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Pain threshold, tolerance and intensity in adolescents born very preterm or with low birth weight

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ABSTRACT

Background: Data on long-term consequences of neonatal pain is limited.
Aim: To assess whether perinatal factors, later pain experience and pain coping strategies are associated with altered pain threshold, pain tolerance and pain intensity in adolescents born preterm.
Study design: Observational, longitudinal study (Project on Preterm and SGA-infants, POPS-19).
Subjects: We analyzed data of 412 adolescents at the age of 19 years, who were born at a gestational age < 32 weeks or with a birth weight < 1500 g.
Outcome measures: Participants performed a standardized cold pressor test to assess pain threshold, tolerance and intensity. Furthermore, they completed a pain coping questionnaire (PCQ).
Results: In univariate analysis, female gender and necrotizing enterocolitis (NEC) were associated with lower pain tolerance, indicated by reaching the ceiling time of 180 s in ice water (females 19% vs males 29%, NEC 7% vs no NEC 25%). Female gender was associated with higher pain intensity (mean difference 0.58; 95%CI 0.21; 0.95) and lower pain threshold (log rank test p 0.007). In a multivariate Cox regression analyses, emotion focused avoidance pain coping style was significantly associated with lower pain threshold (hazard ratio HR 1.38; 95%CI 1.02; 1.87) and pain tolerance (HR 1.72; 95%CI 1.21; 2.42). NEC was significantly associated with lower pain threshold (HR 1.47; 95%CI 1.01; 2.14) and pain tolerance (HR 1.63; 95%CI 1.09; 2.41).
Conclusion: In adolescence, maladaptive pain coping strategy was associated with lower pain threshold, pain tolerance and higher pain intensity. NEC was associated with altered pain response in adolescents born preterm.

1. Introduction

Despite the increasing awareness regarding pain and pain management in the neonatal intensive care unit (NICU), preterm infants are subjected to 11–14 painful procedures every day [1,2]. Repeated procedural pain and stress in neonatal life have been associated with long-term effects on pain response and pain behavior [3]. Pain response and pain behavior are mainly determined by pain threshold and pain tolerance. Pain threshold is defined as the minimum intensity of an external stimulus that is perceived as painful [4]. Pain tolerance is the maximum level of pain that a subject is able to tolerate [4].

Pain threshold and tolerance have been studied in NICU survivors [5–8]. While in two studies a decrease in thermal sensitivity in NICU survivors when compared to healthy term controls was found [5,6] others have shown an increase [7,8]. Pain intensity in children born preterm, subjected to cold pressor tests (CPT), was found to be similar to healthy controls [8]. Gender differences in CPT test results have been reported but are inconsistent across studies [5,8,9]. Pain coping strategy has been reported to modulate pain tolerance. Internalizing pain coping strategies have been associated with lower pain tolerance

Abbreviations: AGA, Appropriate for Gestational Age; CPT, Cold Pressor Test; CI, Confidence Interval; IVH, Intraventricular Hemorrhage; NEC, Necrotizing enterocolitis; NICU, Neonatal Intensive Care Unit; NRS, Numerical Rating Scale; PCQ, Pain Coping Questionnaire; POPS, Project on Preterm and Small for gestational age infants; PTH, Pain Threshold; PTO, Pain Tolerance; SD, Standard Deviation; SGA, Small for Gestational Age

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[10], but in a more recent study no such association was found [11]. We reported a limited effect of neonatal demographics and disease severity on pain coping strategy in adolescence [12]. However, a positive association between intraventricular hemorrhage and emotion focused avoidance was found [12]. Emotion focused avoidance is a pain coping style, comprising internalizing and externalizing pain coping strategies [13].

Altered pain responses in NICU survivors may be mediated by pain experiences in the neonatal period. The Collaborative Project on Preterm and Small for Gestational Age Infants in the Netherlands (POPS-1983) is a national follow-up study on the effects of preterm birth or growth restriction on later outcome in childhood and adolescence. In this large population-based cohort, we examined at the age of 19 years pain threshold, tolerance, and intensity using the CPT. We hypothesized that key neonatal demographic variables and estimates of disease severity would be associated with altered pain response and behavior in later life in children born preterm or with very low birth weight. Neonatal variables such as birth weight and gestational age are inversely related to the number of painful procedures [14]. Also serious disease conditions (e.g. sepsis and NEC) lead to an increase of skin breaking events, as intermittent blood sampling and intravenous catheter placement are necessary. Furthermore, we were interested if pain response was influenced by pain coping strategies or current pain in adolescence.

2. Methods

2.1. Subjects

The Collaborative Project on Preterm and Small for Gestational Age Infants in the Netherlands (POPS-1983) cohort comprised 94% (n = 1338) of all babies born alive in the Netherlands in 1983 with a gestational age below 32 weeks or a birth weight < 1500 g [15].

2.2. Procedure

At the age of 19 years, 959 survivors were invited to participate in an extensive follow-up program, including assessment of pain threshold, tolerance and intensity with a standardized CPT. All medical ethics review boards of the participating medical centers approved the study protocol. All subjects provided written informed consent to participate in the study. Details, logistics and response rate have been reported previously [16].

For the CPT, a cooling box was filled with water and ice-cubes. As small differences in water temperature might contribute to conflicting results [9], we included in our analysis only tests in which water temperature remained stable between 4 and 6 °C during the test. The ice cubes were removed during the immersion, to prevent contact between ice and skin. The subject was asked to place the forearm in the ice water with fingertips resting on the bottom. During the test, the subject was asked to verbally mark the beginning of the first painful sensation (pain threshold T1, expressed in s). Pain tolerance was defined as the moment the subject removed the arm from the water (T2, expressed in s). After 180 s the test was discontinued, a ceiling time that is recommended in pediatric populations [17]. Participants were not informed about the ceiling time before the start of the test. During immersion every subject was asked to grade the pain with the Numerical Rating Scale (NRS) at pain threshold (NRS1) and pain tolerance (NRS2). NRS is scored on a 0 to 10 point scale, 0 indicating no pain and 10 indicating the most intense pain imaginable [18,19].

2.3. Background characteristics

Basic demographic data were extracted from the POPS database. We selected the following neonatal variables as estimates of disease severity: necrotizing enterocolitis (NEC, stages ≥ 2 according to Bell's criteria [20]), sepsis (defined as positive blood culture [21]), intraventricular hemorrhage (IVH, all grades, according to Papile [22]), days on respiratory support (need for CPAP and/or mechanical ventilation) and length of NICU stay. To account for the effect of multiple morbidities during the neonatal intensive care period, we calculated a cumulative co-morbidity score based on presence (score 1) or absence (score 0) of being Small for Gestational Age (SGA), NEC, sepsis, IVH and respiratory support. We selected from the follow-up participants variables indicating current episodes of headache, pain in muscles, joints, back or stomach, and earache. Likewise, the presence or absence of these variables yielded a cumulative current pain score.

2.4. Pain Coping Questionnaire (PCQ)

The PCQ is a validated instrument to assess pain coping strategy in adolescents [13]. The PCQ comprises 39 coping items categorized across three higher order factors. The higher order factor 'emotion focused avoidance' comprises externalizing and internalizing, both maladaptive coping styles. The higher order factors 'problem focused avoidance' and 'approach' reflect adaptive coping styles [13].

2.5. Statistical analysis

For normally distributed data, mean and standard deviation (SD) were calculated, otherwise median and interquartile range (IQR) were calculated. Differences between the cohort with complete CPT and PCQ test and POPS participants without CPT within the specified temperature range were calculated with the chi-square test for dichotomous data and with the Student-*t*-test or Mann-Whitney *U* test for normal and non-normal continuous data, respectively. We tested the internal consistency of the higher order scales of the PCQ by calculating Cronbach's alpha.

2.5.1. Pain threshold and tolerance analysis

Mean (SD) for time spent in ice water was calculated for all dichotomous variables. In addition we calculated the proportion of participants reaching the ceiling time of 180 s before pain threshold or pain tolerance was reached. Kaplan-Meier analysis was used to calculate differences in time spent in ice water and surviving to the ceiling time of 180 s across dichotomous subgroups. Statistical significance was tested using the log rank test. For continuous variables, we calculated hazard ratios with 95% confidence intervals using a univariate Cox regression model. Subsequently, variables that were significantly associated with pain threshold and tolerance in univariate analyses were included in a multiple Cox regression model to identify factors that were independently associated with pain threshold and pain tolerance.

2.5.2. Pain intensity analysis

Associations between neonatal demographic variables, estimates of disease severity, cumulative co-morbidities, cumulative current pain, PCQ higher order factors and NRS scores at pain threshold and pain tolerance were tested with Student *t*-test for dichotomous predictors, and linear regression otherwise.

Data were analyzed with the SPSS v19.0.0 software program (IBM, New York, USA). A two-sided p-value < 0.05 was considered statistically significant in all analysis.

3. Results

Of the 959 survivors in the POPS data set, 431 (45%) underwent a CPT in water with a temperature ranging from 4 to 6 °C. Mean (SD) age of study participants was 19.3 (0.2) years. In total 412 candidates completed both CPT and PCQ testing (Fig. 1). Cronbach's alpha for the approach, problem focused avoidance and emotion focused avoidance higher order factors of the PCQ were 0.89, 0.91 and 0.86 respectively,