a central source of information and expertise for industry
- ▶ contribute to strengthening the foundations of the European research area in the context of community framework programmes for research, technological development and demonstration activities
- ▶ benefit the paediatric population

An implementing strategy was adopted 26 January 2008 by the EMA management board.

<http://www.ema.europa.eu/pdfs/human/paediatrics/54352307en.pdf>

There are many advantages to joining the network:

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Joining the network is easy; contact us with your details via [enpremea@ema.europa.eu](mailto:enpremea@ema.europa.eu).

Contact details will allow the EMA to set up an initial mailing list of networks, who will be invited for an implementation meeting to be held at the EMA in London, planned for February 2009.

The meeting will:

- ▶ discuss and agree mandate and objectives
- ▶ define scientific and operational quality standards and recognition criteria
- ▶ implement coordinating group



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*Arch Dis Child Fetal Neonatal Ed* 2009 94: F35-F38 originally published online May 22, 2008  
doi: 10.1136/adc.2007.133777

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