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Multidimensional response to vaccination pain in very preterm, moderate- to-late preterm and full-term infants at age three months

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ABSTRACT

Background: Very early life pain exposure and stress induces alterations in the developing brain and leads to altered pain sensitivity. In premature infants with a history of numerous early postnatal adverse events, behavioral responsiveness and hypothalamic–pituitary–adrenal (HPA) axis reactivity may show alterations as well.
Aims: We compared a multidimensional response to a painful situation (vaccination) in three month old infants. The study involved very preterm, moderate to late preterm infants and full-term infants with varying exposure to pain and stress within the first weeks of life.
Study design: At the age of three months, we evaluated the infants' reactivity to intramuscular injections for immunization.
Subjects: The study included 61 very preterm infants, 30 moderate to late preterm infants and 30 full-term infants.
Outcome measures: We assessed heart rate recovery, Bernese pain Score and increase of salivary cortisol following vaccination. We also evaluated the flexor withdrawal reflex threshold as well as Prechtl's General Movements. Secondly, we assessed factors potentially influencing pain reactivity such as exposure to pain/stress, gender, use of steroids or opioids and mechanical ventilation.
Results: Very preterm, moderate to late preterm and full-term infants showed different reactivity to pain in all analyzed aspects. Very preterm infants showed a lower level of behavioral and physiologic reactivity and exposure to pain/stress predicted lower cortisol increase.
Conclusion: At three months of age, very preterm infants show an altered level of HPA axis reactivity. Efforts aiming at minimizing pain and stress in premature infants should be taken.

1. Introduction

Preterm infants show an increased risk of delay in development. In addition to existing well-defined factors like intraventricular hemorrhage or infection, recent research has shown that exposure to pain and stress are associative factors for the development of neurocognitive impairment [1–3].

In preterm infants brain development including differentiation of neurons, formation of synapses and differentiation of glial cells [4,5] has to take place in the extrauterine environment of the neonatal intensive care unit (NICU) where infants are exposed to numerous skin-breaking procedures, handlings and painful interventions. As suspected, higher pain exposure during the NICU stay was associated with decreased brain size at term [6] and retardation in white and gray matter maturation [1]. Furthermore, Anand and Scalzo postulated that exposure to repetitive pain causes excitotoxic damage to developing neurons as a result of excessive NMDA activation which negatively affects central nervous system organization [7]. Functional magnetic resonance imaging (MRI) examinations in school-aged children with experience in a neonatal intensive care unit after preterm birth showed significantly higher pain-specific activations indicating permanently altered central pain pathways [8].

Apart from these morphologic and functional changes, early postnatal adverse events are associated with alteration of stress factors and behavioral responsiveness to stressors throughout infancy and childhood up to adult age [9–11]. Early programming of the hypothalamic–pituitary–adrenal (HPA) axis plays a key role in this context [12]. Salivary cortisol has been frequently used as a stress biomarker for evaluation of HPA axis reactivity and was validated for numerous cohorts, including preterm infants [13].

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Thus, changes in brain morphology, function and neurocognitive outcome have been undeniably linked to adverse pain- and stressful events during the NICU stay in preterm infants. Studies that aim to dissect the underlying causes, however, are lacking to date.

We therefore evaluated a multidimensional response to a painful situation (vaccination) at three months of age in three groups of infants: very preterm, moderate to late premature and full-term infants. Evaluated parameters included behavioral, physiologic and hormonal reactivity as well as pain sensitivity. We hypothesized that reactivity to intramuscular injections for immunization at three months of age depended on the respective degree of immaturity at birth and that infants show different responses in all evaluated aspects. We additionally hypothesized that factors such as gender, mechanical ventilation, exposure to pain and stress and exposure to opioids or pre- or postnatal steroids during the NICU stay independently affected reactivity to pain.

2. Patients and methods

From October 2008 to January 2012, a total of 121 infants were consecutively included in the study. The study population consisted of 61 very preterm (gestational age (GA) < 32 weeks and birthweight < 1500 g), 30 moderate to late preterm (GA ≥ 32 and <37 weeks) and 30 full-term infants (GA ≥ 37 and <42 weeks). Recruitment of very preterm and moderate to late preterm infants was performed by the Department of Neonatology, and full-term infants were recruited from the Department of Obstetrics of the University Hospital of Cologne.

We did not include infants suffering from intraventricular hemorrhage (IVH) > grade 2, periventricular leukomalacia, neuromuscular disease, severe malformations and infants that were small for gestational age (birth weight < 3rd percentile).

The study was approved by the Ethics Committee of the University of Cologne. Prior to all study procedures, we obtained informed consent from all parents.

3. Method

Pain reactivity was assessed in response to two intramuscular injections of 0.5 ml volume of immunization vaccine (INFANRIX®·hexa, GlaxoSmithKline Biologicals, Belgium and Prevenar 13®, Pfizer, UK).

According to German recommendations [14], the first vaccination is scheduled at eight weeks of (chronological) age. Very preterm infants have to be at least 60 days old and have a weight of >1800 g before the vaccination procedure is recommended. Immunization procedures involve two intramuscular injections into the left and right anterior thigh. For ethical reasons, both injections were administered one after the other without any break and within a short period of time (within seconds). Infants were positioned supine on the examination table while injections were administered. Parents were present and non-pharmacologic analgesic methods including 1 ml glucose 20% and non-nutritive sucking on finger or pacifier were applied to all infants before vaccination. Infants could be fed until 1 h before the start of the vaccination procedure.

Administration of immunization vaccinations to late preterm and full-term infants was performed at the neonatal unit and carried out by the attending pediatrician. Visits were scheduled between 8:00 am and 2:00 pm, depending on parental request. Infants born <28 weeks of gestation needed to be monitored for apnea and adverse events for 48 h after vaccination [15]. For this reason, very preterm infants are generally vaccinated shortly before discharge.

4. Clinical data collection

We assessed the following baseline parameters of the infants: Maternal age, mode of delivery, gestational age, weight at birth, Clinical Risk Index for Babies (CRIB) Score [16] (surrogate for illness severity on the first day of life for very preterm infants), use of prenatal and postnatal steroids, and Apgar score at 5 and 10 min after birth. We also recorded length of stay at the NICU and in the hospital, days spent on mechanical ventilation and continuous positive airway pressure (CPAP), opioid treatment and major complications due to prematurity.

4.1. Measures

The summarization of our study workflow is presented in Table 1.

In contrast to other studies [17,18] we did not only assess skin-breaking procedures, but also potentially painful events. The cumulative amount of skin-breaking and non-skin-breaking procedures was used as a cumulative score for pain-related stress from birth to discharge. Skin-breaking procedures included heel lances for capillary blood sampling, venous or arterial puncture for blood sampling, insertion of chest tubes, lumbar punctures, and insertion of peripheral, central venous or arterial catheters. Non skin-breaking procedures with pain or stress potential included pharyngeal and endotracheal suctioning procedures, insertion of gastric tubes, endotracheal intubations and ophthalmic examinations. These pain- and stressful events were analyzed as categorical variables and the number of pain- and stressful events was divided into classes 1–10, 11–100, >100.

The flexion withdrawal reflex which we tested within the first week of life and at the time of vaccination was used as a marker of somatosensory development and pain sensitivity [10]. We used calibrated von-Frey-Filaments made of nylon monofilaments (MARSTOCK nervtest, Marburg, Germany) for reflex testing. The strength of the filaments is arranged logarithmically and was applied in a range of 0.1–18.5 g [19].

Assessment of Prechtl's General Movements (GMs) was performed to identify infants at risk for major neurologic abnormalities. Lack of fidgety movements and a cramped synchronized GM pattern are associated with neurologic deficits [20] and severe neurologic impairment may influence reactivity to pain. GMs are referred to as writhing movements and can be observed up to the first two months after term. At the age of six to nine weeks of corrected age, GMs transition from a writhing pattern to a fidgety pattern. Since very preterm infants were vaccinated at a mean corrected age of two weeks, we primarily assessed writhing GMs in this group and fidgety movements in moderate to late and full-term infants. For the assessment of GMs [20], full-term and late preterm infants were videotaped for 5 min (assessment of fidgety movements) and very preterm infants for 20 min (assessment of writhing movements) as recommended by Prechtl and Einspieler [20] before performing vaccination in a quiet (non-crying) state. Assessment was performed post hoc by two trained raters.

During the vaccination process, videotaping was continued. Rating of behavioral pain using the Bernese pain scale for neonates (BSN) [21] was performed post hoc by two experienced raters (neonatologists). For scoring, merely behavioral items of the BSN were applied, the interrater correlation was 0.7. Cut-off value for painful behavior was set to >8 points [21]. Since the second injection was administered only seconds after the first injection and infants had no opportunity to calm down between injections, and the pain induced by both intramuscular injections was assessed.

Continued heart rate measurement via pulse oximetry was performed. Basal and peak values as well as time to recovery to baseline (seconds) were documented. The baseline value represents an average

Table 1
Summarization of our study workflow.

Parameter	Time of assessment
Cumulative pain score	From birth to discharge
Flexor withdrawal reflex threshold	Within first week of life and at vaccination
Time to recover for heart rate to baseline	At vaccination
Bernese pain score	At vaccination
Prechtl's general movements	At vaccination
Salivary cortisol	Before vaccination and 20 min after