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Effect of increased opiate exposure on three years neurodevelopmental outcome in extremely preterm infants

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ABSTRACT

Background: International guidelines recommend the use of item based scales for the assessment of pain and sedation. In our previous study, the implementation of the Neonatal Pain Agitation and Sedation Scale (N-PASS), and the associated systematic assessment and treatment of pain and sedation reduced pain and over-sedation in our intervention group, but lead to a significant increase of individual opiate exposure. This increased opiate exposure was not associated with impaired motor and mental development at one year of age. As one-year follow-up is not necessarily representative for future outcomes, we retested our sample at three years of age.

Methods: Fifty-three patients after (intervention group) and 61 before implementation (control group) of the N-PASS and the Vienna Protocol for the Management of Neonatal Pain and Sedation (VPNPS), were compared for motor, mental and behavioural development at three-years follow-up using the Bayley Scales of Infant Development.

Results: Cumulative opiate exposure was not associated with mental ($p = .31$) and motor ($p = .20$) problems when controlling for other important medical conditions, but was associated to lower behavioural scores ($p = .007$). No statistically significant differences were found with regard to mental ($p = .65$), psychomotor ($p = .12$) and behavioural ($p = .61$) development before and after the implementation of the N-PASS and the VPNPS.

Conclusion: Implementing a neonatal pain and sedation protocol increased opiate exposure without affecting neurodevelopmental outcome at three-years of age.

1. Introduction

Until the eighties it was widely accepted that newborns, especially those born prematurely, were not able to feel pain and that administration of sedative and analgesic drugs would have more harmful rather than beneficial effects [1]. This hypothesis was based on the fact that the thalamo-cortical connections, essential for the perception of pain at a cortical level, were still absent or developing in the premature brain [1, 2]. The way of thinking changed radically in the following years when different research groups were able to demonstrate that the somatosensory cortex can be activated in response to noxious stimuli in preterm born infants in the 25th week of gestation and thereafter [3, 4]. Extremely preterm infants are constantly exposed to painful and stressful situation that can have an impact on the developing brain [5–10]. Sedative and analgesic drugs, which have the potential to calm the patient and to blunt pain [11], are therefore essential agents in every neonatal intensive care unit.

However, administration of sedative and analgesic drugs may have adverse consequences for the developing brain too [12–15]. Studies have also specifically investigated the effect of opiates on preterm infants at different stages of development, but results are controversial leaving the debate still open [16–23]. In a previous study, we were able to demonstrate that increased opiate exposure had no influence on mental and motor development in our sample at one-year follow-up

Abbreviations: BRS, Behaviour Rating Scale; BSID-ll, Bayley Scale of Infant Development second edition; CRIB, Clinical Risk Index for Babies; ELBWI, Extremely Low Birth Weight Infant; EPIPAGE, Epidémiologique des Petits Ages Gestationnels; MDI, Mental Developmental Index; NICU, Neonatal Intensive Care Unit; N-PASS, Neonatal Pain, Agitation and Sedation Scale; PDI, Psychomotor Developmental Index; SDQ, Strengths and Difficulties Questionnaire; V-PNPS, Vienna Protocol for Neonatal Pain and Sedation

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[24]. However, since one-year follow-up is not strongly representative for later outcomes, we decided to investigate neurodevelopmental outcomes again at the age of three-years.

2. Methods

2.1. Setting

This study was conduced at two 10-bed Neonatal Intensive Care Units (NICUs) of the Medical University of Vienna, a tertiary perinatal center admitting > 180 preterm infants < 1500 g per year.

2.2. Procedure and aim

In 2010, after approval of the institutional review board of the Medical University of Vienna (EN.:704/2010), a score for the systematic assessment of pain and sedation was implemented in our two 10-bed NICUs: the Neonatal Pain, Agitation and Sedation Scale (N-PASS) [25]. The N-PASS was developed as a clinically relevant tool to assess prolonged pain and sedation in infants, as well as acute-procedural pain. Concomitantly with the N-PASS we also implemented a standardized protocol for the management of neonatal pain and sedation called the Vienna Protocol for Neonatal Pain and Sedation (V-PNPS) [26]. The V-PNPS includes well-defined strategies for both non-pharmacologic and pharmacologic interventions based on regular assessments of the Neonatal Pain Agitation and Sedation Scale (N-PASS) [26]. The implementation of the N-PASS and V-PNPS resulted in an increased opiate administration without any effect on in-hospital and one-year neurodevelopmental outcomes [24, 26]. However, since one-year outcomes are not strongly representative for later development, we decided to test our sample again at the age of three years.

2.3. Patients

To analyse the effect of the implementation of a systematic evaluation of pain and sedation in extremely premature neonates, we compared our intervention group (one year after the implementation of the VPNPS) with an historical control group (up to one year before the implementation).

2.4. Measure

All children were tested using the Bayley Scale of Infant Development Second Edition (BSID-ll) [27]. The BSID-ll is a valid and reliable tool for the assessment of a broad spectrum of skills during the first years of development. It includes cognitive abilities such as memory, language and problem solving as well as motor abilities such as co-ordination, fine manipulation and degree of body control, and it also includes a rating scale for the assessment of behavioural problems.

2.5. Statistical analysis

For qualitative data, counts and percentages were calculated; for quantitative data, the mean and standard deviation (SD) were calculated. Baseline characteristics, outcomes, and population characteristics at follow-up before and after intervention were compared using 2-sample *t*-tests for continuous outcomes and Chi-square test for categorical outcomes. Neurodevelopmental outcomes were analysed using a multivariable Tobit regression model by means of “proc qlim” in SAS 9.4 (SAS Institute, Cary, NC, USA). These analyses included adjustment for the following baseline characteristics and risk factors: group assignment, postmenstrual age, severe intraventricular haemorrhage (IVH), severe retinopathy of prematurity (ROP), necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD) (defined as oxygen/need for respiratory support at 36 weeks' corrected age) and cumulative opiate exposure. Repeated measurements were taken into account by inclusion of a patient specific random effect for the intercept. Analyses were performed using SAS and SPSS 21 for Mac (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA). p-Values < .05 were considered statistically significant but should be interpreted as exploratory only due to the retrospective nature of the study. Confidence intervals were also provided.

3. Results

Compared to the previous study [24], 26 patients (18.5%) were lost to follow-up (12 in the intervention group vs. 14 in the control group) at three years of age. This is in line with the dropout ratio of our follow-up clinic as well as in accordance to the literature [28].

One-hundred-fourteen patients were available for statistical analysis. A significant decline in motor abilities and behavioural performance was noted for all patients in the BSID-ll between one and three years of age (PDI: p = .003, estimate: −4748; BRS: p = .001, estimate: 13,350). No differences were found in the mental developmental index (MDI: p = .216, estimate: 1614) when looking at the performance of our patients longitudinally. Patients in the intervention group were

Table 1
Population characteristics and in-hospital outcome of patients seen in follow-up.

	Intervention group = 53	Control group = 61	95% Confidence interval		p-values
Descriptive characteristics					
Male (n,%)	30 (56.6)	33 (54.1)	0.43	1.89	.851
Gestational week at birth (mean ± SD)	25.81 ± 1.95	25.84 ± 1.62	−0.63	0.68	.941
Birth weight, g (mean ± SD)	791.04 ± 237.85	846.46 ± 217.50	−29.10	139.94	.197
Cumulative opiate exposure (mg/kg)	94.73 ± 244.38	13.38 ± 35.71	−149.27	−13.42	.020
CRIB Score (mean ± SD)	5.73 ± 3.27	4.40 ± 3.32	−2.55	−0.09	.035
Mechanical ventilation (n,%)	32 (60.4)	37 (60.7)	0.46	2.09	.564
Days on mechanical ventilation (mean ± SD)	3.3 ± 6.0	4.9 ± 8.6	−1.05	4.63	.216
No. of patients with central catheter (n,%)	53 (100)	59 (96.7)	1.59	2.26	.498
Time to full enteral feeds, days (mean ± SD)	41.42 ± 15.1	38.69 ± 24.99	−6.63	12.01	.569
Oxygen at 36 weeks (n,%)	21 (39.6)	12 (19.7)	1.16	6.19	.023
IVH grade ¾ (n,%)	3 (5.7)	6 (9.8)	0.13	2.31	.500
ROP ¾ (n,%)	17 (32.1)	14 (23.0)	0.69	3.63	.298
NEC requiring surgery (n,%)	5 (9.4)	8 (13.1)	0.21	2.25	.571
Patients with bacteremia (n,%)	17 (32.1)	20 (32.8)	0.44	2.12	.541
Time to discharge from NICU, days (mean ± SD)	74.7 ± 35.6	72.1 ± 34.3	−15.03	11.00	.759
Weight at 3 years follow-up, Kg (mean ± SD)	13.64 ± 1.55	13.80 ± 1.63	−0.92	1.24	.771
Length at 3 years follow-up, cm (mean ± SD)	94.58 ± 5.94	95.09 ± 3.30	2.51	3.54	.776
Head circumference at 3 years follow-up, cm (mean ± SD)	49.31 ± 1.5	48.70 ± 1.4	−1.62	0.40	.232