Clinical, Physiologic, and Biologic Impact of Environmental and Behavioral Interventions in Neonates During a Routine Nursing Procedure

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Abstract: **The aim of this randomized crossover study was to evaluate the impact of environmental and behavioral interventions (EBI) on behavioral, physiologic, and biologic stress response during a weighing procedure in neonates. Three groups of 15 neonates included (A) gestational age (GA), ≤32 weeks; (B) GA, 32 weeks, 1 day to 36 weeks, 6 days; and (C) GA, ≥37 weeks. Each neonate experienced 2 weighing procedures with and without EBI. Pain was evaluated by using the Neonatal Infant Pain Scale (NIPS) and the Neonatal Pain and Discomfort Scale (EDIN). Heart rate and oxygen saturation were recorded. Salivary samples were obtained for cortisol assay. Cerebral tissue oxygenation index (TOI) was recorded with near-infrared spectroscopy. A significant decrease of NIPS and EDIN was observed with EBI versus control. Mean heart rate was lower with EBI. No difference in cortisol level changes was observed. For groups A and B, a trend of increased TOI was observed with EBI. We concluded that EBI during a nursing procedure provides a decrease in pain scores in preterm and term neonates with changes in heart rate.**

Perspective: ***This study evaluates the impact of combined environmental and behavioral interventions on pain responses in neonates during a weighing procedure. The results indicate a decrease in behavioral pain scores and in heart rate for preterm and term neonates and a trend in increased brain oxygenation depending on gestational age.***

Key words: *Procedural pain, infant, neonate, developmental care, cortisol, NIDCAP.*

Perinatal brain vulnerability increases the risks of early painful events.[4] Repeated painful procedures in hospitalized neonates might lead to short-term and long-term consequences.[20,26] Allodynia defined by the International Association for Study of Pain as "pain due to a stimulus that does not normally provoke pain"[23] has been demonstrated in animal models of early development. Fitzgerald and de Lima[17] suggested that the same mechanism could occur in neonates undergoing intensive care. Porter and al[31] reported an increase in neonatal pain response with handling and immobilization. It can be hypothesized that noninvasive routine nursing procedures in neonatal intensive care units (NICUs) can provoke pain behaviors.[15]

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Treating procedural pain in NICU is now a widely accepted goal. Pharmacologic strategies including opioids and sedatives cannot be routinely used for noninvasive procedures because some concerns exist about their potential side effects.[5] Environmental and behavioral interventions (EBI), commonly called nonpharmacologic strategies, are of interest alone or in combination with pharmacologic treatment.[16] These strategies include kangaroo care, swaddling, maintaining flexed position, rocking, non-nutritive sucking, and touch. Most of the studies on EBI have been conducted in full-term or near-term neonates, with single intervention, for single invasive procedures such as a heel stick.[13,24] Als et al[1] have developed and tested a family-centered, developmentally supportive approach to newborn intensive care referred to as Newborn Individualized Developmental Care and Assessment Program (NIDCAP). Heller et al[22] have reported a decrease in amount of sedatives used in severely ill preterm neonates with NIDCAP as compared with control. A recent trial demonstrated a decrease in physiologic and behavioral responses to diaper change in preterm neonates by using EBI in a NIDCAP-reliable NICU.[33]

The main purpose of this study was to determine the impact of combined EBI on physiologic, behavioral, and biologic responses in preterm and full-term infants dur-

Table 1. Clinical Characteristics of the Study Population (Mean ± Standard Deviation)

	Group A (n = 15)	*Group B (n = 15)*	*Group C (n = 15)*
GA (wk)	30.1 ± 1	34.2 ± 1	39.1 ± 1
Birth weight (g)	1232 ± 243	2140 ± 481	3458 ± 403
Antenatal steroids (n)	14	5	0
Surfactant (number of subjects)	9	1	0
Indomethacin (n)	2	0	0
Caffeine (n)	15	1	0
Age at inclusion (days)	4.8 ± 1.85	3.4 ± 1.64	3.13 ± 1.68
CPAP (n)	11	3	0
CPAP during study procedure (n)	4	2	0
Invasive procedures before inclusion (n)	7.7 ± 2.15	6 ± 2.87	6.33 ± 2.9
Weighing procedures before inclusion (n)	1.73 ± 0.7	1.66 ± 0.6	2.2 ± 1

Group A, GA ≤32 wk; group B, GA 32 wk, 1 day to 36 wk, 6 days; group C, GA ≥37 wk.

Abbreviations: GA, gestational age; CPAP, continuous positive airway pressure.

ing a weighing procedure. We also considered the impact on brain oxygenation by using near-infrared spectroscopy (NIRS).

Methods

Subjects

The study was conducted in a NIDCAP-reliable NICU (NIDCAP training level II; National NIDCAP Training Center, Boston, Mass) at a university hospital. Forty-five patients (18 female and 27 male) younger than 7 days old were studied (Table 1). Three groups were formed according to gestational age (GA): group A with GA ≤32 weeks, group B with GA 32 weeks, 1 day to 36 weeks, 6 days, and group C with GA ≥37 weeks.

Criteria for exclusion were treatment with muscle relaxant, sedative, antiepileptic, or analgesic drug (except sucrose) during the last 24 hours, a congenital defect, a neurologic abnormality including convulsion, intraventricular hemorrhage grade higher than II according to the Papile scale, and periventricular leukomalacia. None received postnatal steroids. This study was approved by the Institutional Research Ethics Committee, and written informed consent from parents was obtained for each patient.

Procedure

All neonates were observed during a weighing procedure. Each neonate was his own control (randomized crossover design) and was weighed twice at 24-hour intervals at the same time of the day, once with EBI and once without. Ordering of conditions was determined randomly by a computer-generated program. The weighing procedure was performed by the nurse in charge of the neonate at the time of the procedure. Some of the nurses were certified to use the NIDCAP assessment tool (NIDCAP training level I; National NIDCAP Training Center). All nurses have received basic education on the NIDCAP approach including the use of EBI. According to the NIDCAP model, EBI included attenuated noise and light with closed doors and covered incubator, lateral posture with head, back, and feet contacting supportive bedding, and opportunity for grasping or sucking. Before the weighing, the neonate was wrapped up, allowing a continuous postural support during transport out of the incubator and during the weighing. The control weighing was performed without specific protection for light or noise, supine posture without swaddling, or any postural support.

Fig 1 summarizes the experimental sequence.

Measures

Behavioral Indices of Pain

Two pain scales were used. The Neonatal Infant Pain Scale (NIPS) developed by Lawrence,[25] ranging from 0 to 7, integrates one physiologic parameter (breathing patterns) and different behavioral components: facial expression, limb activity, cry and state of arousal. Inter-rater reliability and internal consistency reported by Lawrence ranged from 0.92 to 0.97 and 0.87 to 0.95, respectively. The Neonatal Pain and Discomfort Scale (EDIN), a behavioral pain and stress scale developed by Debillon and al,[14] ranging from 0 to 15, was used to evaluate chronic pain and stress. Inter-rater reliability and internal consistency reported by Debillon et al ranged from 0.59 to 0.74 and 0.86 to 0.94, respectively.

The NIPS and EDIN were assessed 2 minutes before and 5 and 30 minutes after the weighing procedure. The NIPS was also assessed during weighing. To avoid any interference with the nurse, only 3 items from the EDIN (facial activity, body movements, and quality of sleep) were scored. Video recordings were performed 2 minutes 30 seconds before, during, and until 5 minutes after the weighing and then 30 minutes after the weighing during 1 minute by using a camera (JVC compact VHS Camcorder, JVC, Japan). Pain scores were independently assessed by 2 coders by using the Video-pro Observer (Noldus, Wageningen, The Netherlands), allowing flashback and slowing down. Individual scorings were compared. Inter-rater reliability was 0.6 and 0.55 for NIPS and EDIN, respectively. A third joint coding was performed for scores with difference higher than 1.

Physiologic Measures

Heart rate and transcutaneous oxygen saturation were continuously monitored (Hewlett-Packard HP M2360A or HP viridia 24C or Agilent monitor M3046A, Palo Alto, Calif). These 2 parameters were collected 2 minutes before the weighing, just before and after weighing, and 5 and 30 minutes after the weighing.

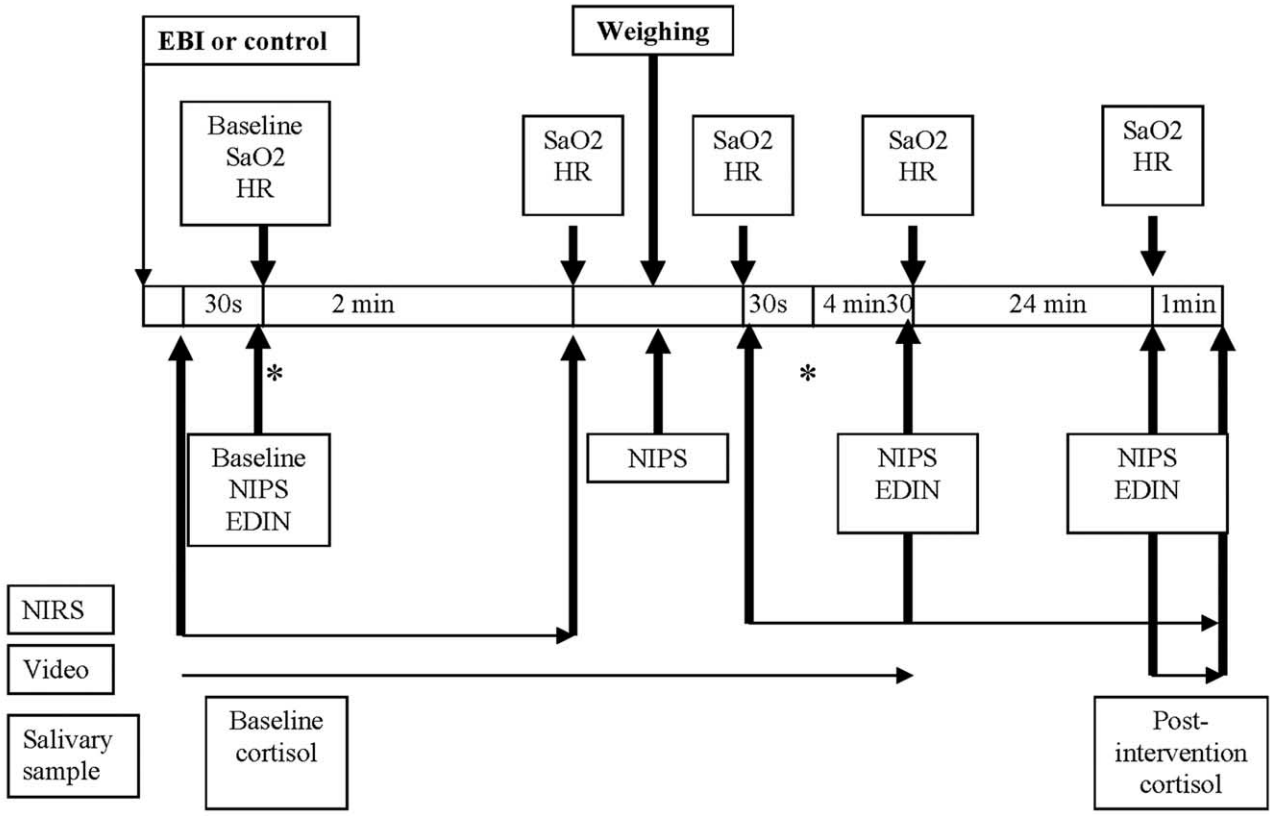

Figure 1. Time line of the experimental procedure. HR, heart rate; SaO2, oxygen saturation. *NIRS zero set.

Salivary Cortisol

Samples of saliva were collected before the NIRS and video recording and 30 minutes after each weighing and at least 1 hour after breast milk tube or oral feeding to avoid milk-related cortisol contamination. Samples were taken by using aseptic filter paper strips (Whatman grade 42 paper, 2.5 × 9 cm). Salivary cortisol concentration was measured by using a commercial high-sensitivity enzyme immunoassay (EIA) kit (detection level range from 0.007 to 1.8 μg/dL) by technicians not informed about the aim of this study (University of Colorado Health Sciences Center, Behavioral Immunology Laboratory, Boulder, Colo).

NIRS

Cerebral oxygenation was measured by using a near-infrared spectroscope (NIRO-300, Hamamatsu, Japan). The optodes were placed at the frontotemporal side with an interoptode distance of 4 cm and a differential path length factor of 3.85. After the NIRO initialization, the baseline was set to zero 2 minutes before the weighing, and recorded data were continuously transferred to a computer. Because of the research design inducing postural changes, a new baseline zero was performed after weighing. By using the spatial resolved spectroscopy method, the tissue oxygenation index (TOI) was recorded 2 minutes 30 seconds before, during, and 5 minutes after the weighing. The average of each curve of difference was determined as the signal was considered horizontal. The same author performed all the NIRS measurements.

Nurses' Satisfaction Index

This index was assessed by using the 18-item self-report questionnaire designed by Westrup et al.[37] Each nurse performing the weighing procedure reported her opinion on the benefit of NIDCAP on the basis of a visual analogue scale ranging from –5 (worse) to + 5 (better).

Number of Invasive Procedures

The number of invasive (blood sampling, intubation, chest tube) and weighing procedures was retrospectively calculated from the medical chart.

Statistical Analysis

Group Size

The NIPS score during weighing was the primary outcome. According to Lawrence,[25] a NIPS score of 4.8 ± 2.5 has been observed during a nursing intervention in neonates. A decrease of 2 points was expected with EBI. For α risk of 5% and β of 10%, fifteen babies were necessary in each GA group (http://oms2.b3e.jussieu.fr/biostaTGV/).

Analysis

Because several measurements were performed on the same subject, correlation between those measurements was analyzed by use of analysis of variance for repeated

measurements (PROC GLM, SAS software; SAS Institute Inc, Cary, NC). Effects of interest were between-subject effects (procedures with or without EBI, GA groups) and within-subject effects (time of measurement, random order of intervention). Results were displayed as pain scores, heart rate, oxygen saturation, and cortisol level adjusted means on baseline measurement (before weighing), GA groups, and order of intervention (±standard errors of the mean) by using least squared estimators (PROC GLM, SAS software).

The correlation between the NIPS score and the nurses' satisfaction was studied by using the Mann-Whitney test.

For the TOI index, the curve of the difference (experimental minus control care) was calculated before and after the weighing. For each neonate, the *t* test was used to compare the average of the TOI curves. A test of frequency conformity was used to evaluate an imbalance of significant positive (index higher with developmental care) and significant negative (index lower with developmental care) results for each group. For all these tests, a *P* value $<.05$ was considered significant.

Results

Pain Assessment

Results for pain score are presented in Fig 2.

For the NIPS, the time effect was statistically significant ($P < .0001$). This time effect was statistically different for the intervention studied ($P = .0018$), with no significant interaction with the order of intervention ($P = .934$) or with the GA group ($P = .17$).

No significant correlation was found between the NIPS score during weighing and the number of former procedures or the nurse satisfaction index ($r = 0.158$; 95% confidence interval, 0.39 to 0.62). The NIPS score during weighing was significantly lower when the nurse was NIDCAP reliable versus nonreliable (0.33 ± 0.51 vs 1.62 ± 1.3; $P = .02$).

For the simplified EDIN, no statistically significant time effect was detected ($P = .19$). Ignoring within-subject effect, the main effect for intervention was significant ($P < .0001$), with no significant interaction with the order of intervention or with the GA group.

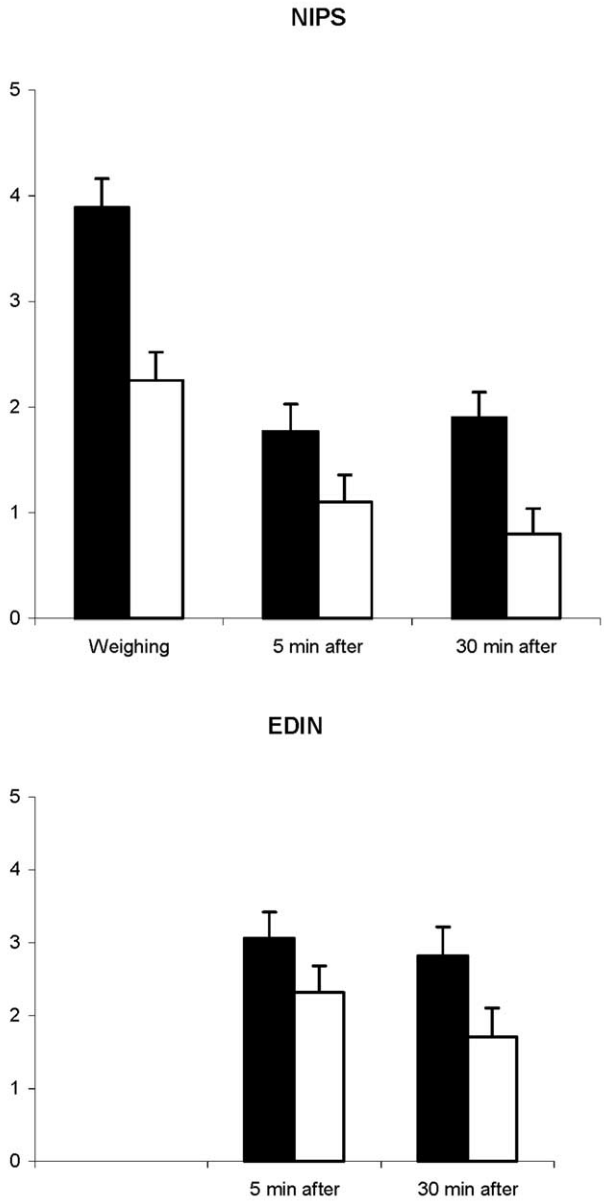

Figure 2. Effects of intervention on NIPS ($P = .0018$) and EDIN ($P < .0001$) scores assessed by analysis of variance for repeated measurements. Means (standard error of the mean) are adjusted on baseline measurement, GA groups, and order of intervention. Filled bars, control; shaded bars, EBI.

Physiologic Parameters

Results are presented in Fig 3. The heart rate was significantly lower with EBI versus control ($P = .0028$), without any interaction of the gestational group and the order of intervention. No significant difference was observed for mean oxygen saturation.

Salivary Cortisol

No significant difference was observed with intervention, the order of intervention, or the gestational group.

TOI

Data from 13 neonates in group A and 14 in groups B and C were available. Results are presented in Table 2. For group A, the number of neonates with a TOI significantly higher with EBI versus control is greater before and after the weighing. This difference is only significant before the weighing ($P < .02$, test of frequency conformity). For group B, the observed trend for an increased TOI with EBI is not significant.

Discussion

The main finding of this study is the significant decrease in pain scores in preterm and full-term neonates with EBI during a weighing procedure. This decrease was observed during the procedure and up to 30 minutes after.

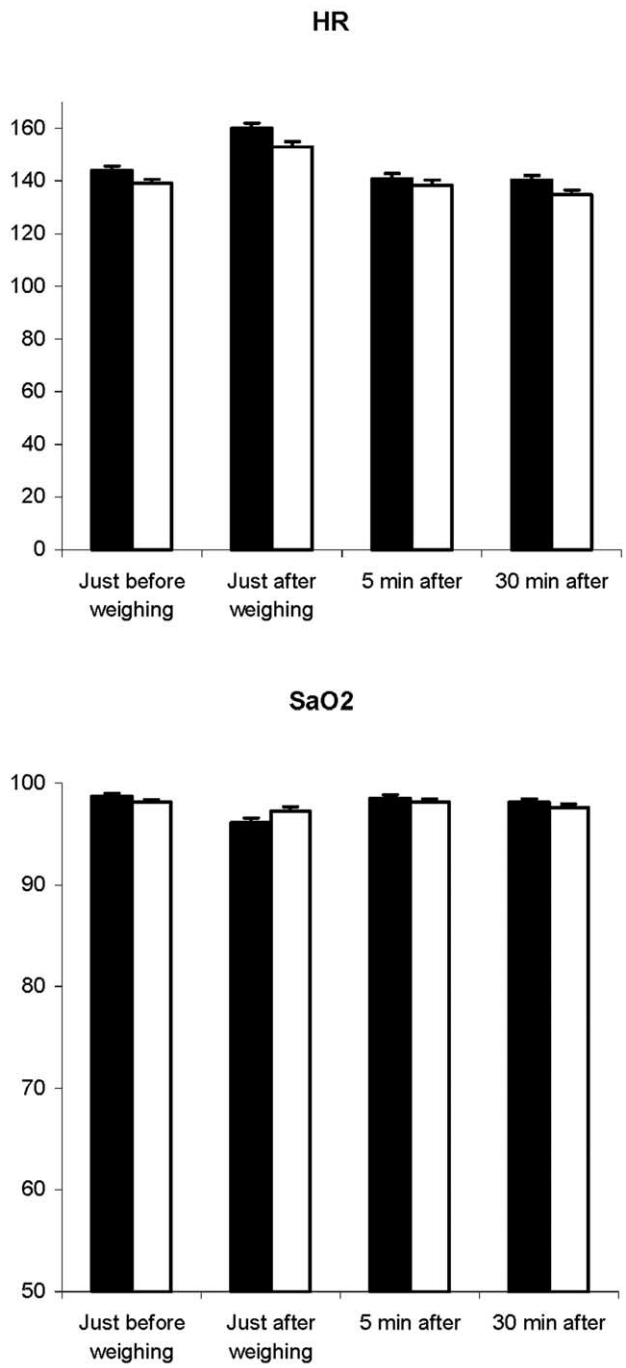

Figure 3. Effects of intervention on heart rate (HR) ($P = .0028$) and oxygen saturation (SaO2) (nonsignificant) scores assessed by analysis of variance for repeated measurements. Means (standard error of the mean) are adjusted on baseline measurement, GA groups, and order of intervention. Filled bars, control; shaded bars, EBI.

To our knowledge, this is the first study exploring the impact of EBI combining physiologic, behavioral, and biologic markers and using NIRS for brain oxygenation evaluation. Nevertheless, our study presents design limitations that are commonly observed in environmental or behavioral trials because of the nature of the intervention[36]: blinding of the intervention was not possible, and blinding of outcome assessment was only possible for cortisol and NIRS evaluation. We tried to limit design bias by using blind randomization, limiting contamination of the control condition, and using standardized pain assessment methods with 2 independent raters.

Several studies have demonstrated the positive impact of single EBI on invasive procedures by using a pain score. Evidence is available on efficiency of non nutritive sucking,[30] sucrose,[35] and kangaroo care.[24] Containing and positioning using swaddling, facilitated tucking, breast feeding, as well as association of interventions have been less studied. Multisensory stimulation described by Bellieni et al[7,8] (side posture, visual and auditory stimuli, massage, olfactory stimuli with perfume, and 33% glucose) was found to be more effective than isolated intervention (sucking or glucose) during heel pricks in preterm and full-term neonates. We have previously demonstrated the positive impact of EBI within the NIDCAP approach in preterm neonates during a diaper change procedure.[33] With the same individualized approach in routine nursing procedures, Becker et al[6] reported a decreased motor activity in preterm neonates. Our study demonstrates the behavioral positive impact in both preterm and full-term neonates.

We demonstrated a positive impact of EBI on heart rate but not on oxygen saturation. This could be explained by a lack of power or a dissociation between physiologic and behavioral stress markers as previously reported.[27,33]

Cortisol is one of the biologic markers of the stress response.[18] Cortisol level has been commonly studied in neonatal pain and stress conditions[3] and in analgesic trials.[21] Salivary cortisol has been suggested as a useful pain-free sampling method for pain and stress research.[10] A good correlation between plasma and salivary cortisol levels has been demonstrated.[12] Filter paper strips allow for sampling a small quantity of saliva (100 μL). This noninvasive sampling technique with the small volume required for analysis could be a method of choice for research on pain in neonates. In our study, no significant change in cortisol level was observed. More research is needed to explore the influence of GA on cortisol response and the ideal timing of sampling after the studied procedure.

NIRS is an attractive method for assessing change in neonatal cerebral oxygenation in physiologic and pathologic conditions and during pharmacologic and nonpharmacologic interventions because it is noninvasive and repeatable.[29] NIRS has been used for assessing change in cerebral oxygenation during stressful or painful interventions.[11,34] Most of the NIRS values are not absolute but relative to the starting point. Inversely, TOI is an absolute value that can be analyzed at different times in the same patient.[28] In our study, a trend indicating an increase of TOI was observed with EBI versus control in preterm neonates. A TOI increase during the first 3 days has been reported by Naulaers et al,[28] probably reflecting an increase in cerebral blood flow. Schulz et al[32] described a significant TOI decrease in preterm neonates undergoing rapid blood sampling from an umbili-

Table 2. Number of Patients According to Change of Tissue Oxygenation Index Induced by Environmental and Behavioral Intervention Vs Control: Significant Increase (Pattern I), Significant Decrease (Pattern II), No Significant Change (Pattern III)

	Group A		Group B		Group C	
	Before Weighing	After Weighing	Before Weighing	After Weighing	Before Weighing	After Weighing
Pattern I	11	8	9	10	5	6
Pattern II	2	4	4	4	9	7
Pattern III	0	1	1	0	0	1

Group A, GA ≤32 wk; group B, GA 32 wk, 1 day to 36 wk, 6 days; group C, GA ≥37 wk.

cal artery catheter. Increase of TOI could be due to oxyhemoglobin increase or total hemoglobin decrease, but interpretation of NIRS data remains difficult.[29]

We did not observe any correlation between the nurses' satisfaction and the NIPS score, excluding potential bias because the intervention was not blind. In contrast, the NIPS score was significantly reduced with a NIDCAP-reliable nurse intervention. The NIDCAP provides an objective tool for identifying individual neonate's threshold of tolerance and providing adapted strategies for neonatal pain and stress control.[19]

The International Evidence-based Group for Neonatal Pain recommends association of pharmacologic strategies and EBI.[5] Franck and Lawhon[16] argue that EBI are not alternatives or substitutes for pharmacologic interventions but represent the basis for pain and stress control. Our study, demonstrating a positive impact of NIDCAP-based EBI, provides additional arguments for this statement and might contribute to better comfort care in NICU.

This study was limited to short-term evaluation. The physiologic and behavioral changes associated with repeated stressful procedures in neonates can be related to long-term sequelae.

Long-term impact of EBI on preterm neonates' neurobehavioral development remains unexplored. Als et al[2] demonstrated recently in a randomized controlled study the positive impact of the complete NIDCAP approach on neurobehavioral development and brain structure evaluated by magnetic resonance diffusion tensor imaging. Underlying mechanisms are unclear, but Anand and Scalzo[4] and Bhutta and Anand[9] speculated that repetitive stress exposure in NICU might cause an excessive N-methyl-*D*-aspartate activation leading to excitotoxic damage on the immature brain. More clinical investigations involving larger patient numbers are needed.

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