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Main results of the feasibility study

VARIABILITY IN PAIN RESPONSE TO A NON-PHARMACOLOGICAL INTERVENTION ACROSS REPEATED PAIN EXPOSURE IN PRETERM INFANTS IN A NICU. A FEASIBILITY STUDY

Study as part of the research portfolio "PAin Management In NeonAtes" (PAMINA)
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1. MAIN RESULTS OF THE FEASIBILITY STUDY

1.1 AIMS OF THE FEASIBILITY STUDY

The purposes of this feasibility study was to examine the variability in pain reactivity of neonates receiving a standard of care non-pharmacological intervention (Sucrose) for pain across repeated painful procedures and to examine the feasibility of performing the research procedures planned for a subsequent pilot study (randomized clinical trial) comparing the impact of non-pharmacological interventions on pain reactivity and the sustainability of their benefit across pain procedures. We planned to submit a grant proposal for the subsequent trial to the Swiss National Science Foundation.

Therefore, we performed a descriptive-explorative feasibility study in two sites (NICU in Basel and Bern) during the time period from 1st November to 31st December 2007 in order a) to examine a realistic recruitment rate, b) to examine the feasibility of the planned procedures (oral saliva cortisol sampling, videotaping, pain assessment by different tools and amplitude-integrated electroencephalogram as a measure of alertness in preterm infants) and c) to explore the variability in pain responses during repeated heel sticks in preterm infants receiving 20% oral sucrose prior to each heel stick and d) to test the interrater-reliability of pain measurements between raters assessing pain by three tools ("Bernese Pain Scale for Neonates", "Premature Infant Pain Profile", "Visual Analogue Scale"). We performed the measurements during 5 routine heel sticks taking place in the first 14 days of life (5 time points).

1.2 RECRUITMENT RATE AND FEASIBILITY OF PROCEDURES

During the two months time period 9 out of 10 infants (6 males and 3 females) could be included. The mean gestational age at birth was of 29 5/7 weeks (SD ± 1.4), the mean weight at birth was 1'418.89g (SD ± 327.8). Each child was exposed to a mean of 180.6 (SD ± 56.07) procedures during the first 14 days of life, resulting in a mean of 12.9 procedures per day per child (SD ± 4.01), of which 70% are considered to be painful. Videotaping before, during and after the heel stick procedures could be performed without any major technical problems and the randomized videos could be showed to 4 blinded raters for pain assessment with three tools. We encountered major problems with the application of the amplitude-integrated electroencephalogram electrodes and the continuous measurement. The few tracings that we were able to obtain were not interpretable so aEEG is not considered to be reliable for measurement in this patient population of very low birth weight preterm infants and will be not performed in the proposed pilot study.

1.3 CHANGES IN CORTISOL LEVELS

In total ninety (90) cortisol samples were taken before and after the 5 heel sticks. As saliva cortisol is produced in only small and inconsistent amounts in preterm infants, its sampling and analysis can be difficult [1]. The sampling of cortisol by a dental roll (Visispears, Salimetrics) did not pose any major problems. We sampled the first saliva cortisol 15 to 20 minutes before the heel stick procedure (Time 1) and the second one 30 minutes after the procedure (Time 2) has ended. We placed the dental roll into the infant's mouth for at least 15 minutes. A first lab analysis made by the specialized cortisol-laboratory at the University in Trier (D) showed that after first centrifugation, a satisfactory amount of cortisol necessary to proceed with further analysis could be detected in only 20% of the total sample. Following further highly sophisticated lab-analysis for extraction of the maximal amount of cortisol, an adequate amount to permit detailed analysis was extracted even in the samples that did not initially yield a satisfactory amount of cortisol.

Overall, no significant difference in the amount of cortisol levels produced by the infants could be detected before and after the heel stick, indicating stability in cortisol production before and after the heelstick, without a stress-induced peak after the painful intervention. This could be an indication for the effectiveness of orally administrated sucrose across time.

Table 1: Total cortisol level produced before and after the heel stick

	Median	IQR	Mean	Std	Min	Max
Time 1	23.36µ/L	16.28	27.36µ/L	17.95	0.00	79.84
Time 2	21.15µ/L	21.06	31.69µ/L	29.63	0.00	114.69

Wilcoxon signed-rank test: S=55; p = 0.55

Table 3 and 4 show a gradual decrease of cortisol levels over the heel sticks for time 1 (before heel stick) as for time 2 (after heel stick), respectively. In both cases, a repeated-measures regression showed that these trends were statistically significant.

Table 2: Total cortisol level produced at Time 1 (before heel stick)

	Median	IQR	Mean	Std	Min	Max
Heel stick 1	32.80µ/L	21.09	38.18µ/L	21.15	9.73	79.84
Heel stick 2	30.33µ/L	11.62	34.36µ/L	20.34	10.69	75.04
Heel stick 3	24.04µ/L	14.17	27.76µ/L	18.38	7.25	59.59
Heel stick 4	22.64µ/L	1.88	23.73µ/L	5.76	19.65	38.66
Heel stick 5	15.74µ/L	16.22	12.76µ/L	9.88	0.00	26.81

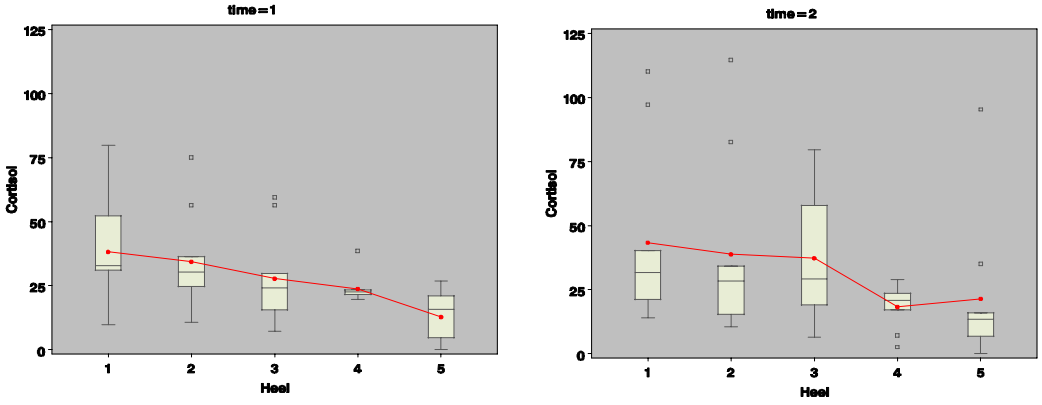
F=19.29; p = <.0001

Table 3: Total cortisol level produced at Time 2 (after heel stick)

	Median	IQR	Mean	Std	Min	Max
Heel stick 1	31.58µ/L	19.03	43.33µ/L	35.40	14.07	110.17
Heel stick 2	28.45µ/L	18.87	38.76µ/L	35.96	10.44	114.69
Heel stick 3	29.17µ/L	38.90	37.28µ/L	27.64	6.40	79.66
Heel stick 4	20.76µ/L	6.28	18.25µ/L	8.50	2.61	28.95
Heel stick 5	13.52µ/L	9.07	21.43µ/L	29.53	0.00	95.37

F=4.43; p = 0.04

Figure 1: Boxplots with cortisol levels across 5 heel sticks (T1 and T2)



A similar decrease in cortisol across time in very preterm infants was described by Grunau et al. [2]. In their study Grunau et al. stated that repeated neonatal procedural pain exposure among neuro-developmentally immature preterm infants was associated with down-regulation of the hypothalamic-pituitary-adrenal axis [2]. This dampened response to stress suggests alterations or immaturity in the HPA response in extremely early gestational age preterm infants in the NICU.

According to the results of our feasibility study an infant was exposed to a mean of 180.6 in the first 14 days of life or 12.9 procedures per day. The sample of our feasibility study was too small to control for the number of procedures in the just reported cortisol analysis. However, the question of a possible association will be investigated in the proposed pilot study and the following main study.

1.4 VARIABILITY IN PAIN RESPONSE WITHIN AND BETWEEN THE INFANTS

We used random intercept regression analysis to divide variability of the "Bernese Pains Scale for Neonates"-Scores (pain reactivity) into two parts (within and between subjects). The variability within subjects was consistently higher than between subjects; 72% - 94% of the variability was within-subject variability indicating inconsistency of pain reactivity across the 5 heel sticks of a preterm infant. The within subject variability was highest during the heel stick (t2) and lowest before and after the heel stick. Based on the high within-subject variability in the feasibility study, we will videotape each of the heel sticks in the proposed pilot study.

1.5 INTERRATER-RELIABILITY AMONG BLINDED RATERS

To establish consistency of pain measurements between the raters we calculated the Cronbach's alpha coefficient for each heel stick, each instrument and measurement time point. The alpha coefficient is generally used to estimate how strongly a score obtained from a multi-item instrument would correlate with an equally long instrument, composed of items randomly sampled from the overarching hypothetical domain of items. In the case of inter-rater reliability, alpha can be equivalently interpreted, in that it represents the expected correlation of the sum score of a panel of raters with the hypothetical score from another sample. In both ways, Cronbach's alpha measures the consistency with which a single reality is estimated through multiple attempts [3, 4].
Interrater agreement was highest during heel sticks 1 – 3 (T1 Median $\alpha = 0.97$, IQR 0.12; T2 Median $\alpha = 0.92$, IQR 0.06; T3 Median $\alpha = 0.96$, IQR 0.11) and decreased during heel stick 4 and 5 (T4 $\alpha = 0.77$, IQR 0.09; T5 $\alpha = 0.88$, IQR 0.11), indicating a possible dampening of behavioral pain patterns of the infants across time. This is consistent with Johnston et al.'s findings [5]. Furthermore interrater-reliability between the pain assessment tools was similar for all the three used instruments ("Bernese Pain Scale for Neonates" Cronbachs Alpha range $\alpha = 0.69 – 0.99$; "Premature Infant Pain Profile" Cronbachs Alpha range $\alpha = 0.60 – 0.99$; and "Visual Analogue Scale" Cronbachs Alpha range $\alpha = 0.69 – 0.99$). We will use the Bernese Pain Scale for Neonates in the proposed pilot study.

No statement can be formulated regarding the effect of oral sucrose across the 5 heel sticks as the sample of the feasibility study was too small and the study was not designed to test this aim.

1.6 CONCLUSIONS

- The feasibility study showed a **satisfying recruitment rate** among highly vulnerable preterm infants with just one denial of parents being asked.
- The feasibility study showed a **high variability in pain reaction of preterms < 32 weeks of gestation** particularly between heel stick 4 and 5, indicating a possible dampening of pain response due to exhaustion. Based on the high within-subject variability, we will include at least 5 heel sticks for the videotaping across time in the upcoming pilot study.
- The feasibility study showed **a high interrater-agreement for the three pain assessment instruments** (Bernese Pain Scale for Neonates, Premature Infant Pain Profile, Visual Analogue Scale). We will use the Bernese Pain Scale for Neonates in the proposed pilot study.
- **Oral salivary cortisol sampling and analysis is feasible in preterm infants < 32 weeks** of gestation and will be included as a procedure in the proposed pilot study.
- Overall, no significant difference in the amount of cortisol levels produced by the infants could be detected before and after the heel stick, **indicating stability in cortisol production before and after the heelstick,** without a stress-induced peak after the painful intervention. This could be an indication for the effectiveness of orally administrated sucrose across time.
- The results of the feasibility study provide **evidence to be further investigated** in the context of a pilot study.

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