CLINICAL SCIENCE

Differences between uni- and multidimensional scales for assessing pain in term newborn infants at the bedside

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OBJECTIVES: This study sought to determine the level of agreement between behavioral and multidimensional pain assessment scales in term newborn infants submitted to an acute nociceptive stimulus.

METHODS: This cross-sectional study was performed on 400 healthy term newborns who received an intramuscular injection of vitamin K during the first 6 hours of life. Two behavioral pain scales (the Neonatal Facial Coding System and the Behavioral Indicators of Infant Pain) and one multidimensional tool (the Premature Infant Pain Profile) were applied by a single observer before the procedure, during cleansing, during injection and two minutes after injection. The Cochran Q, McNemar and kappa tests were used to compare the presence and degree of agreement between the three scales. The Hotelling T2 test was used to compare the groups of newborns for which the scales showed agreement or disagreement. A generalized linear regression was used to compare the results of the Neonatal Facial Coding System and the Behavioral Indicators of Infant Pain across the four study time points.

RESULTS: The neonates studied had a gestational age of 39 ± 1 weeks, a birth weight of 3169 ± 316 g and and postnatal age of 67 ± 45 minutes. During the stimulus procedure, 80% of the newborns exhibited pain behaviors according to the Neonatal Facial Coding System and the Behavioral Indicators of Infant Pain, and 70% experienced pain according to the Premature Infant Pain Profile ($p<0.001$). The frequencies of the detection of pain using the Behavioral Indicators of Infant Pain and the Neonatal Facial Coding System were similar. The characteristics of the neonates were not associated with the level of agreement between the scales.

CONCLUSION: The Neonatal Facial Coding System and the Behavioral Indicators of Infant Pain behavioral scales are more sensitive for the identification of pain in healthy term newborn infants than the multidimensional Premature Infant Pain Profile scale.

KEYWORDS: Pain; Newborn Infant; Pain Measurement.

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INTRODUCTION

Starting at birth, critically ill newborn babies undergo repetitive, painful stimuli as part of diagnostic and therapeutic procedures that are necessary for their survival (1). In the neonatal intensive care unit (NICU) during the first two weeks after birth, newborns are exposed to approximately 16 invasive procedures per day, of which only one-third are completed under analgesia (2). The cardiovascular and respiratory effects associated with the endocrine-metabolic response to acute nociceptive stimuli may increase neonatal morbidity and mortality (3). The under-treatment of pain can trigger behavioral responses in the newborn and may have long-lasting effects on the nociceptive system that result in an altered processing of pain and stress (4,5) and an increased susceptibility to psychosomatic (6) and psychiatric (7) changes during childhood and adolescence.

It is widely acknowledged that the application of a valid and reliable tool to assess pain in newborns is essential for proper diagnosis, which is the first step towards effective treatment (8). However, the assessment of pain in newborns represents a great challenge. Two of the major limitations to achieving pain relief in clinical practice include the lack of a reliable biomarker and the absence of a gold standard scale that is capable of measuring the intensity of the pain, the need for treatment and the effectiveness of the intervention. Although there are more than 30 scales for assessing pain in newborns, no specific scale has demonstrated superiority. Most of these instruments rely on physiological and behavioral parameters, which are indirect responses to the painful stimulus.

No potential conflict of interest was reported.

Physiological parameters, including heart rate, respiratory rate, oxygen saturation, intracranial and blood pressure, among others, have the advantage of being objective measures, but changes in these parameters are not specific to painful phenomenon (9). Behavioral responses are the language used by infants to communicate with their caregivers, but their operational definitions are sometimes subjective, diminishing the sensitivity and specificity of these parameters as indicators of pain (10). The main behavioral responses to pain in preverbal infants are crying and body and facial movements. The facial expression reflects the painful experience effectively and specifically (11,12); indeed, facial movements correlate best with cortical activity during a painful stimulus in comparison with physiologic indicators as demonstrated by Slater et al. in a study using near-infrared spectroscopy following a clinical required nociceptive stimulus (13). Facial actions used as pain indicators are lowering of the brows, squeezing the eyes shut, deepening of the nasolabial furrow, opening of the lips, stretching of the mouth, tightening the tong, pursing of the lips and quivering of the chi (10,11); different neonatal pain scales are based on these indicators. Similarly, body movements are behavioral indicators of pain, and some authors have suggested that hand movements, especially the presence of finger splay and fisting, are associated specifically with acute stress and are more frequently displayed in the infant with acute pain (14).

The complexity of pain suggests that the use of multidimensional pain scales would improve the pain assessment. However, the dissociation that occurs between behavioral and physiological indicators of pain could hinder the recognition of newborns that require analgesic treatment (15). The dissociation of responses to pain displayed by the newborn can be observed when the patient exhibits a behavior that is consistent with pain, although the physiological indicators suggest that the intensity of the nociceptive stimulus is not sufficient to trigger responses in different organs and systems. This phenomenon may be related to problems in the integrity of the central and peripheral nervous system that are associated with the clinical condition of the newborn and to the immaturity of the nociceptive neonatal pain pathways (16,17).

In this context, different neonatal pain evaluation tools available at the clinical setting may lead to heterogeneous results, which could contribute to the difficulty in recognizing the need for pain relief in newborn infants. The aim of the present study was to determine the best strategy for the assessment of pain in healthy term newborns during the first hours of life by comparing the frequency of the detection of pain with uni-dimensional and multi-dimensional scales during an intramuscular injection of vitamin K.

MATERIAL AND METHODS

A cross-sectional study with prospective data collection was performed. The research methods followed the guidelines and standards for research on human subjects of the National Health Council and were initiated with the approval of the Ethics Committee on Research of the Federal University of São Paulo and Padre Albino Hospital.

All patients fulfilled the following inclusion criteria: written informed consent; gestational age between $37^{0/7}$ and $41^{6/7}$ weeks, as determined using the best obstetric estimate; appropriate weight for gestational age (18); and an Apgar score >7 at the first and fifth minutes of life without the need for any resuscitation procedures in the delivery room. Patients were excluded from the study if their mothers had used opioids during pregnancy, labor or delivery or had received general anesthesia for the delivery. In addition, patients with early neonatal morbidities were excluded, as were those patients with major congenital malformations and/or chromosomal syndromes. Finally, neonates born using assisted vaginal delivery or those who experienced a birth injury were also excluded from the study because such conditions would introduce a confounding variable related to the experience of pain.

In the first hour of life, each eligible newborn was placed in an incubator and was naked except for a diaper. After placing an oximeter on his/her right foot, the newborn remained at rest in the supine position, without any handling, for 8 minutes. Immediately following this period, the first pain assessment was performed (T0 or Rest). Two minutes later, a nurse cleaned the lateral left thigh of the newborn using a 70% alcohol swab at room temperature for 30 seconds. After cleansing, another pain assessment was performed (T1 or Cleansing). One minute after cleansing, the same nurse administered 1 mg of vitamin K intramuscularly in the same location using a 1-mL syringe and a 13x4.5-mm needle. During insertion of the needle, the third pain assessment was performed (T2 or Injection). After mild compression with dry cotton, the newborn remained at rest in the supine position for 2 minutes, after which time another pain assessment was conducted (T3 or Recovery). The infants were assessed in real time at the bedside without filming. Before starting the study, specific training with respect to the administration of vitamin K was given by the head nurse to all of the nurses to standardize the procedure. Newborn infants submitted to routine vitamin K injection after birth did not receive analgesia, as per hospital standards at that time.

The pain assessment was performed by evaluating the following scales: the Neonatal Facial Coding System (NFCS), in which pain represented a NFCS score >3 (11,12,19), and the Behavioral Indicators of Infant Pain (BIIP), which defined the presence of pain as a BIIP score ≥5 (20,21). The same observer also assessed the items that make up the multidimensional Premature Infant Pain Profile (PIPP), in which the presence of pain was defined as a PIPP score ≥7 (22). The heart rate and oxygen saturation of the newborns were measured using a pulse oximeter. The translation of the text describing the BIIP was performed by the last author (RG), who had also translated the NFCS and PIPP into Portuguese in 1991 and 1997, respectively. Because all scales were objectively applied by a single observer, the heterogeneity in evaluating the same items in different patients was limited. A pilot study of 50 full-term newborns infants was conducted, and the NFCS, BIIP and PIPP were simultaneously scored during vitamin K injection by the first author as well as a neonatal attending with expertise in pain assessment. This pilot study showed 90-95% agreement between the raters for the individual items of the three scales and aided in the design of a functional flow sheet that would allow a single observer to collect all of the necessary data. A scoring sheet adapted from Hoslti et al. (20) displayed all individual items to be checked as present or absent in the study periods and included space for the heart rate and oxygen saturation values. The observer was unaware of the PIPP, BIIP and NFCS scores

Table 1 - Pain scale scores (NFCS, BIIP and PIPP) for the 4 studied time periods.

		Rest	Cleansing	Injection	Recovery
NFCS	Mean±SD	0.49±1.19	1.35±1.88	5.68 2.88	1.06±1.71
	% RN NFCS >3	15 (4%)	58 (15%)	310 (78%)	41 (10%)
BIIP	Mean±SD	1.41±1.11	2.42±1.68	5.84±2.22	2.07±1.54
	% RN BIIP >4	12 (3%)	64 (16%)	314 (79%)	45 (11%)
PIPP*	Mean ± SD	-	-	8.06±3.32	-
	% RN PIPP >6	-	-	278 (70%)	-

SD: Standard Deviation; * The PIPP score was obtained by comparing T2 (Injection) and T0 (rest).

during the observation of the infants. The full scores were given for each scale after the collection of all data.

The sample size was calculated for a type I error of 5%, a sample power of 90% and a two-tailed hypothesis, assuming that the NFCS would identify 90% of the term infants who experienced pain during acute nociceptive stimulation and that the PIPP and BIIP scales could identify 80% of the term infants who experienced pain in response to the same acute painful stimulus. Given these assumptions, 393 newborns had to be examined simultaneously using the three scales for statistically significant results to be obtained.

The Q and Cochran tests were used to determine the level of agreement between the three rating scales with respect to the presence of pain during the injection (T2), and the McNemar test was then applied to determine the level of agreement between pairs of the scales (two by two). Additionally, a kappa analysis was performed to determine the degree of concordance between the scales with respect to the presence or absence of pain. To compare those newborns for whom the three scales were in agreement concerning the presence or absence of pain to those newborns for whom disagreement was observed between the scales, the Hotelling T^2 test and Bonferroni confidence intervals were applied. Finally, the NFCS and BIIP scores obtained for the four study periods (T0, T1, T2, and T3) were compared using generalized linear regression models with the Bernoulli distribution.

RESULTS

Four hundred newborns (200 males and 200 females) with the following characteristics were enrolled in the study: gestational age of 39±1 weeks, birth weight of 3169±316 g, postnatal age of 67±45 minutes and median Apgar scores in the first and fifth minutes of life of 9 and 10, respectively. Sixty-five percent of the infants were delivered by cesarean section. In the delivery room, 100% of the infants were placed under a radiant warmer. According to hospital routine at the time of data collection, none of the newborns was breastfed or received skin-to-skin contact with the mother in the delivery room.

The NFCS, BIIP and PIPP scores are presented in Table 1. The PIPP scores were obtained by comparing the T2 (injection) and T0 (rest) time points. Measurements were not obtained for three patients due to the poor quality of the plethysmographic waves captured by the pulse oximeter. According to the NFCS and BIIP scales, 3-4% of the newborns exhibited pain-related behaviors in the resting state. During cleansing, this frequency increased to 15% and reached approximately 80% during the injection. Two minutes after the injection, 10% of the newborns still exhibited pain-related behaviors. According to the PIPP, 70% of the newborns had scores that suggested the presence of pain during the injection of vitamin K.

To determine the level of agreement or disagreement between the pain scales during the injection, the number of neonates who exceeded the cutoff score associated with pain using all three tools (agreement) was compared to the frequency at which only one or two of the three scales were indicative of pain (disagreement). Overall, agreement was observed in 85% of the evaluated newborns. In 59 (15%) patients, only two scales showed the presence of pain during the intramuscular injection. Of these 59 patients, 45 (76%) had NFCS and BIIP scores that were suggestive of pain and PIPP scores that were below the pain cutoff (Table 2). The Cochran Q test revealed significant disagreement between the three scales ($p<0.001$).

The Bonferroni confidence interval (CI) was used to determine whether the characteristics of the neonates were associated with the disagreement observed between the three pain scales. Therefore, the patients were grouped according to number of scales whose results agreed with respect to the presence of pain during the intramuscular injection (three scales in agreement, n = 338; two scales in agreement, n = 59), and the results are shown in Table 3. The Hotelling T^2 test demonstrated that there were no differences between the group of newborns for whom the three scales were in agreement regarding the presence of pain during T2 and the group of newborns with disagreement for at least one scale ($p = 0.83$), which indicated that none of the studied neonatal characteristics was associated with the scales used to assess pain.

In view of the disagreement between the assessment tools employed during the painful procedure, we attempted to identify the differences between the scales using the following pairwise comparisons at the time of injection: NFCS *vs.* PIPP, BIIP *vs.* PIPP and NFCS *vs.* BIIP. The comparison of the NFCS to the PIPP with respect to the presence of pain using the McNemar test revealed a

Table 2 - Number (%) of newborns with scores indicative of pain according to the NFCS, BIIP and PIPP scales at the time of vitamin K injection.

	NFCS	BIIP	PIPP	n (%)
Agreement between the 3 scales				338 (85.1%)
NFCS *vs.* BIIP *vs.* PIPP	Pain	Pain	Pain	265 (66.8%)
NFCS *vs.* BIIP *vs.* PIPP	No Pain	No Pain	No Pain	73 (18.4%)
Agreement between 2 scales				59 (14.9%)
NFCS *vs.* BIIP	Pain	Pain	No Pain	37 (9.3%)
	No Pain	No Pain	Pain	8 (2.0%)
NFCS *vs.* PIPP	Pain	No Pain	Pain	1 (0.3%)
	No Pain	Pain	No Pain	5 (1.3%)
BIIP *vs.* PIPP	No Pain	Pain	Pain	4 (1.0%)
	Pain	No Pain	No Pain	4 (1.0%)

Table 3 - Characteristics of the neonates according to the agreement or disagreement between the NFCS, BIIP and PIPP scales regarding the presence of pain during vitamin K injection (T2).

	Agreement	Disagreement	Bonferroni 95% CI
NFCS *vs.* BIIP *vs.* PIPP			
Number	338	59	
Birthweight (g)	3174±320	3146±298	-146.3 to 194.8
Gestational age (weeks)	39.2±1.3	39.1±1.2	-0.6 to 0.8
Postnatal age (minutes)	67.5±45.4	66.3±46.8	-24.9 to 24.2
Male sex (%)	50	51	-0.05 to 0.07
Cesarean section (%)	65	68	-0.06 to 0.12
NFCS *vs.* PIPP			
Number	344	53	
Birthweight (g)	3173±318	3153±311	-148.0 to 187.9
Gestational age (weeks)	39.2±1	39.1±1.2	-0.6 to 0.8
Postnatal age (minutes)	67.5±45.2	66.4±47.9	-23.1 to 25.2
Male sex (%)	65	66	-0.05 to 0.09
Cesarean section (%)	50	47	-0.06 to 0.12
BIIP *vs.* PIPP			
Number	346	51	
Birthweight (g)	3173±319	3149±301	-154.1 to 202.6
Gestational age (weeks)	39.2±1.3	39.1±1.2	-0.6 to 0.8
Postnatal age (minutes)	67.3±45.2	67.7±48.1	-26.0 to 25.3
Male sex (%)	50	49	-0.05 to 0.07
Cesarean section (%)	65	67	-0.06 to 0.10
NFCS *vs.* BIIP			
Number	386	14	
Birthweight (g)	3171±318	3111±238	-253.4 to 373.1
Gestational age (weeks)	39.2±1.3	38.9±1.2	-1.0 to 1.6
Postnatal age (minutes)	67.6±45.7	60.7±37.7	-38.1 to 51.9
Male sex (%)	49	71	-0.19 to 0.63
Cesarean section (%)	64	79	-0.20 to 0.50

95%CI = 95% confidence interval.

significant difference ($p<0.001$), with a kappa index value of 0.66 (CI 0.58-0.74). There were no differences with respect to neonatal characteristics between the newborns for whom the NFCS and PIPP assessments were concordant (n = 344) and those for whom these assessments were discordant (n = 73) (Hotelling T^2 test: p = 0.86), as shown in Table 3. Similar results were found when comparing the BIIP and PIPP; the McNemar test showed a significant difference ($p<0.001$) between these scales, with a kappa index of 0.67 (CI 0.59-0.75), but the characteristics of the neonates in the groups of patients in which BIIP and PIPP were in agreement (n = 346) or disagreement (n = 51) regarding the presence/absence of pain at T2 were similar (Table 3; Hotelling T^2 test: $p = 0.86$).

Finally, the results of the NFCS and BIIP were compared across the four studied time periods. At T0 (rest), 15 (4%) and 12 (3%) newborns exhibited pain behaviors according to the NFCS and BIIP, respectively. At T1 (cleansing), these values were 58 (15%) and 64 (16%), respectively, whereas at T2 (injection), these values increased to 310 (78%) and 314 (79%), respectively, demonstrating scores indicative of pain. At T3 (recovery), these values were 41 (10%) and 45 (11%), respectively, also demonstrating scores indicative of pain. The McNemar test did not reveal any differences between the two scales ($p = 0.47$) at T2. The kappa index values for the four study periods are shown in Table 4. A comparison between the NFCS and the BIIP using generalized linear regression, based on the Bernoulli distribution, showed a significant main effect of time ($p = 0.0004$) but no differences with respect to the main effect of the scale ($p = 0.90$) or the interaction between time and the scale ($p = 0.80$). Both scales changed similarly over time and achieved a maximum score at T2; however, there were no differences in the pain assessment according to the scale, and the scores for the NFCS and BIIP scales failed to change differently over time. Furthermore, there were no differences with respect to the neonatal characteristics between the group for whom the NFCS and BIIP assessments were concordant (n = 386) and the group for whom they were discordant (n = 14) (Hotelling T^2 test $p = 0.79$)

Table 4 - Agreement between the BIIP and NFCS behavioral scales for the 4 studied time periods.

	Pain in both	No pain in both	Pain only in BIIP	Pain only in NFCS	Kappa (95% CI)
Rest	11	384	1	4	0.81 (0.64-0.97)
Cleansing	52	330	12	6	0.83 (0.75-0.90)
Injection	305	81	9	5	0.90 (0.85-0.95)
Recovery	37	351	8	4	0.84 (0.76-0.93)

95%CI = 95% confidence interval.

DISCUSSION

The present study compared the NFCS, BIIP and PIPP scales regarding their ability to assess pain in 400 healthy term neonates during the first hour of life during an injection of vitamin K and found that the unidimensional scales were more sensitive for the detection of pain than the multidimensional scale. The presence of pain was diagnosed 10% more frequently in newborns who were evaluated using the NFCS or BIIP relative to the number diagnosed using the PIPP. However, disagreement was observed between the NFCS and PIPP scales and between the BIIP and PIPP scales. Both behavioral scales, the NFCS and BIIP, changed similarly over time and achieved a

maximum score at the time of vitamin K injection, and an almost perfect agreement was observed between the NFCS and BIIP during the painful stimulus. None of the studied neonatal characteristics were associated with agreement or disagreement among the scales.

To our knowledge, this study is the first to evaluate pain in full-term newborn infants using BIIP at the bedside. The results of the behavioral scales were similar when cutoff scores ≥ 5 for the BIIP and ≥ 4 for the NFCS were used to indicate the presence of pain. In the literature, only three papers report the use of the BIIP to evaluate neonatal pain (20,21,23). In the first two of these studies (20,23), the score used to indicate the presence of pain was not clear, but an average BIIP score of 5 was obtained during the procedural pain stimulus. In the first study (20), 92 infants with a gestational age between 23 and 32 weeks were analyzed, and the BIIP scores at baseline, during heel lancing and during recovery were 1.0 ± 1.8, 5.3 ± 2.6 and 1.8 ± 0.3, respectively. In the second study (21), 69 infants with a gestational age between 24 and 32 weeks were studied, and the BIIP scores at baseline, during heel lancing and during recovery were 1.0 ± 1.7, 5.0 ± 2.6 and 1.6 ± 2, respectively. In the same study, the BIIP scores for heel lancing after a diaper change during the three study periods were 1.0 ± 1.6, 6.0 ± 2.7 and 1.5 ± 2.5, respectively. Therefore, a score of five or greater was selected as indicative of the presence of pain during vitamin K injection in full-term neonates. Our results indicate that this BIIP cutoff is as appropriate as the previously published NFCS cutoff for the diagnosis of neonatal pain at the bedside (19). However, additional studies using different BIIP cutoffs for term and preterm infants and studies comparing the BIIP to other pain scales are needed. In addition, studies using imaging exams to show the location of activated nociceptive pathways should also be conducted.

The PIPP scale is a multidimensional tool that is considered by many researchers and clinicians to be the most suitable scale for the study of acute pain in newborns, especially in preterm neonates (22,24). However, some studies have reported dissociation between physiological and behavioral pain responses (15,25), which reduces the sensitivity of this multidimensional tool. In a study of newborns between the post-menstrual ages of 25 and 43 weeks who underwent clinically required heel lancing, pain was assessed using the PIPP and was correlated with cortical hemodynamic activity using near-infrared spectroscopy (NIRS) (13). The authors observed good correlation between the behavioral parameters of the PIPP scale and cortical activity but only moderate correlation between the physiological variables of the PIPP and cortical activity. These findings are consistent with the results of other studies demonstrating that facial expression is the most specific indicator of pain in neonates (11,12,19). Perhaps the expression of pain in this age group is predominantly displayed through facial movements because the nociceptive pathways in newborn infants activate primarily the nucleus of the brainstem, which is responsible for such movements, rather than the central control regions that are linked to the heart and respiratory rates (13).

The NFCS scale is a diagnostic tool that evaluates only facial movements and enables the differentiation of term (12) and preterm (19) neonates who are subjected to painful and tactile, non-painful stimuli. Moreover, this scale is easy to use at the bedside and has adequate reliability (26). The BIIP is a behavioral tool that combines an assessment of the wake/sleep state with two specific hand movements (finger splay, fisting) and facial actions. This study demonstrated that this scale can also be assessed in real time at the bedside. This scale has the ability to identify pain in premature or critically ill newborns with attenuated facial expressions (27) and in cases where lower facial expressions are not readily observable, such as those infants wearing CPAP masks (21). Studies investigating neonates have suggested that the hand movements evaluated in the BIIP scale occur more frequently in infants of a younger gestational age (28), which potentially indicates a greater sensitivity to pain in this group of infants (29).

Assuming that the intramuscular injection of vitamin K is sufficiently painful to be experienced as pain in healthy term neonates, the pain score will depend on the ability of the employed tool to measure the nociceptive phenomenon. In this context, the results of the present study point to a greater sensitivity of behavioral tools over multidimensional tools in the assessment of acute pain in newborn infants. The inclusion of hand movements and the wake/sleep state did not increase the sensitivity of pain evaluation in healthy term neonates beyond the use of facial movements alone. In preterm infants or patients exposed to multiple painful stimuli, perhaps the attenuation of facial expressiveness and the modulation of pain responses by the wake/sleep state will reveal some difference in the sensitivity of pain assessments using the BIIP or NFCS scales; however, this hypothesis remains to be tested.

Finally, no association between neonatal characteristics, including birth weight, gestational age, sex, type of delivery and postnatal age, and agreement or disagreement between the different pain scales was detected. No studies in the literature have evaluated neonatal characteristics as determinants of agreement or disagreement among different pain assessment tools. The study of healthy infants during the first hours of life reduces the effects that confounders, such as early pain exposure and neonatal illness, may have on pain responses. Thus, the differences observed in the present study with respect to the ability to identify pain in newborns are likely due to the intrinsic properties of the scales themselves.

It is important to note that intramuscular injections are known to be painful and that analgesia should have been considered prior to this study. However, when this study was conducted, vitamin K injections to protect against hemorrhagic disease in newborns were routinely given without any analgesia in the delivery room, and there was much resistance to changing this routine procedure. The results of this study were shown to hospital administrators and health professionals, which led to a change in policy, and now all injections are performed with non-pharmacological analgesia.

The primary limitation of this research, as well as that of all studies that have attempted to assess pain in newborns, is the lack of a gold standard evaluation method to use as a reference tool. Based on the results of this study, behavioral scales may be more sensitive than multidimensional tools for the identification of acute pain during the first hours of life in healthy term newborn infants.

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AUTHOR CONTRIBUTIONS

Arias MC participated in the study design, collection of the neonatal data, data analysis, discussion of the results and writing of the manuscript. Guinsburg R participated in the study design, collection of the neonatal data, data analysis, discussion of the results and writing and revision of the manuscript.

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