Reduction of pain response in premature infants using intraoral sucrose

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Abstract

The potential of sucrose to reduce the pain response in a group of healthy premature infants was investigated. Fifteen infants of 32–34 weeks postmenstrual age were tested in a blind crossover manner on two separate occasions no more than two days apart. Either 1 ml of 25% sucrose solution or sterile water was syringed into the baby's mouth 2 minutes before routine heel lancing. Response to the painful stimuli was measured by duration of cry and by facial expression (pain score).

There was a significant reduction in the duration of first cry, the percentage of time spent crying in the 5 minutes after heel prick, and the pain score in the sucrose treated group. It is concluded that sucrose has analgesic effects in healthy premature infants.

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The traditional view that newborns cannot feel pain has now been challenged. We know that newborns show a clinical behavioural response to a painful stimulus that is consistent with a more complex reflex nociceptive response. Crying is the primary method of communication in newborns and remains the most common clinical expression to measure their pain experience.

Distinct facial expressions are also described as being associated with pain and have been objectively classified and often used to study nociception in neonates.^{1–5}

Physiological responses to painful stimuli in the neonatal period are also reflected in hormonal, metabolic, and cardiorespiratory changes which are similar to those observed in adults.^{4,5}

A potential factor affecting newborns' expression of pain is their state of alertness.^{1,6} In fact, sleeping newborns often cry less in response to sampling. Theoretically, we could reduce pain during normal invasive procedures by performing these during the sleep states, but this is impractical.

Analgesia and sedation are frequently required during intensive care of critically ill neonates, but it is inappropriate to consider the use of drugs in healthy newborns to prevent pain during discontinuous and isolated procedures. For this reason several alternative methods have been proposed, such as the promotion of endogenous opiate release by placing small volumes of sucrose solution on to

the anterior tongue of newborn infants before invasive procedures.⁷ We have recently shown a dose response effect of sucrose concentration on duration of cry in healthy full term infants.⁸

Studies demonstrating the antinociceptive effect of intraoral sucrose have, until now, been performed only on full term newborns. The aim of this study is to investigate the effects of oral sucrose on reducing the perception of pain in healthy preterm infants related to individual response to painful procedures.

Methods

Healthy preterm infants, ranging in postmenstrual age between 32 and 34 weeks and postnatal age of more than 24 hours, who needed heel prick blood sampling for determination of glucose or bilirubin concentrations, were studied. They were in a stable medical condition and no infant had received either additional oxygen or sedation during the previous five days. The study was of a blind crossover design. Premature newborns were recruited if it was likely that they would require at least two heel prick blood sample within a period of no longer than 48 hours.

Each baby was studied twice and was randomly allocated to receive either solution A (25% sucrose) or solution B (sterile water) on the first occasion; the alternative solution was given on the second occasion. The longest time interval between the two blood samplings was 48 hours, so that the effects on the anatomical and functional maturity of the baby would be comparable. The indication for blood sampling was the same (either BM stick test or serum bilirubin) for each of the paired tests in each baby. Each baby received either solution A or B before each one of the two blood samples, and the infants were studied at least one hour after the last feed. Test solution (1 ml) was administered by syringe into the baby's mouth for 1 minute. Two minutes after beginning to administer the sucrose, the heel prick was performed by lancing and gently squeezing the heel which had been cleaned with a sterile swab. Because the method of performing blood samples may affect the nociceptive response, the two studied heel pricks were inflicted on each baby by the same experienced neonatal operator (nurse or doctor) standardising the procedure; the time spent squeezing the heel was also recorded.

Infants were fully clothed apart from the foot which was used for sampling. Before skin preparation a pulse oximeter was applied to the baby's hand or contralateral foot to monitor heart rate throughout the study period. Crying during sampling and in the 5 minutes after

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Table 1 Details of infants studied

	Median	Range	IQ range
Gestational age at birth (weeks)	33	29–34	
Postmenstrual age (weeks)	34	32–34	
Birthweight (kg)	1.98	1.34–2.52	
Postnatal age (days)			
Control	2	1–29	
25% Sucrose	2	1–31	
Squeeze time (seconds) (n=14)			
Control	40		31–74
25% Sucrose	58 (P=0.8)		31–84
First cry (seconds)			
Control	23		15–45
25% Sucrose	12 (P=0.004)		8–22
Percentage cry over 5 minutes			
Control	16.6		5–27.3
25% Sucrose	6 (P=0.018)		3.3–15.3

IQ=interquartile.

sampling were recorded on to an audio tape recorder and later analysed without knowledge of the solution group. The duration of the first cry, defined as audible distressed vocalisations with a continuous pattern before a quiet interval of 5 seconds soon after the painful stimulus, was recorded over the first 5 minutes following heel prick. Changes in four facial expressions (brow bulge, eye squeeze, nasolabial furrow and open mouth) and the presence of crying related to the heel prick were recorded every minute on a 0–5 scale, giving a score of 1 if present and 0 if absent to each item for each criterion. The baby's behavioural state was scored before heel lancing.¹⁶

A clinical estimation of the intensity of the sucking was attempted as a 0–2 score, because a greater amplitude in the tongue movement during the sucking of sweet solution has been noted.⁹

Results were analysed using the statistical package Minitab, and differences between the results obtained when using each solution were

assessed using the Wilcoxon matched pairs signed rank test.

The study was approved by the hospital ethics committee and informed parental consent was obtained before each infant's enrolment. The parents were invited to attend if they wished, but did not interact with their infant during the study.

Results

Fifteen newborn infants were studied twice and details of the infants are shown in table 1. There was no significant difference in behavioural state before heel prick between the two groups (P=0.8). The median crying time over 5 minutes and the median duration of the first cry is shown in fig 1. There was a significant reduction in both the total percentage crying time over 5 minutes (P=0.018) and the duration of the first cry (P=0.004) when the babies received sucrose, compared with water. There was no significant difference in the time spent squeezing the heel between the two groups of measurements (P=0.8).

The clinical interpretation of the quality of sucking was significantly more 'intense' in the babies given sucrose solution than the control group (P=0.04).

There was no significant difference in the heart rate between the two groups at any time during the study period (table 2). When the babies received placebo they showed a significantly higher pain score at 1 (P=0.01) and 3 (P=0.03) minutes after the heel prick. Changes in the pain scores are shown in fig 2.

Discussion

Small volumes of sucrose applied on to the anterior tongue seem to exert an antinociceptive effect that has a short latency and lasts well after the administration is concluded. According to the present data, we have independently duplicated and extended the first observation of Blass *et al* to healthy preterm infants.⁷

The absence of a significant difference between the squeeze time in the two groups of measurements and the single operator performing the heel prick in each baby minimised the between examination variability. The problem is potentially further compounded by the wide range of individual responses to painful stimuli. These methodological problems were excluded by studying the same babies twice within a few days of each other.¹⁰

To avoid the theoretical risk of necrotising enterocolitis in preterm babies as the result

Figure 1 Duration (seconds) of the first cry following the heel prick and percentage time crying over 5 minutes in the 15 newborns when given 0 (control) or 25% oral sucrose. Paired values are connected by solid lines. When receiving sucrose, babies had a shorter duration of the first cry (P=0.004) and a significant reduction in total percentage time crying over 5 minutes (P=0.018).

Table 2 Heart rate (bpm) in response to heel lance

Time (minutes) from heel lance	25% Sucrose solution		Control solution	
	Median	IQ range	Median	IQ range
-2	136	128–148	138	135–144
0	148	138–160	148	145–158
1	157	146–166	159	148–162
3	144	137–155	160	139–169
5	137	133–156	144	131–155

IQ=interquartile.

Figure 2 Mean pain scores following heel lance in preterm infants. Pain score was significantly lower at the first ($P=0.01$) and third ($P=0.03$) minute when babies received 25% oral sucrose.

of the hypertonic solution we administered a maximum of 1 ml of 25% sucrose solution rather than 50% solution.⁸ No adverse effects were found.

Preterm infants have a lower threshold to noxious stimuli than those born at full term, but the crying time and pain response in these infants seem to be less when given 25% sucrose rather than control solution.¹¹ The decrease of the cry duration was more noticeable for the first cry after heel prick than over the entire observation period of 5 minutes. This agrees with the current notion that the first cry following pain is the most sensitive to the noxious stimulus.¹ The significantly higher pain score (graded facial grimacing and cry) during the first and the third minute after heel prick, when the babies were treated with the control solution, tends to confirm the antinociceptive effect of sucrose. Our data failed to show a significantly higher heart rate in the placebo group in contrast to a previous study in term babies, and we are uncertain of the reasons for this.⁸

Although the mechanisms mediating the effects of sucrose cannot be determined by the present study, much work has shown a primary role for the endogenous opioid system.^{4,7,12,13} This hypothesis was at first proposed by Blass, based on the antagonist effect of naltrexone in animal models.¹⁴ How intraoral sucrose effectively causes the release of endogenous opioids in human newborns remains to be determined. Clinical investigations on newborns and experimental studies on animals suggest that this acute effect is mediated by a preabsorptive mechanism.^{12,14} In all probability it is based on sweet taste perception, a human sense well developed even among premature infants at birth.¹⁵ The sucrose should therefore be administered mainly to the anterior part of the tongue to best promote the taste perception, because about 90% of all taste buds are distributed within the first 2 cm from the tip of the tongue.¹⁶

Intraoral sucrose also has a calming effect on full term newborns, eliciting mouthing and hand-mouth contact.¹² These effects are unlikely to be mediated by a postabsorptive mechanism. Instead they may indicate the rapid recruiting of central endogenous opioid secretion through taste stimulation by the sugar.

At birth newborns demonstrate a limited taste discrimination that is critical for judging

the acceptability of foods.^{9,17,18} The sweet taste may have positive reinforcement properties which contribute to sufficient consumption of sugar based calories by allowing a more vigorous sucking-feeding action.^{9,18} We know that in adults the enjoyment of tasting a sweet solution decreases on satiety.¹⁹ Therefore, it may be important to investigate sucrose effects relating to taste perception as long after the last feed as possible, because the sense of satiety could influence perception in newborns as well.¹² Moreover, these data suggest that the ability to recruit endogenous opioid mediation by means of tasting sucrose decreases during the second month of life in human babies. Some studies have shown that the sucking response to taste in the newborn can be considered a subcortical reflex, not a cortically recognisable one, which might gradually decrease like any other primitive reflex.²⁰

Our data cannot clarify this aspect but confirm that intraoral sucrose has potential clinical relevance as an antinociceptive agent in preterm infants. This may be important, as recent studies show that the effects of pain experienced by baby boys reinforce responses to subsequent nociceptive insults.²¹

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