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Pain Reduction on Insertion of a Feeding Tube in Preterm Infants: A Randomized Controlled Trial

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KEY WORDS
pain measurement, pain assessment, infant, premature, gastric feeding tube

ABBREVIATIONS
PIPP—Premature Infant Pain Profile
PMA—postmenstrual age
CPAP—continuous positive airway pressure

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WHAT'S KNOWN ON THIS SUBJECT: Insertion of a feeding tube is commonly done in preterm infants, but the degree of pain and discomfort—as well any measures to reduce pain—have not been well investigated.

WHAT THIS STUDY ADDS: Insertion of a feeding tube leads to brief but measurable pain and discomfort. Pain relief was best achieved by combining a pacifier with 30% sucrose in these preterm infants.

abstract

BACKGROUND: Gavage feeding is required in preterm infants who cannot feed by themselves. Insertion of the feeding tube is painful, and reducing the discomfort in these patients is desirable.

OBJECTIVE: The aim of this study was to assess pain and discomfort during nasal insertion of a feeding tube, and to evaluate different measures for pain relief.

METHODS: We included 24 preterm infants with postmenstrual age 28 to 32 weeks' who were in stable condition. Each infant acted as his or her own control over a 3-week period during which the tube was changed 6 times. On these occasions, 6 different treatment combinations were given in randomized order: pacifier or no pacifier, combined with no fluid, sterile water, or 30% sucrose. Pain and discomfort were assessed by at least 2 independent and experienced observers using a pain assessment tool, the Premature Infant Pain Profile; score range: 0 to 21. In general, scores of 4 to 6 are interpreted as normal or no discomfort; ≥12 usually signals significant pain and distress.

RESULTS: The median Premature Infant Pain Profile score during the procedure was 9 and decreased gradually toward 4 after 5 minutes. The lowest pain score was achieved by combining a pacifier with oral sucrose. Sterile water without a pacifier gave the highest score.

CONCLUSIONS: Insertion of a feeding tube in preterm infants leads to a measurable degree of pain and discomfort, according to the Premature Infant Pain Profile assessment tool. Pain relief was best achieved by combining a pacifier with 30% sucrose. *Pediatrics* 2011;127: e1449–e1454

Preterm infants in NICUs undergo numerous painful procedures.[1] Nasogastric tube insertion is required for gavage feeding in preterm infants because they are unable to properly coordinate their sucking, swallowing, and breathing.[2] In a study among adult patients, insertion of a nasogastric tube resulted in a higher pain score than fracture reduction or urethral catheterization.[3] Among preterm infants, many studies have shown that sweet solutions given orally before painful procedures such as blood sampling provide good pain relief.[4–8] The precise dose of sucrose given is not well defined, but in a study by Johnston et al,[9] a small dose of 24% sucrose (0.05 mL) provided significant pain relief in preterm infants. According to Eriksson et al,[10] repeated doses of sweet solutions (glucose) do not reduce their pain-relieving effect. Harrison et al[11] support this view by reporting that sucrose and glucose reduce pain in infants up to 12 months of age. McCullough et al[12] demonstrated that preterm infants had a pain response during nasogastric tube insertion, and that sucrose given orally provided good pain relief. Our clinical observation was that the combination of sucrose and a pacifier might provide even better pain relief during nasogastric insertion. Wetting the pacifier with pure water might also be beneficial by facilitating swallowing.

Special observation methods are needed to quantify pain and discomfort in preterm infants because of their immature way of expressing pain.[13] The Premature Infant Pain Profile (PIPP) is a 7-item, 4-point scale for assessment of pain in premature infants.[14] It is a well-documented and validated assessment tool.[14] Inclusion of a placebo control should minimize the problem of using a partly subjective assessment scale.

The aim of the present study was to investigate the use of pacifier, water, sucrose, and their combination for pain relief during and immediately after insertion of a feeding tube in preterm infants.

METHODS

Protocol

The study was conducted at the NICU at St Olav's University Hospital (Trondheim, Norway) between January 2005 and June 2008. The regional committee for medical research ethics approved the study. Informed written consent was obtained in advance from the parents.

We included infants with a gestational age at time for first intervention (later called postmenstrual age [PMA]) between 28 and 32 weeks, in stable condition, and at low risk for neurologic sequelae. Infants on a ventilator or those receiving continuous positive airway pressure (CPAP) or opioid treatment were excluded, as were infants with ongoing serious infections. Infants who needed to have their tube inserted by mouth were not included.

The study was designed to investigate the effect of 2 factors. The first factor ("pacifier") had 2 levels (alternatives)—pacifier or not; the second factor ("fluid") had 3 levels—no fluid, sterile water, or 30% sucrose. This factorial design thus requires 6 different interventions to be applied to each infant, in any order: nothing, sterile water only, sucrose only, pacifier only, pacifier plus sterile water, and pacifier plus sucrose (Table 1). In this crossover design, each infant thus acted as his or her own control, and the nasogastric tube was changed twice a week during the 3-week study period.

Randomization

Mathematically, the 6 interventions can be applied in a total number of 6 * 5 * 4 * 3 * 2 * 1 = 720 different se-

TABLE 1 Characteristics of the Study Infants at the Different Interventions

	No Pacifier			Pacifier		
	No Fluid	Sterile Water	Sucrose 30%	No Fluid	Sterile Water	Sucrose 30%
PMA, wk + d, median (range)	32 + 2 (29 + 6–34 + 4)	32 + 1 (29 + 3–34 + 6)	32 + 0 (29 + 2–35 + 1)	32 + 1 (29 + 1–34 + 1)	32 + 1 (29 + 4–33 + 6)	32 + 2 (28 + 6–35 + 4)
Prechtl score, median (range)	3 (2–4)	2.5 (1–5)	2.5 (1–4)	3 (1–4)	2 (1–4)	3 (1–4)
Total points for contextual indicators (behavior and PMA), median (range)	3 (1–5)	4 (1–5)	3.5 (1–5)	3 (1–5)	3 (1–5)	3 (1–4)
Weight, g, median (range)	1580 (750–2470)	1460 (970–2160)	1540 (990–2250)	1600 (1010–2360)	1520 (830–2190)	1540 (880–2530)
Continuous enteral feeding, *n*	3	3	4	4	3	4
Time to next planned meal, min, median (range)	20 (0–75	13 (0–45)	8 (0–75)	10 (0–60)	15 (0–90)	3 (0–40)
Oxygen therapy, *n*	13	14	12	15	12	14
CPAP, *n*	11	12	11	15	11	13
Antibiotic use, *n*	2	1	2	1	0	1

quences (ie, orderings). A random list of these possible sequences was prepared in advance using the software R (R Foundation for Statistical Computing, Vienna, Austria).[15] On inclusion in the study, every infant was consecutively assigned a (unique) sequence from the list. Only the study leader had access to the list.

Pain Score

The PIPP scale was used as a pain measurement tool.[14] It is a multidimensional score comprising 5 items related to pain and discomfort, plus 2 items that adjust for gestational age and level of alertness (contextual indicators). Each item is scored from 0 to 3. Contextual indicator points define the total possible score: the behavioral state observed before intervention (more is needed to wake a sleeping infant, who therefore gets more points) and the infant's PMA at time of intervention (younger infants show less reaction and thus get more points). For the 5 items related to pain and discomfort, the score depends on the amount or duration of the following signs (more is worse): increase in heart rate, decrease in oxygen saturation, eyebrow bulging, eye squeezing, and presence of a nasolabial furrow. In response to a stimulus, the total (sum) PIPP score thus indicates the degree of pain and discomfort, with adjustment for PMA and behavioral state. The score ranges from 0 (no pain, gestational age >36 weeks' and active awake state) to 21 (maximum pain in a quiet sleeping child <28 weeks' gestation). In general, scores of 4 to 6 are interpreted as normal or no discomfort; ≥12 usually signals significant pain and distress.

Interventions

Nasogastric tubes were changed twice a week according to the recommendations from the manufacturer (Unomedical, Birkerød, Denmark). This procedure was also the standard scheme on the ward at the time of the study. Assuming a stable clinical condition, the in-dwelling nasogastric tube was removed after the last meal, with the goal to insert the new tube right before the next planned meal. A 5 French nasogastric tube was used in neonates with weight <1500 g and a 6 French for those weighing ≤1500 g. If the neonate was established on intermittent CPAP, the nasal prongs were removed before the procedure. All neonates were in a supine position in their bed or incubator, and their body was covered with a blanket. The nasogastric tube insertion was done by 2 alternating, experienced nurses. Alternating nostrils were used. The sucrose solution was prepared by adding 30 g of sucrose to 100 mL of boiled spring water, and aspirated into a sterile syringe (Oral/Enteral Dispenser, 1 mL; Baxa Ltd, Bracknell, United Kingdom) by the nurse who performed the nasogastric insertion. The neonate was observed continuously for 15 seconds before the procedure to determine baseline values for heart rate, oxygen saturation, and behavioral state. The Prechtl score was registered in addition to further evaluate the alertness of the neonate right before start of the procedure.[16] The observers were asked to turn away for a brief period to avoid seeing if anything was given orally. As indicated by the randomization list, 0.2 mL of fluid was given slowly (in 2–4 seconds) on the tip of the tongue either together with a pacifier or no pacifier. This was done immediately (ie, within seconds) before tube insertion. Concealment of pacifier use was considered to be unrealistic and therefore not attempted.

Each infant underwent 6 tube changes during a 3-week period, at which each intervention was given in the specified (randomized) order. At these events, the infants were observed by at least 2 experienced neonatal nurses who recorded the infant's PIPP score according to protocol.[14] The first registration of PIPP score (the primary outcome) was completed within 30 seconds of tube insertion, the second 1 minute later, and the last registration after 5 minutes. The mean PIPP value from the observers in each infant and intervention was used in the analysis, and the same contextual indicators (additional points for PMA and alertness), as well as baseline registrations of heart rate and oxygen saturation, were used at all time points. The nasogastric tube was fixed and checked for correct placement before the last observation. One nurse acted as timekeeper during the entire procedure.

Statistics

Pilot observations suggested a difference between pacifier or not of 2.5 on the PIPP scale, with an SD of 1.8 (ie, a standardized difference of 1.4). With a total sample size of 18 patients and a 2-sided significance level of 5%, a 2-sample Student's *t* test would detect such a difference with 80% power.[17] We settled for a total sample size of 24, thereby allowing for some uncertainty, as well as adding the factor "fluid" to the design. Friedman's nonparametric test for repeated measurements was applied to the mean values in each infant at the 6 treatment combinations. The factorial design was analyzed as a linear mixed effects model (an extension of multiple regression), in which each infant is assigned an individual intercept as a random factor. This allows for correlation because of repeated measurements on the same individual. Examination of the residuals suggested that the SD was proportional to the mean (ie, a constant coefficient of variation), and this was allowed for in the final model. We investigated overall model significance using a maximum likelihood test, with pacifier, fluid, and their inter-

actions as fixed factors. The statistical software R[15] and its package *nlme* were used for the analyses. A P value <0.05 was considered statistically significant.

RESULTS

A total of 26 neonates had to be recruited to meet the required sample size, because 2 infants were transferred to another hospital and did not complete the study. These patients were excluded from the analysis. Complete observations from 24 infants (7 boys, 17 girls) at the 6 treatment combinations resulted in 144 discrete events being observed. A total of 296 individual PIPP recordings were made, however, because there were always at least 2 observers present (range: 2–4).

Weight at the first observation varied from 750 to 1790 g, and gestational age at birth varied from 26 + 0 (weeks + days) to 31 + 5. All patients had a PMA between 28 and 32 weeks at first intervention. The maximum possible PIPP score at each intervention was thus 19 or 20, as the range of the infants' PMA was between 29 + 1 and 35 + 4 weeks. Table 1 shows the characteristics of the infants at the different interventions.

Observed PIPP scores immediately after tube insertion ranged from 3 to 18, with a median value of 9. Friedman's test of (no) overall difference among the 6 combinations, and the maximum likelihood test of the full factorial model, were both statistically significant ($P = .003$ and $P < .0001$, respectively). One or more levels within the factors fluid, pacifier, and their interactions were statistically significant at the 0.05 level.

The observed median and expected (ie, mean) PIPP score at each treatment combination is given in Table 2 and shown graphically in Fig 1. The combination of sucrose and pacifier during tube insertion provided the most effective pain reduction ($P < .001$ versus no treatment). Perhaps surprisingly, sterile water alone seemed to make things worse.

As shown in Figure 1, pain and discomfort decreased rapidly to a median of 6 after one minute and a median of 4 five minutes after the procedure.

TABLE 2 PIPP Scores With Measures of Spread During Insertion of the Nasogastric Tube,[a] According to the Different Interventions

	Observed		Model Estimates	
	Median Value	IQR	Expected Value	SE
None	9	(7–11)	9.20	0.50
Sterile water only	11	(8–14)	10.5	0.55
30% Sucrose only	8	(6–10)	8.3	0.46
Pacifier only	10	(7.8–11.3)	9.6	0.52
Pacifier and sterile water	9	(6–12.3)	9.2	0.49
Pacifier and 30% sucrose	7	(5–9)	7.3	0.43

IQR indicates interquartile range.
[a] Shown in left panel of Fig 1.

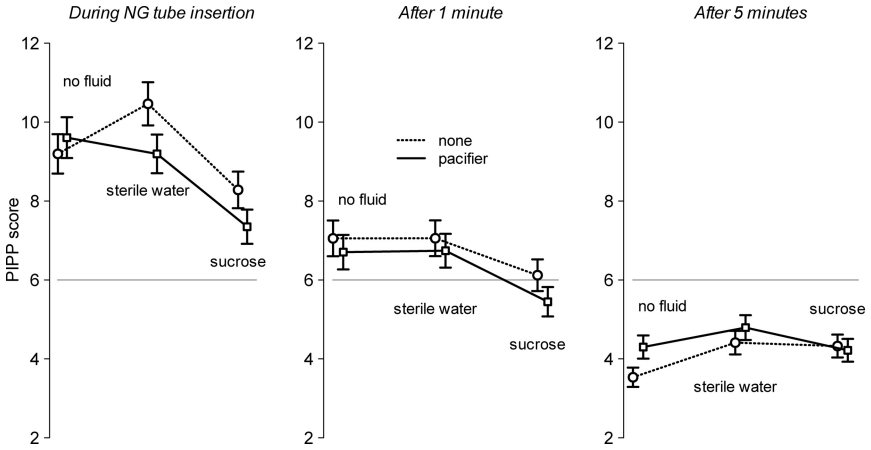

FIGURE 1
Pain and discomfort as measured with the PIPP tool, with expected values (ie, mean [SE]values) in the 3 situations and 6 treatment combinations. A gray line is drawn at PIPP = 6, the value that is considered to signal pain and discomfort. Actual numerical values during tube insertion (left panel) are given in Table 2. NG indicates nasogastric.

DISCUSSION

The main finding in this study of pain associated with nasogastric tube insertion in premature infants was that sucrose in combination with a pacifier yielded the best relief. If a pacifier is not suitable or available, sucrose alone is a good alternative.

To our knowledge, this is the first randomized study of nasogastric tube insertion in preterm infants that investigates sucrose and/or a pacifier for pain relief in a factorial design. It is a clinically relevant problem because nasogastric tube insertion is done in virtually every preterm neonate irrespective of disease status, in contrast to more painful procedures such as blood sampling.

The use of sucrose for pain relief has been extensively studied. A Cochrane review concluded that sucrose is safe and effective for reducing procedural pain such as venous puncture and heel prick in neonates. As described by Stevens et al,[4] there is inconsistency with respect to the most effective dose of sucrose. Because there is no recommended dose, we standardized the solution of liquid to 0.2 mL, independent of weight.

The PIPP score was chosen as the pain measurement tool in this study because it was developed to assess acute pain in preterm neonates for both research and clinical purposes,[14] and because several studies[1,10,18–20] have used this instrument. Pacifiers are commonly used to comfort neonates in NICUs. A Cochrane review conducted by Pinelli and Symington[21] reported no negative outcomes in use of nonnutritive sucking to promoting physiologic stability and nutrition in preterm infants. This is consistent with the daily practice and experiences in our unit. Curtis et al[22] studied the effect on pain relief of sucrose, pacifiers, and the combination of these related to blood sampling. They concluded that sucrose seemed to provide additional benefit to nonnutritive sucking when used in the age group 0 to 3 months. Our results thus agree with these previously published studies and further strengthen the observation that pain relief is achieved by the combination of sucrose and a pacifier. As noted by Holsti et al,[23] however, more research is needed on the mechanism of sweet solutions in neonates as well as the long-term neurodevelopmental effects of repeated sucrose use.

It is difficult to explain why the addition of sterile water gave the highest pain score; this finding could, of course, be incidental. Ramenghi et al[24] reported a similar result in their study. They saw a significant reduction of crying time when the infant received intraoral sucrose compared with sterile water. Greenberg[7] found that infants who received water-coated pacifiers had almost a similar duration of cry as the control group who had no intervention. McCullough et al[12] did not report any similar reaction when using water as a placebo.

In the present study, we also noted the duration of pain from insertion of a feeding tube. To determine this score, we calculated changes in heart rate and saturation from the same baseline (before the intervention) at all occasions. Although this calculation might not be in accordance with the original PIPP tool manual, it yielded supplementary information about the time course. The highest score was measured during the procedure. Shortly after the procedure, the pain score had decreased to ~6. In contrast, Elserafy et al[8] reported that the pain score measured with PIPP is highest 1 minute after blood sampling, but this procedure is clearly a more painful stimulus. We found that the median PIPP score during the procedure was ~9, suggesting light-to-moderate pain. After 5 minutes, the PIPP score had decreased toward a score of ~4 (Fig 1). The reduction in score was similar for all interventions, even when no fluid or pacifier was given. Thus, the discomfort is brief per se but not to be ignored. Duration of pain might be an important factor that needs further study. Repeated invasive procedures may contribute to long-term changes in the stress system in neonates.[25]

Even if we selected a strictly low-risk group of preterm infants, some patient heterogeneity is inevitable. This problem is reduced with the crossover design, because each infant in our study acted as his or her own control. Interpretation of the results must nevertheless take into consideration that only clinically stable infants were included, and that the observations were done over a limited interval of PMAs. Neonates who were in need of CPAP or ventilator support were excluded, because such interventions make the observation of facial expression more difficult to perform, possibly leading to incorrect pain assessment. Infants receiving sedation were also excluded because it was assumed that this group has different pain signals. The inclusion criteria were chosen to avoid such difficulties.

The randomized, semi-blinded, placebo-controlled design of this study strengthens our results, and ought to reduce the influence of adaptation and learning in the infant as well as among the observers. This design is well suited for studying similar repeated interventions in a population with changing maturation and expressions of physical parameters such as in preterm infants.

CONCLUSIONS

Insertion of a feeding tube in preterm infants causes measurable pain and discomfort as measured by the PIPP pain assessment tool. Pain relief was best achieved by combining a pacifier with 30% sucrose.

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