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Salivary Cortisol and Pain Scoring to Compare the Efficacy of Oral Dextrose and Pacifier for Neonatal Pain Control

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Objective: Pain assessment usually involves the use of subjective pain scales; as their use may be associated with inter-/intra-observer bias, objective pain measurements, such as assessment of cortisol response to pain, are needed. This study aimed to compare the efficacy of oral dextrose and a pacifier in neonatal pain control using an objective measurement of salivary cortisol level and subjective pain scoring.

Methods: This prospective, randomized, partially blinded clinical trial included healthy newborns from a nursery (n=142). Blood was sampled using a lancet and newborns were randomly assigned to four groups by drawing lots: control (n=33), sterile water (n=35), 25% dextrose (n=35), and pacifier group (n=39). For all groups, neonatal infant pain scale, neonatal facial coding system, and premature infant pain profile scores were evaluated before, during, and 2 minutes after newborn screening test by two independent observers who watched recorded videos. Moreover, samples of saliva were collected before and 30 minutes after the pain procedure, and salivary cortisol level was measured using an enzyme-linked immunosorbent assay.

Results: Subjective pain scores were not statistically different among the four groups before, during, and after blood sampling using a lancet. However, the salivary cortisol level in the 25% dextrose group was significantly lower than that in the other groups (P=0.045).

Conclusion: Oral administration of 25% dextrose solution for pain control during the newborn screening test led to a significantly lower salivary cortisol level than the use of sterile water or a pacifier. However, no difference in pain scores was found among groups.

Key Words: Newborn, Pain, Glucose, Cortisol, Pain measurement

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Introduction

Neonatal pain control is becoming increasingly important because of the negative effects of neonatal pain reported by studies.[1–3] Methods for neonatal pain control are usually divided into pharmacologic and nonpharmacologic methods. According to a tiered approach to analgesia in newborns, nonpharmacologic methods are frequently used to control pain during minor painful procedures such as heel stick, finger stick, adhesive removal, arterial puncture, and venipuncture,[4] and these methods generally include oral administration of sucrose or dextrose/glucose, use of pacifier, skin–to–skin care, and breastfeeding. Subjective methods for assessing pain intensity during a pain procedure include the use of pain scales to determine physiologic and behavioral responses to pain, whereas objective methods include the measurement of stress–associated hormone levels and the use of amplitude–integrated electroencephalography (aEEG) and functional magnetic resonance imaging (fMRI).[5,6] Some guidelines and policies on methods for neonatal pain control exist despite the many limitations with regard to their actual application in clinical practice.[4,7–9]

This study aimed to compare the efficacy of oral dextrose and a pacifier in nonpharmacologic pain control during a newborn screening test using objective measurement of salivary cortisol level and subjective pain scoring.

Methods

1. Inclusion criteria

This prospective, randomized, partially blinded clinical trial was approved by the institutional review board of Gangneung Asan Hospital (IRB 2011-014). Between June 2012 and January 2013, we enrolled healthy newborns without other medical problems at the nursery of Gangneung Asan Hospital, Gangneung, Korea in this study; informed consents were obtained from the newborns' parents. Newborns with a gestational age of <35 weeks, birth weight of <2,300 g, and 1-minute and 5-minute Apgar score of <7; those who required clinical observation because of unstable vital signs; those who did not undergo a newborn screening test; and those whose parents did not provide informed consent were excluded.

2. Grouping

A total of 200 healthy newborns were divided into four groups by drawing lots. For randomization, we prepared two drawing boxes for boys and girls, with each box having lots for four groups. In the control group (n=50), no treatment was administered before the pain procedure. In the sterile water group (n=50), 1 mL of sterile water was administered before the pain procedure. In the dextrose group (n=50), 1 mL of 25% dextrose solution was administered before the pain procedure. Sterile water and 25% dextrose solution were dropped at the anterior tongue of the newborn using a 5-mL syringe. In the pacifier group (n=50), a pacifier was used 2 min before the pain procedure.

3. Pain procedure

The pain procedure used was a newborn screening test, which was performed as usual with cleansing using 83% ethanol and blood sampling using a lancet. Blood samples equivalent in amount to three capillary tubes were obtained from each newborn. Before the procedure, an oxygen sensor was attached to the left foot, and video recording was started for blinded pain scoring.

4. Pain scoring

Recorded videos were watched to evaluate the scores for the neonatal infant pain scale (NIPS),[10] neonatal facial coding system (NFCS),[11] and premature infant pain profile (PIPP),[12] which were used to assess neonatal pain. Pain in newborns was scored thrice by two independent observers who were not involved in the pain procedure and video recording, namely before (baseline phase), during (pain phase), and 2 minutes after (recovery phase) the pain procedure.

5. Salivary cortisol level

Saliva was collected using cotton ball sticks for the analysis of cortisol level before and 30 minutes after the pain procedure, and the samples were subsequently frozen. The salivary cortisol level was then measured using an enzyme-linked immunosorbent assay (ELISA) (Salivary Cortisol ELISA Kit, Salimetrics, State College, PA, USA).

6. Statistical analyses

We compared the pain scores for NIPS and NFCS of the four groups through repeated-measures multivariate analysis of variance, taking the pain control effect and time effect and the interaction effect between them into consideration. PIPP scores were compared among the four groups using the Kruskal-Wallis test because they were not normally distributed data. The change in salivary cortisol level from the baseline phase to the pain phase was compared among the treatment groups and control group through analysis of variance, and *post-hoc* analysis using the Dunnett's test was performed. All P-values were considered significant at $P<0.05$.

Results

A total of 200 newborns participated in this study and were randomly divided into four groups, with each group comprising 50 newborns. However, 58 newborns were excluded because of their transfer to the neonatal intensive care unit, insufficient amount of saliva collected, or video recording errors. Finally, the clinical characteristics, pain scores, and salivary cortisol

level of 142 newborns were statistically analyzed (Fig. 1).

Maternal and neonatal characteristics were similar among the four groups, with no difference in possible stressful factors that could affect the newborns, premature rupture of membranes, Apgar score, and time to procedure after birth (Table 1). No statistically significant difference in crying time was found among the four different nonpharmacologic methods that were attempted to relieve pain (Table 1).

Table 2 presents the mean pain scores for NIPS, NFCS, and PIPP assessed by the two observers before, during, and after the pain procedure. Inter-observer reliability showed good agreement; intra-class correlation coefficients (ICCs) were >0.8 for all scores, except for NIPS baseline score (0.727) and NFCS baseline score (0.673). No statistical differences in all scores were found among the four groups at each phase (P>0.05 for all). Moreover, the PIPP scores were similar (P>0.05) (Table 2). When we compared the changes in NIPS and NFCS scores from the baseline phase to the pain phase and those from the baseline phase to the recovery phase among the groups, the interaction effect of group and time effects on NIPS changes were significant (P=0.02), but the group effect was not significant at each phase (P>0.05). However, change in NFCS score was not significant at both P values (P>0.05) (Table 3).

Table 4 shows the salivary cortisol level at baseline and pain phase. The decrease in the salivary cortisol level from the baseline phase to the recovery phase was statistically significant in the dextrose group compared with the control group (0.052±1.577 vs. 0.897±1.567 μg/dL, P=0.046) (Table 4).

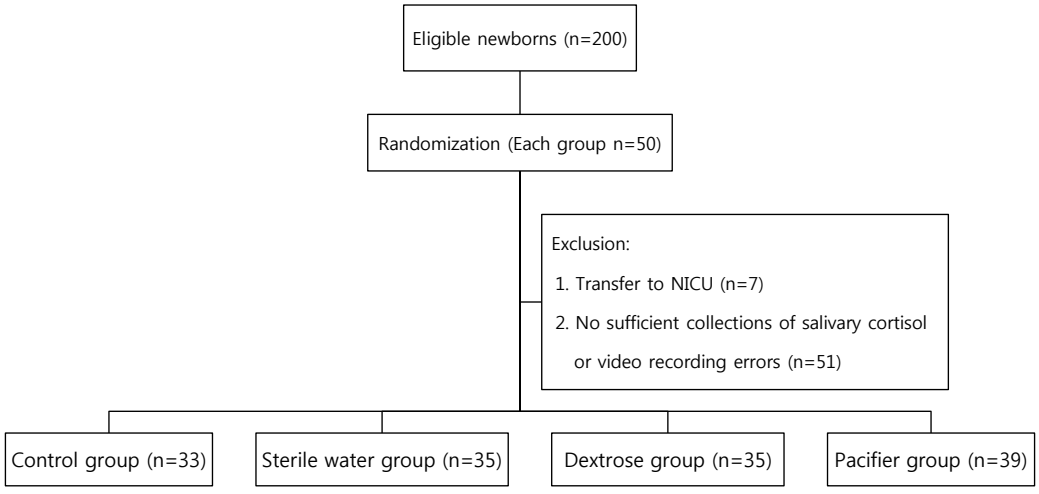

Fig. 1. Trial profile and newborns flow. NICU, neonatal intensive care unit.

Table 1. Clinical Characteristics of Newborns

	Control group (n=33)	Sterile water group (n=35)	Dextrose group (n=35)	Pacifier group (n=39)
Birth weight (g)	3,257.5±704.2	3,224.5±381.6	3,225.0±365.6	3,331.3±453.6
Gestational age (wks^{days})	$38^{6}\pm0^{6}$	$38^{4}\pm0^{6}$	$38^{2}\pm0^{5}$	$38^{4}\pm1^{1}$
Mother age (yrs)	33.2±4.0	32.3±4.3	33.1±5.2	33.8±0.5
PROM	0 (0)	1 (2.9)	1 (2.9)	1 (2.6)
Male	17 (51.5)	20 (57.1)	16 (45.7)	23 (59.0)
1 minute Apgar	8.3±0.8	8.2±0.8	8.1±0.8	8.4±0.6
5 minutes Apgar	9.3±0.6	9.2±0.6	9.1±0.6	9.4±0.5
Time to procedure after birth (hrs)	86.0±7.2	86.9±8.8	89.2±3.3	88.1±4.2
Crying time (seconds)	514.8±277.2	499.4±566.0	332.3±298.0	421.8±280.2

Values are presented as mean±standard deviation or number (%).
All P values are >0.05 by analysis of variance (ANOVA).
Abbreviation: PROM, premature rupture of membrane.

Table 2. Neonatal Pain Scores according to Analgesic Procedures

	NIPS scores			NFCS scores			PIPP scores
	Baseline	Pain	Recovery	Baseline	Pain	Recovery	
Control group	2.5±2.0	6.2±1.5	5.0±2.3	2.1±2.0	6.6±1.9	5.0±2.7	11.2±4.5
Sterile water group	2.6±2.3	5.6±2.1	4.5±2.6	2.2±2.1	6.3±2.6	4.5±2.9	9.8±5.1
Dextrose group	2.3±2.1	6.1±1.7	4.1±2.8	1.9±1.9	6.7±2.5	4.2±3.0	10.1±5.1
Pacifier group	2.1±2.0	5.8±2.4	5.2±2.6	1.9±1.9	6.7±2.6	5.5±2.8	11.5±5.2

Values are presented as mean±standard deviation.
All *P* values comparing 4 groups at each time point are >0.05 by Kruskal-Wallis test.
Abbreviations: NIPS, Neonatal Infant Pain Scores; NFCS, Neonatal Facial Coding System Scores; PIPP, Premature Infant Pain Profile.

Table 3. Comparison of Score Changes of Neonatal Infant Pain Scale and Neonatal Facial Coding System from Baseline to Injection and Recovery

	NIPS scores*		NFCS scores†	
	Δ Pain‡	Δ Recovery§	Δ Pain‡	Δ Recovery§
Control group	3.7±2.0	2.4±2.2	4.5±2.2	2.9±2.6
Sterile water group	3.0±2.1	1.9±2.8	4.1±2.4	2.3±2.9
Dextrose group	3.8±1.9	1.8±3.0	4.8±2.1	2.4±3.0
Pacifier group	3.7±2.3	3.0±2.5	4.9±2.6	3.6±2.8

Values are presented as mean±standard deviation.
Abbreviations: NIPS, Neonatal Infant Pain Scores; NFCS, Neonatal Facial Coding System Scores.
**P* value for interaction of group and time effect=0.02, but *P* value for group effect >0.05 at each time points by repeated measures analysis of variance (MANOVA).
†*P* value for interaction of group and time effect and group effect >0.05 by MANOVA.
‡Score changes from baseline to pain phase.
§Score changes from baseline to recovery phase.

Table 4. Comparison of Cortisol Levels and Changes of Cortisol Levels from Baseline to Pain

	Baseline (μg/dL)	Pain (μg/dL)	Δ Pain*	*P* value†
Control group	1.260±1.121	2.156±1.908	0.897±1.567	Reference
Sterile water group	1.240±0.958	1.553±1.060	0.313±1.181	0.229
Dextrose group	1.194±1.281	1.246±0.959	0.052±1.577	0.046
Pacifier group	1.162±1.434	1.532±1.380	0.369±1.430	0.284

Values are presented as mean±standard deviation.
*Cortisol level changes for baseline to pain phase.
†*P* values comparing four groups <0.05 by the Analysis of variance (ANOVA) and the *post-hoc* analysis for comparison against control group was done based on the Dunnett correction method.

Discussion

In this study, we compared the analgesic efficacy of commonly used nonpharmacologic pain control methods, namely oral dextrose and a pacifier, during a newborn screening test. Further, we showed that there was no significant difference in pain scores among the groups and that only the decrease in salivary cortisol level with oral dextrose was statistically significant.

A tiered approach to pain control is recommended in newborns.[4] In this study, oral dextrose and pacifier were used to relieve pain during a newborn screening test, which is a relatively minor procedure. However, we could not find a decrease in pain scores for NIPS, NFCS and PIPP, which were the subjective methods of pain assessment in this study. We think that there are several reasons for this. First, the pain from blood sampling using a lancet during the newborn screening test was perhaps too intense to be relieved with nonpharmacologic methods, such as oral dextrose and pacifier. The pain during heel lancet prick is classified as a minor pain, but squeezing during the blood collection procedure is more painful, with some reports even indicating that venipuncture is a less painful sampling method than heel prick.[13] Second, pain assessment was limited. Accurate pain assessment is essential for efficient pain control. However, verbal self-report, the gold standard for pain assessment, is obviously impossible in newborns. In this study, we generally used pain scales that use physiologic, and behavioral indicators of pain in newborns. Such comprehensive and multidimensional tools have advantages and limitations. The use of tools can be limited by the severity of illness, gestational age, poor correlation between physiologic and behavioral indicators, blunted behavioral responses to pharmacologic agents, and opposing effects on homeostasis.[14] In this study, the statistical differences could not be confirmed, although commonly used pain scales (NIPS, NFCS, and PIPP) were used, pain was scored by two researchers who were not involved in the pain treatment to reduce inter-observer bias, and ICC was relatively good (ICC>0.6).

Although no difference in pain scores was found among groups at each phase, the decrease in salivary cortisol level was significant in the dextrose group. Many limitations of objective methods used for pain assessment exist. For example, special procedures are needed such as aEEG or fMRI, as well as blood sampling for some stress-associated hormones (e.g., cortisol, epinephrine, growth hormone), which could be a new source of pain. Because of the aforementioned reasons, measurement of salivary cortisol level was selected as the objective method in this study. Some studies have reported the association between pain and salivary cortisol level.[15-17] However, an absence of relationship has also been reported by some studies.[18,19] Generally cortisol level peak shortly after birth and return to baseline by 3 to 5 days of life.[20-22] Therefore, we made an effort to perform the newborn screening test 3 days after birth (time to procedure in all neonates was 87.8±6.5 hours after birth). Corisol responses were noted to be greater following painful procedures than after routine handling, and behavioral responses did not correlate well with the peak cortisol levels. Peak cortisol responses have been detected 20 to 30 minutes post stimulus, with recovery to baseline at 120 to 150 minutes post manipulation; therefore, most salivary cortisol measurements in neonatal pain studies are collected at 30 minutes after the pain stimulus.[20,23,24] Because wide variation in cortisol levels have been noted in infants, assessing for change in cortisol patterns, rather than absolute values, may be more significant. Therefore we collected saliva two times before and 30 minutes after the pain procedure. In our study, with respect to the comparison between subjective pain scoring and objective measurement of salivary cortisol level, only the decrease in the salivary cortisol level in the dextrose group was statistically significant.

Previous studies comparing the effects of a sweet solution (sucrose, glucose, dextrose) and a pacifier (including nonnutritive sucking) have not clearly concluded which is better.[25-29] In our previous study, we reported that dextrose further lowered the pain scores compared to the pacifier and that dextrose was superior with respect to neonatal pain control.[30] Unlike in this study, hepatitis B vaccination was used as the pain procedure in the previous study, and an objective indicator of salivary cortisol level was not used. Although prevention and management of pain in neonates should be the goal of all caregivers, there are major gaps in the knowledge regarding the most effective method to accomplish this. The results of our previous study and this study have revealed that dextrose is more effective method than a pacifier as a non-pharmacologic pain control method in neonates; however, they have also shown there is a limitation in pain assessments by subjective and objective methods. It was also noted that different types of pain control methods should be considered for different types of pain stimuli, such as hepatitis vaccination and the newborn screening test.

This study has several limitations. First, we could not collect sufficient amounts of saliva to analyze salivary cortisol level, and video recording errors occurred during the pain scoring in some of the included newborns. Second, this study had a partial randomization design because the observers could see the analgesic treatment when they watched the videos for pain scoring. Third, we did not measure blood glucose levels, so we could not evaluate the association between glucose and cortisol levels.

The results of this study suggest that the objective measurement of salivary cortisol level is better than subjective pain scoring and that dextrose is better than a pacifier as a nonpharmacologic pain reliever. Further, we believe that many limitations and uncertainty still exist and further studies on neonatal pain control are needed. No standard guideline for neonatal pain control currently exists in Korea, and we hope that the results of this study contribute to its development; further studies are needed for this.

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Conflict of interest

No potential conflict of interest relevant to this article was

reported.

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