Sensitivity and Specificity of the Newborn Infant Parasympathetic Evaluation Index in Pain Assessment of Very Low Birth Weight Infants

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Abstract

Objective This article describes the results of a study investigating the sensitivity and specificity of the Newborn Infant Parasympathetic Evaluation (NIPE) index for detecting the physiological changes resulting from nociception in painful procedures in very low birth weight (VLBW) infants.

Study Design A prospective observational study was carried on of 44 newborns at 23 to 32 weeks' gestational age. The sensitivity and specificity of the NIPE index are analyzed using a receiver operating characteristic curve. Most of the painful procedures performed were skin-lancing and venipunctures. Nonpainful procedures consist of no intervention, with an interval of at least 1 hour with painful procedures in each newborn.

Results The accuracy of the NIPE index to diagnose mild nociceptive stimulation in VLBW newborns is 73.2%.

Conclusion The NIPE index is a useful technique for assessing nociceptive stimulation in newborns, presenting less observer-dependent variability than other pain assessment scales.

Keywords

- pain
- newborn
- premature infant
- Newborn Infant Parasympathetic Evaluation
- Premature Infant Pain Profile

Key Points

- The NIPE index offers an objective assessment of pain.
- Moderate-high sensitivity of the NIPE index in the evaluation of pain in premature newborns.
- Painful procedures in VLBW newborns are reflected as a decrease in the NIPE score.

Newborns with a lower gestational age (GA) are less likely to demonstrate objective responses to pain, due to their incomplete neuroanatomical development, which can cause variability in pain assessment scales in premature newborns.[1,2] Painful and tactile stimuli are known to provoke specific hemodynamic responses in the somatosensory cortex, which means that even very immature neonates have conscious sensory perceptions of pain, similar to that experienced by full-term infants.[3] The newborn can respond to pain by developing three types of response: physiological (increased heart rate and decreased peripheral oxygen saturation), biochemical (secretion of cortisol), and behavioral (change in facial expression, agitation, crying). To try to integrate these responses, different scales for assessing pain in newborns have been developed,[4] the main drawback of which is the interobserver variability reported by some authors.[5] Several nociception monitoring systems are commercially available.[6] However, only two technologies claim to be useful

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for pain measurement in newborns or infants: the Newborn Infants Parasympathetic Evaluation (NIPE; Mdoloris Medical Systems, Loos, France), based on heart rate variability,[5] and the PainMonitor, based on skin conductance (PainMonitor, MedStorm, Oslo, Norway).[7] The NIPE is an adaptation of the Analgesia Nociception Index (Mdoloris Medical Systems), which was developed for monitoring adults during surgery under general anesthesia.[8]

In general terms the spectral analysis of electrocardiogram (ECG) data generates three components of clinical interest: (1) low-frequency (LF: 0.04–0.15 Hz) component, mainly related to sympathetic activity; (2) high-frequency (HF: 0.15–1 Hz) component, related to parasympathetic activity[9]; and (3) the ratio between the two (LF/HF) which is proposed as an index of autonomic balance, although this is not evaluated by the NIPE monitor. In adults, at high frequencies (>0.15 Hz), pain, anxiety, or fear are accompanied by a decrease in heart rate variability, which would indicate a decrease in parasympathetic tone during nociceptive stimulation and/or unpleasant emotions.[10,11] In newborns, although few studies in this regard have been conducted, some authors have reported a decrease in the influence of the parasympathetic tone during nociceptive stimuli, suggesting that this tone could be evaluated as an objective means of recording acute and chronic pain experienced by the newborn.[12,13]

In newborns, although few studies in this regard have been conducted, some authors have reported a decrease of the parasympathetic tone during nociceptive stimuli, that could be registered with the NIPE index.[12,13] Furthermore, an association has been observed between the number of skin punctures (by lancet) received by premature newborns and their restricted cognitive and motor development.[14,15]

The aim of this study is to investigate the sensitivity and specificity of the NIPE index to detect physiological changes resulting from mild nociceptive procedures in very low birth weight (VLBW) infants.

Materials and Methods

This prospective, observational study was conducted in the neonatal intensive care unit of San Cecilio Hospital (Granada, Spain). For this purpose, newborns with a GA of 23 to 32 weeks were recruited during the period from January 31, 2018, to June 25, 2021. The study was approved by the appropriate Institutional Review Board and Provincial Bioethics Committee (number: d9a7f200b19530b41cdb1abb31c6e2686b88bce5) (January 14, 2018). The newborns' parents/guardians were informed that they could withdraw the newborn from the study at any time and written informed consent was obtained.

The following exclusion criteria were applied: the existence of any degree of intraventricular hemorrhage, periventricular leukomalacia, or congenital malformation, the use of adrenergic agonist or antagonists or that of analgesics up to 48 hours before the procedure, required mechanical ventilation, painful procedures with less than 2 hours interval between them, and use of sucrose during procedures.

The painful procedures were classified by their invasive nature, and the swaddling method was used to mitigate pain during all procedures. Nonpainful procedures consist of no intervention, with an interval of at least 1 hour with painful procedures in each newborn.

NIPE values measured in the context of a mild nociceptive intervention were compared with values recorded when the infant was left alone and seemed comfortable. This experimental design attempts to determine whether the NIPE is able to distinguish mild nociceptive intervention from nonpainful intervention. Receiver operating characteristic curve analyses were performed, first classifying nonpainful interventions as negative and mild nociceptive interventions as positive and analyzing the corresponding NIPE values.

It has been shown that both environmental noise and lighting influence the physiological constants of the newborn, inducing changes in heart rate, respiration, oxygenation, sleep phases, and hormonal status, and may produce desaturation and increased intracranial pressure in very unstable children. All the newborns in our study received caffeine during the registries as prophylaxis of apnea of prematurity.

The NIPE monitor is connected to the ECG monitor, which enables data to be obtained in a noninvasive way. The NIPE monitor performs a sampling of the RR (RR interval of the electrocardiogram)series by measuring the area generated by the respiratory pattern. This approach is based on the understanding that the higher the parasympathetic tone, the greater the area generated by the ventilatory cycle. The NIPE index is expressed on a scale ranging from 0 to 100. This form of evaluation is objective and excludes interobserver variability. It reflects the activity of the parasympathetic system and gives a proportionate reading of the parasympathetic tone compared with that of the autonomic nervous system.

Sensitivity and specificity analyses enabled us to establish the optimal cutoff point for the NIPE using nonpainful procedures a reference in VLBW newborns. We use the SPSS v.20.0 statistical package.

Results

Our results were obtained after NIPE recordings in 44 VLBW newborns out of 217 painful procedures and 217 nonpainful procedures. Seventy-two procedures were performed in newborns less than 28 weeks of GA, 60 procedures between 28 and 30 weeks of GA, and 85 procedures above 30 weeks of GA (►**Fig. 1**). ►**Table 1** shows the characteristics of the newborns included in our study. The newborns' mean GA at birth was 27.7 weeks and the mean birth weight was 1,055 g. The following clinical procedures were performed: dermal puncture with lancet (skin lancing; 32.2%, $n = 140$), venous puncture for analysis (14.5%, $n = 63$), and other pain procedures such as bladder catheterization and orogastric tube placement (3.3%, $n = 14$).

We analyzed 217 painful procedures and 217 nonpainful procedures. The area under the curve (AUC) can be used as an index of the overall accuracy of a diagnostic test. In this sense, the accuracy of the NIPE index to diagnose pain using

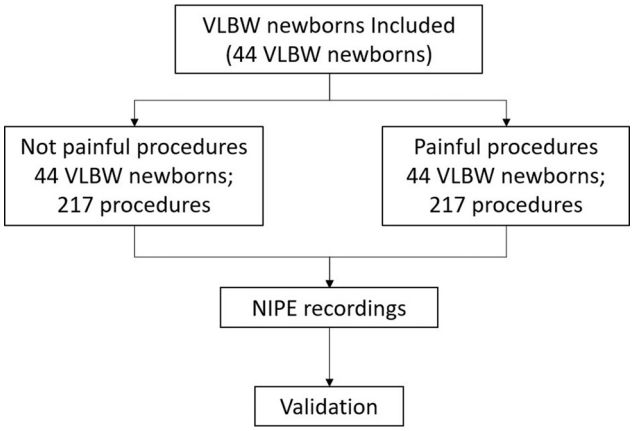


Fig. 1 Study flow diagram. NIPE, Newborn Infant Parasympathetic Evaluation; VLBW, very low birth weight.

nonpainful procedures as a reference in VLBW newborns is 73.2% (AUC = 0.732; $p < 0.001$; 95% confidence interval [CI]: 0.68–0.78; ►**Table 2**). In ►**Table 2**, we can establish the optimal cut-off point for the NIPE index using nonpainful procedures as a reference in VLBW newborns at 47 weeks, by minimizing both false positive and false negative diagnostics of pain. At this point, the sensitivity is 72.8% (95% CI: 66.3–78.6) and the specificity is 65.3% (95% CI: 58.2–75.9%). However, as can be seen in ►**Table 2**, NIPE index values below 42 show a diagnostic sensitivity of pain above 90%, although with low specificities.

Discussion

Our findings indicate a moderate-to-high sensitivity of the NIPE index in the evaluation of pain in premature newborns. Neonatal stress is known to produce negative effects on neurodevelopment,[14,15] and therefore it is important to validate objective techniques for the detection of pain. Our results show that painful procedures in VLBW newborns are reflected as a decrease in the NIPE score and establish the sensitivity and specificity of the cut-off points of each value of this procedure. The feasibility of using NIPE for short-duration painful procedures remains controversial in the opinion of some authors,[16,17] while for other authors[18] its usefulness in the evaluation of chronic pain or of long evolution is indisputable. Gendras et al[5] and Cremillieux et al[16] found no significant correlations between the NIPE index and the Premature Infant Pain Profile-Revised (PIPP-R) score during routine painful procedures in preterm infants. Our study did reveal a decrease in the NIPE index after acute painful procedures were performed, for all three GA strata. In the published works and reviews,[6,19] the reliability and adequate cutoff points of the NIPE index have not been sufficiently defined in the population of newborns and even more so in that of VLBW newborns.

Walas et al[17] reported that the NIPE index values fell significantly shortly after the application of painful procedures. These findings are consistent with those obtained in our study. In other studies, the relationships evidenced between pain scales for newborns and the NIPE index are very heterogeneous. Recher et al[6] conducted a systematic review of studies conducted in this context, using a wide range of procedures. The authors conclude that clinical studies are heterogeneous in their methodology and outcomes, and that no clear conclusion can be drawn from the existing literature. On the other hand, some procedures described as painful may only be "slightly painful," which may lead to heterogeneity in the results observed. In another study, Buyuktiryaki et al[18] observed significant correlations between the Neonatal Pain and Discomfort Scale (EDIN) and the NIPE index in 23 newborns with 33 to 35 weeks of GA who underwent drainage of the pneumothorax with thoracotomy. Similarly, Faye et al[12] assessed postoperative pain in 28 newborns aged > 34 weeks of GA and recorded a significant correlation between the EDIN scale and the NIPE index. Finally, Alexandre et al,[20] in their study of newborns aged 33 weeks of GA, reported a significant correlation between the infant's comfort level and the NIPE index.

Another factor that may be relevant to the NIPE index is the absence of interobserver variability. This aspect has previously been mentioned by Bellieni et al,[21] who reported detecting interobserver variability in the PIPP-R score and noted the difficulty of interpreting the newborn's facial response to nociceptive stimuli, especially in the case of very immature newborns. In premature newborns, GA is a determining factor of the degree of myelination and modulation of the pain stimulus.[22] Accordingly, for these neonates, the cutoff points of the NIPE above which we assume the existence of pain may be lower than those applicable to full-term infants.[17]

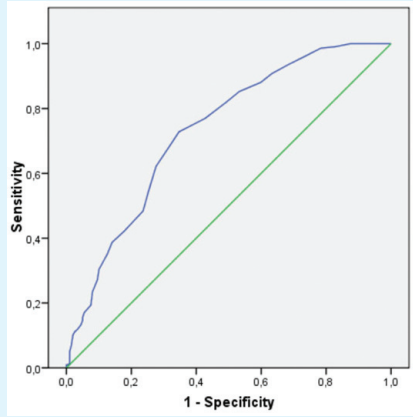
Table 1 Characteristics of the patients at birth and clinical procedures studied

Patients ($n = 44$)			
GA at birth (wk)[a]	27.7 ± 2.7	Male *n* (%)	21 (51.6)
Age at inclusion (d)[a]	13.6 ± 12.4	C-section *n* (%)	26 (62.9)
Corrected GA (wk) in the procedure[a]	29.6 ± 2.6		
Birth weight (g)[a]	1,055 ± 339	Apgar's score at 5 minutes[b]	8 (7–9)

Abbreviations: C-section, caesarean section; GA, gestational age.
[a]Mean ± SD (standard deviation).
[b]Median (interquartile ratio).

Table 2 Coordinates of the ROC curve for different NIPE index using nonpainful procedures as a reference in VLBW newborns

NIPE index	Sensitivity	1-Specificity	AUC = 0.732; 95% CI: 0.68–0.78; $p < 0.001$
38	0.991	0.829	
39	0.986	0.784	
40	0.963	0.739	
41	0.935	0.683	
42	0.908	0.633	
43	0.880	0.598	
44	0.853	0.533	
45	0.816	0.487	
46	0.770	0.427	
47	**0.728**	**0.347**	
48	0.682	0.317	
49	0.622	0.276	
50	0.539	0.251	
51	0.484	0.236	
52	0.419	0.176	
53	0.387	0.141	
54	0.350	0.126	
55	0.304	0.101	
56	0.272	0.095	
57	0.235	0.080	
58	0.194	0.075	
59	0.171	0.055	
60	0.157	0.050	
61	0.147	0.050	
62	0.134	0.045	
63	0.120	0.035	
64	0.111	0.025	
65	0.101	0.020	



Abbreviations: AUC, area under the curve; CI, confidence interval; NIPE, Newborn Infant Parasympathetic Evaluation; ROC, receiver operating characteristic; VLBW, very low birth weight.
Note: The cut-off point of greater sensitivity and specificity is shown in bold (NIPE index = 47).

In our opinion, the NIPE index is useful for evaluating the presence of acute or chronic pain in the preterm newborn, as it is not subject to the interobserver variability that may affect the PIPP-R score.

Conclusion

The NIPE index is a useful technique for assessing pain in newborns, presenting less observer-dependent variability than other pain assessment scales.

Statement of Compliance with Research Ethics Codes

The authors declare that the work presented in this manuscript is original and is not currently being evaluated by any other journal. The authors have no relevant conflicts of interest to declare. The consent of the parents or guardian of the patients was required. The study protocol was approved by the Ethics Committee of the hospital, and all current regulations regarding data confidentiality were respected.

Authors' Contributions

J.U. designed the analysis and data interpretation procedures, co-wrote the article, and critically reviewed it for important intellectual content. He approves the present version for publication. He accepts responsibility for all aspects of the work, including the proper investigation and resolution of questions related to its accuracy and completeness. J.L.G.-S., A.C.-M., E.F.-M., and A.R.-L. made substantial contributions to the conception and design of the study, co-wrote the article, and critically reviewed it for important intellectual content. They approve the present version for publication. They accept responsibility for all aspects of the work, including the proper

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Conflict of Interest

None declared.

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References

1 Bozzette M. Observation of pain behavior in the NICU: an exploratory study. J Perinat Neonatal Nurs 1993;7(01):76–87
2 Schiavenato M, von Baeyer CL. A quantitative examination of extreme facial pain expression in neonates: the primal face of pain across time. Pain Res Treat 2012;2012:251625
3 Bartocci M, Bergqvist LL, Lagercrantz H, Anand KJ. Pain activates cortical areas in the preterm newborn brain. Pain 2006;122(1-2):109–117
4 Cong X, McGrath JM, Cusson RM, Zhang D. Pain assessment and measurement in neonates: an updated review. Adv Neonatal Care 2013;13(06):379–395
5 Gendras J, Lavenant P, Sicard-Cras I, et al. The newborn infant parasympathetic evaluation index for acute procedural pain assessment in preterm infants. Pediatr Res 2021;89(07):1840–1847
6 Recher M, Boukhris MR, Jeanne M, et al. The newborn infant parasympathetic evaluation in pediatric and neonatology: a literature review. J Clin Monit Comput 2021;35(05):959–966
7 Passariello A, Montaldo P, Palma M, et al. Neonatal painful stimuli: Skin Conductance Algesimeter index to measure efficacy 24% of sucrose oral solution. J Matern Fetal Neonatal Med 2020;33(21):3596–3601
8 De Jonckheere J, Rommel D, Nandrino JL, Jeanne M, Logier R. Heart rate variability analysis as an index of emotion regulation processes: interest of the Analgesia Nociception Index (ANI). Annu Int Conf IEEE Eng Med Biol Soc 2012;2012:3432–3435
9 Manning SM, Talos DM, Zhou C, et al. NMDA receptor blockade with memantine attenuates white matter injury in a rat model of periventricular leukomalacia. J Neurosci 2008;28(26):6670–6678
10 Appelhans BM, Luecken LJ. Heart rate variability and pain: associations of two interrelated homeostatic processes. Biol Psychol 2008;77(02):174–182
11 Miu AC, Heilman RM, Miclea M. Reduced heart rate variability and vagal tone in anxiety: trait versus state, and the effects of autogenic training. Auton Neurosci 2009;145(1-2):99–103
12 Faye PM, De Jonckheere J, Logier R, et al. Newborn infant pain assessment using heart rate variability analysis. Clin J Pain 2010;26(09):777–782
13 Oberlander TF, Grunau RE, Whitfield MF, Fitzgerald C, Pitfield S, Saul JP. Biobehavioral pain responses in former extremely low birth weight infants at four months' corrected age. Pediatrics 2000;105(01):e6
14 Grunau RE, Whitfield MF, Petrie-Thomas J, et al. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. Pain 2009;143(1-2):138–146
15 Brummelte S, Grunau RE, Chau V, et al. Procedural pain and brain development in premature newborns. Ann Neurol 2012;71(03):385–396
16 Cremillieux C, Makhlouf A, Pichot V, Trombert B, Patural H. Objective assessment of induced acute pain in neonatology with the Newborn Infant Parasympathetic Evaluation index. Eur J Pain 2018;22(06):1071–1079
17 Walas W, Latka-Grot J, Maroszyńska I, et al. Newborn Infant Parasympathetic Evaluation index for the assessment of procedural pain in nonanesthetized infants: a multicenter pilot study. Am J Perinatol 2021;38(S 01):e224–e230
18 Buyuktiryaki M, Uras N, Okur N, et al. Evaluation of prolonged pain in preterm infants with pneumothorax using heart rate variability analysis and EDIN (Échelle Douleur Inconfort Nouveau-Né, neonatal pain and discomfort scale) scores. Korean J Pediatr 2018;61(10):322–326
19 Lim BG. Nociception monitoring tools using autonomic tone changes for intraoperative analgesic guidance in pediatric patients. Anesth Pain Med 2019;14(04):380–392
20 Alexandre C, De Jonckheere J, Rakza T, et al. Impact of cocooning and maternal voice on the autonomic nervous system activity in the premature newborn infant [in French]. Arch Pediatr 2013;20(09):963–968
21 Bellieni CV, Cordelli DM, Caliani C, et al. Inter-observer reliability of two pain scales for newborns. Early Hum Dev 2007;83(08):549–552
22 Fitzgerald M. The development of nociceptive circuits. Nat Rev Neurosci 2005;6(07):507–520

