ABSTRACT—During their stay in a neonatal intensive care unit (NICU), preterm infants are exposed to adverse stressful experiences that deplete their resources and often result in problematic functioning and developmental outcomes. The impact of specific developmental care practices (e.g., kangaroo care) on preterm infants has been researched extensively. Moreover, the dissemination of knowledge about developmental care has facilitated broader neuroprotective care (NC) that combines different kinds of developmental care practices in different NICUs. However, little is known about how variation in NC affects infants and their long-term developmental outcomes. Using the findings from the Neonatal Adequate Care for Quality of Life project, in this article, we discuss how variation in the NC incorporated by NICUs into standard care affects short- and long-term outcomes in children born preterm.

KEYWORDS—preterm infants; neonatal intensive care unit; developmental care

In the last decades, advances in medical care have increased the survival of infants born preterm. Nevertheless, very preterm infants are at high risk for developing long-term neurodevelopmental impairment. Because of their immaturity and medical status, they require long-term treatment in a neonatal intensive care unit (NICU). As a consequence of their need for life-saving care, neonates are exposed to many stressors, including painful stimuli, disrupted sleep, excessive noise and light levels, frequent handling associated with procedures, separation from their mothers, and disrupted parenting. Preterm infants are unprepared physiologically for the stress outside the intrauterine environment, and these necessary procedures deplete their resources for recovering and developing. Although the health status and neurobehavioral profile of these infants are related to brain immaturity and clinical conditions, preterm infants’ problematic development is at least partly due to physical and psychosocial stressors experienced during their stays in the NICU (1). Infants are often separated from their caregivers, which harms infants’ physiological stability and brain development (2), as well as parents’ psychosocial well-being (3). The lack of emotional and physical closeness between parents and
infants, together with parents’ emotional distress (e.g., depression, anxiety) can negatively affect the parent–infant relationship and result in adverse outcomes for infants’ socioemotional development (4). With that in mind, developmental care and family-centered supportive models of care have been developed to minimize the negative effects of preterm birth, optimize infants’ neurobehavioral development, and improve interactions between parents and infants (2, 5).

Developmental care includes control of external stimuli (e.g., vestibular, auditory, visual, tactile), parental involvement and family-centered care (e.g., kangaroo care, a technique in which infants are placed in direct, skin-to-skin contact with a parent, usually on the breast), breastfeeding, encouraging parent visits, promoting infant–parent bonding, nursing interventions to promote stability (e.g., nesting, swaddling, prone positioning), and pain management in infants (e.g., nonpharmacological analgesia such as non-nutritive sucking, glucose, containment with towels or blankets [6], and analgesia [7]). These interventions may be incorporated into conventional care either as an assortment of activities or using a structured method, such as the Neonatal Individualized Developmental Care and Assessment Program (NIDCAP; 8), the Wee Care Program (9), or the Family Nurture Intervention (10).

Developmental care interventions have been associated with both short- and long-term neurodevelopmental outcomes. Kangaroo care has been linked with positive infant benefits and emotional well-being for parents (11). When preterm infants whose parents participated in parenting programs were discharged from the hospital, the maturation and connectivity of their brains’ white matter were enhanced (12) and they had a more optimal neurobehavioral profile (13). Encouraging parents to hold their babies (14) and using nonpharmacological interventions decreased behavioral distress during pain from medical procedures (i.e., heel pricks). In a meta-analysis, parenting programs led to more positive cognitive outcomes in early childhood (15). Parents also benefited (e.g., they had lower stress levels) when they were supported to improve interactions with their infants during their stay in the NICU (16). Taken together, these findings point to the efficacy of developmental and family-centered supportive care models in NICUs for both infants and parents, and some researchers have recommended these practices (17). In this article, we refer to these practices as neuroprotective care (NC).

The dissemination of research on developmental and family-centered care has slowly shaped the delivery of care to preterm infants and their families. As a result, many NICUs have incorporated some developmentally supportive care into routine management of infants. Nevertheless, most NICUs do not use systematic developmental care methods. Instead, the application in NICUs of procedures and programs considered developmentally appropriate varies considerably (18). In a study in eight European countries, parents were allowed to visit their premature infants in the NICU at any time in most countries, especially in Northern Europe and the United Kingdom. However, in Spain and Italy, fewer than one third of NICUs allowed open access for both parents (19). In a study on developmental care in the United Kingdom, although about 90% of NICUs reported an open visiting policy for parents and 80% of NICUs frequently used kangaroo care, only 64% of NICUs had developmental care personnel and only 57% had staff trained in developmental care (20). In several European countries, rates of breastfeeding (21) and use of nonpharmacological analgesia for pain management (22, 23) varied greatly. Some NICUs have implemented procedures to control external stimuli (e.g., noise), but in some NICUs, staff have failed to support parents’ involvement (24). Thus, while incorporating even some developmental care and family practices is an important advance, NICUs’ care practices vary considerably.

This variation limits the possibility of evaluating the effectiveness of developmental care across NICUs. Developmental care research has typically investigated the effectiveness of single procedures and practices (e.g., kangaroo care) or assessed the effects of structured intervention programs (e.g., NIDCAP). As a result, little is known about how different NC practices and combinations incorporated into NICU routines affect the short- and long-term outcomes of infants and their parents.

**THE NEONATAL ADEQUATE CARE FOR QUALITY OF LIFE PROJECT: AN OVERVIEW**

To learn more about these approaches and their effects, we need to measure the overall level of NC incorporated by NICUs to determine how developmental care practices and procedures are used. Although researchers have measured the extent to which aspects of developmental care have been incorporated into neonatal practice (18, 20, 22, 24), they have not assessed how variations of care are associated with short- and long-term outcomes. To do so, in 2006, scholars launched a large, prospective, multicenter, longitudinal study in 25 regional NICUs in Italy. The goal of the Neonatal Adequate Care for Quality of Life (NEO-ACQUA) study was to examine the relation between the level of NC, and behavioral, language, and quality of life outcomes at preschool age in children born preterm (gestational age ≥ 29 weeks) and compare them with a control group of children born at full term (gestational age ≥ 37 weeks).

In the preterm group, we compared children’s performance by splitting the 25 NICUs into units with high- and low-quality developmental care, then examining whether children’s outcomes were associated with levels of quality of care. All

---

1The word *neo* comes from the ancient Greek *neos*, which means *new*. In Italian, the word *acqua* means *water*. Thus, NEO-ACQUA, meaning *new water*, is a metaphor for the implementation of developmental care, which we take to mean providing to the greatest degree possible a NICU environment similar to the intrauterine environment and promoting development.
children (low-care group, high-care group, and control group) were assessed when they were discharged from the hospital, then at 18, 36, and 60 months.

Based on the findings of the NEO-ACQUA study, next, we report how variation of NC incorporated by NICUs in conventional care affected infants’ neurodevelopment in the neonatal period, and behavioral problems, language skills, and quality of life outcomes in preterm children at preschool age. Rather than providing a detailed report of the results, we aim to offer a new perspective on the possibility of measuring quality of NC in different NICUs. We also seek to highlight how measuring variation in NC in NICUs is essential for examining the efficacy of developmental care practices, especially when they are not used as part of a formal protocol (e.g., NIDCAP) but in a manner more typical of how most NICUs carry out NC practices (i.e., using only a few practices).

MEASURING NC

To measure the level of NC in the NICUs, we developed the quality of care questionnaire (QCQ; 25, 26). The QCQ features 29 items and measures the developmental care practices used in NICUs in several areas: application of specific developmental care practices and policies with parents (e.g., kangaroo care, breastfeeding, and parents’ access to infants), control of the environment (e.g., lighting and noise levels), and procedures for managing infants’ pain (e.g., pharmacological and nonpharmacological practices used during invasive medical procedures, including non-nutritive sucking and swaddling). At each NICU, a neonatologist with at least 5 years of clinical experience who did not care for infants directly completed the QCQ, and we analyzed the responses using factor analysis.

The results revealed two main factors: First, infant-centered care included allowing parents to visit at anytime, kangaroo care, and holding infants during routine procedures; nursing interventions to reduce infants’ expenditure of energy; and promoting physiological stability (i.e., maintaining one or more vital physiological parameters, such as temperature, breathing, or cardiac activity, within value ranges that vary only slightly in the presence of disturbing internal or external factors). Second, infant pain management included the number of pharmacological and nonpharmacological procedures used and the use of a clinical evaluation scale or protocol to manage newborns’ pain. No significant association emerged between the two factors, suggesting that they represented different features of NC.

To evaluate the relationships between the quality of variation in NC in the NICUs and infants’ outcomes, we subdivided the NICUs into units with high- and low-quality developmental care according to their scores on the infant-centered care and infant pain-management indices. Low-quality levels indicated that NC that comprises both infant-centered care and infant pain management were present but were carried out less often. Infant and toddler outcomes were tested in terms of the NC score of each infant’s NICU. (For an overview of the assessment ages, outcome measures, and main results of the NEO-ACQUA study, see Table 1).

INSIGHTS FROM THE NEO-ACQUA STUDY

Levels of NC and Short-Term Outcomes

In a few studies, both single procedures or practices (e.g., parents’ presence) and structured intervention programs (e.g., NIDCAP) improved infants’ neurobehavioral profile (13, 27). In the NEO-ACQUA study, when preterm infants were discharged...
from the NICU, those from NICUs with greater scores on both infant-centered care and infant pain management had a more optimal neurobehavioral profile (as assessed by the NICU Network Neurobehavioral Scale, 28) than infants from NICUs with lesser quality of care (25). These findings tell us that providing more frequent NC has positive early neurobehavioral consequences for infants.

Levels of NC and Long-Term Outcomes

Research has linked neonatal pain to adverse behavioral outcomes (29). In a recent study, regardless of the degree of prematurity and systemic illness, preterm neonates exposed to greater pain in the NICU were at greater risk for internalizing problems at 18 months (30). In the NEO-ACQUA study, at 18 months, children born preterm who spent time in NICUs with low-quality pain management scored higher on internalizing behaviors than children born preterm who spent time in NICUs with a high-quality pain management (31). This finding suggests that incorporating an array of pain-oriented care may promote more optimal long-term behavioral outcomes in preterms. More frequent NC may serve as a protective factor that reduces the impact of depleted physiological and biological resources on infants and may lead to more typical set points linked to exposure to pain-related stress (32). Additionally, minimizing infants’ pain may reduce parents’ stress and enhance their caretaking (33).

Studies have also documented difficulties in language development, even in children who were born preterm and did not have severe clinical complications in the perinatal period, after controlling for general cognitive level at 36 months (34). In part, language difficulties might be associated with early auditory and communicative experiences that are less than optimal. Indeed, increased amount of parental talk with preterm infants in the NICU was associated with improved language at 18 months (35). In the NEO-ACQUA study, at 36 months, children who spent time in NICUs with high-quality infant-centered care (i.e., NICUs with more parent visitation, kangaroo care, and more opportunities for parents to hold their infants, which might provide opportunities for parents to talk to their infants) scored higher in sentence comprehension than children from NICUs with low-quality infant-centered care (36). Thus, preterms from high-care units would have more exposure to adult language than preterms from low-care units. Although alternative but not mutually exclusive interpretations of this finding (e.g., efforts to facilitate the parent–infant emotional relationship) are likely, these findings suggest that language impairments may be understood more fully by considering the levels of the quality of developmental care provided in the neonatal period.

Our study also evaluated health-related quality of life—the combination of health status and the degree to which a child experiences negative emotions related to his or her health (37). Preterm birth has a long-term impact on health-related quality of life, especially in the preschool years (38). In our study, at 60 months, children from NICUs with high-quality infant-centered care scored higher in this area than children from NICUs with low-quality infant-centered care, even after controlling for families’ socioeconomic status, parents’ distress, and children’s development (i.e., social, self-help, motor, language, and letter and number skills; 39). Although it is unclear which process might be involved (e.g., parents might learn early how to scaffold infants’ self-regulatory capacity and buffer infants from stress; 40), this NEO-ACQUA finding suggests that more frequent NC in the neonatal period can promote quality of life up to age 5.

CRITICAL ISSUES AND DIRECTIONS FOR NC

During their stay in the NICU, preterm infants are exposed to numerous sources of stress, including greater environmental physical stimulation (e.g., lights and sounds), painful practices (e.g., invasive skin-breaking procedures), and prolonged separation from their mothers. These early adverse experiences can affect gene expression through epigenetic mechanisms, which might alter developmental trajectories in preterm infants (41). In several studies, greater pain-related stress was related to increased DNA methylation from birth to discharge (42), and at 3 months, the methylation level was associated with temperament difficulties (43) and increased negativity in response to social stress (i.e., Still-Face paradigm; [44]). Adverse experiences associated with NICU practices increase demands for energy, which further deplete preterm infants’ limited resources. As a consequence, the infants have to use more energetic resources to maintain homeostasis and recover from medical conditions, energy that is taken from growth and development. Moreover, these early adverse experiences may alter children’s capacity to regulate responses to stressful events, likely by epigenetic mechanisms. This perspective may help explain the effect of NC practices that reduce energetic demands on infants (40). Thus, we can think about NC as a way to limit the depletion of energy, which in turn frees infants’ resources for recovery and growth.

The positive long-term outcomes detected in the NEO-ACQUA study appear even more suggestive when we consider that none of the study’s NICUs used structured intervention programs (e.g., NIDCAP), but relied on a mix of interventions. The results seem to strengthen findings related to the efficacy of high levels of NC in the NICU per se. Two additional points are worth noting: First, the NEO-ACQUA study’s findings regarding levels of NC (as measured by infant-centered care and infant pain management) suggest that each of these factors contributes differentially to preterms’ development. As a result, a simple view that integrating some developmental care procedures into the NICU routine helps children’s development intrinsically is, at best, limited. Rather, it seems more realistic to consider that developmental care interventions (or an array of developmental care procedures) act on different developmental domains and trajectories. Second, infant-centered care and infant pain
management are global indices that make it difficult to identify which specific practices are related to the outcomes of infants and children from high-care units. Thus, we need randomized clinical trials to ascertain which level of NC or which combination of developmental care procedures best meet the needs of preterm infants and their families. However, in the absence of accepted established guidelines, policies, and procedures to guide developmental care practices, large, multicenter, longitudinal studies such as the NEO-ACQUA study are essential for developing a scientific consensus about the efficacy of developmental care, beyond the implementation of specific intervention programs.

Most NICUs include in their mission providing developmental care. However, comprehensive developmental care may not yet be available in a nursery-wide program that provides support in all core areas of developmental care (5), and it may not provide for all infants and families, from admission through discharge planning, as well as for NICU follow-up care. This may be because of lack of knowledge, an insufficient incorporation of the full evidence base for NC, and the costs of educating providers and implementing best practices. Challenges may also be related to the need for a cultural transformation of the view of caregiving of preterm infants and their families (45), including changes of staff members’ perceptions about the role of NC and its feasibility in the NICU (46). Overcoming these and other barriers will require supporting awareness among NICU teams that instituting high-quality NC primarily requires a shift in attitude and NICU culture. As Goldstein (47) points out, in addition to having the knowledge and skills, to implement NC effectively, “a health care team . . . [needs] a dedicated and determined state of mind.” (p. e1323)

At the methodological level, the NEO-ACQUA study’s questionnaire, the QCQ, permits quantification of NC, which allows comparative analysis of this type of care in NICUs. Using the QCQ, NICU professionals should be able to clearly measure the quality of developmental care in regular activities (9). Thus, although further research is needed to demonstrate its construct validity, the QCQ is useful for evaluating how different levels of NC relate to infants’ outcomes and parents’ distress, for tracking, maintaining, and improving the quality of care within a NICU over time, and for evaluating NICU teams’ attitude and commitment to NC.

In conclusion, for all developmental domains analyzed in the neonatal period (i.e., the neurobehavioral profile) and at preschool age (i.e., behavior, language, and health-related quality of life), more frequent NC mitigated outcomes to such an extent that preterm children had a profile similar to that of full-term children. Taken together, findings from the NEO-ACQUA study provide a new perspective on the possibility of measuring the quality of different NICUs’ NC, and highlight how measuring the variation in such care is essential for examining the efficacy of developmental care.

REFERENCES


