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ORIGINAL PAPER

Analgesia in preterm newborns: the comparative effects of sucrose and glucose

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Abstract The aim of this study was to evaluate the effectiveness of different oral carbohydrate solutions for alleviation of pain in healthy preterm babies. Thirty-one preterm infants who were having blood drawn by heel prick were given 2 ml of solution A (20% sucrose), solution B (20% glucose) or solution C (placebo, sterile water) into the mouth, 2 min before lancing. Behavioural responses to this painful stimulus were measured by duration of crying and facial expressions (Neonatal Facial Coding System, NFCS) and physiological responses were measured by heart rate (HR), respiratory rate (RR), and oxygen saturation changes (SaO_2). Infants had a mean birth weight (±SD) of 1,401 g (406), gestational age of 30.5 weeks (2.7); at the time of the procedure the postmenstrual age was 32.3 weeks (1.5). There was no significant difference in the time spent squeezing the heel between the three groups (P=0.669). After the heel prick of both the sucrose and glucose groups the duration of first cry and total crying time was significantly reduced (P=0.005 and P=0.007). When the babies received placebo they showed a significantly higher NFCS score at 4 and 5 min after the heel prick (P=0.009 and 0.046 respectively). Following painful stimulus HR increased significantly in the first 3 min compared with baseline, and at the first minute the mean of the HR was found to be significantly higher in the placebo group than in the sucrose and glucose groups (P=0.007). We concluded that both sucrose and glucose administered orally before a heel prick reduce the pain response in preterm infants.

Keywords Preterm · Pain · Sucrose · Glucose

Abbreviations

HR	heart rate
NFCS	Neonatal Facial Coding System
NICU	Neonatal Intensive Care Unit
RR	respiratory rate
SaO_2	oxygen saturation

Introduction

In the neonatal period, pain may occur during many interventions. According to one report, 54 newborns admitted to a Neonatal Intensive Care Unit (NICU) were subjected to painful stimuli 3,283 times during their stay in hospital. Those most often affected are the small premature infants; in the same study, it was shown that one premature baby underwent painful procedures 488 times during her stay in hospital [4]. There is now a growing body of evidence showing that multiple painful and stressful events experienced by infants born prematurely not only induce acute changes, but may also result in permanent structural and functional changes [2, 18, 31].

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Because of the inevitability of the painful interventions in the NICU, various pharmacologic or non-pharmacologic methods have been tried for alleviation of pain. Pharmacologic methods are defined here as the use of opioid or non-opioid analgesics, or the application of topical local anaesthetic creams [32]. Because of their potential side effects, and since they lead to the development of tolerance and addiction, opioids are preferably used only before invasive procedures. On the other hand, it has been shown that paracetamol given orally and anaesthetic creams applied to the heel are not efficacious at relieving pain from heel lancing in term neonates [21–23, 26]. Instead, non-pharmacological interventions are valuable alternatives for pain relief during minor procedures. The main non-pharmacologic interventions are swaddling, non-nutritive sucking, administration of sweet or fatty solutions or breast milk, and providing skin-to-skin contact with the mother [5–9, 13, 14, 20]. The development of the non-pharmacologic, effective and harmless methods is very important, especially for the small premature infants who undergo short but repeated painful procedures.

Oral sucrose administration has been the most frequently studied non-pharmacologic intervention in term and preterm neonates during painful procedures. Sucrose is a disaccharide, a sweet solution consisting of glucose and fructose, that is not otherwise used widely in many NICUs in daily practice. Glucose is a monosaccharide, widely used as a parenteral solution in neonatal care, and is as sweet a solution as sucrose. The analgesic effect of oral glucose to reduce heel lancing pain in term neonates has also been reported [1, 27]. It is also reported that a little dose of oral glucose before subcutaneous injection has an analgesic effect in very preterm babies [10].

The objective of this study was to evaluate and compare the analgesic and soothing effects of various carbohydrates solutions (sucrose and glucose) given orally in healthy preterm infants subjected to heel prick.

Materials and methods

We conducted a prospective, randomised, double blind, placebo-controlled, crossover trial to investigate the effect of sucrose and glucose solutions on the pain of heel prick in preterm infants. Parental informed consent and approval by the hospital Ethical Committee was obtained before study entry.

Participants

The study group was designed to include healthy preterm newborns admitted to the neonatal intensive care unit. Gestational age was assessed by the last menstrual period of the mother and the new Ballard score [3]. Criteria for inclusion were: postmenstrual age less than 37 weeks at the time of the study, clinical stability and no oxygen treatment or administration of sedative medicines within the last 7 days, no intolerance of enteral feedings, no use of drugs other than vitamins and iron, free of perinatal asphyxia, congenital malformations and intra-ventricular haemorrhage, and the requirement of blood sample collection by heel prick.

Randomisation

The infants were tested three times in a crossover manner with sucrose (20 %, 2 ml), glucose (20 %, 2 ml) or 2 ml of placebo (sterile water) on different days. To avoid the differences that would be induced by postnatal anatomic and functional maturity, a time interval of a minimum of 24 h and a maximum of 48 h was set between the tests. The participants were randomly assigned by drawing sealed envelopes to decide which solution each was to receive first. Sucrose solution was prepared by adding 20 g of sucrose into 100 ml of sterile water. As the glucose solution, 20% dextrose solution produced for intravenous treatment was used. The solutions were put into physically identical bottles and coded by a nurse who did not take part in the study. The code was only revealed at the end of the study, after the results had been obtained.

Sample size calculation

We tested the hypothesis that carbohydrate administration before heel lancing would reduce heart rate increments compared with sterile water. We calculated that a sample size of 30 infants per group was necessary to detect a 40% difference in the heart rate changes with a power of 80% and a P value of < 0.05.

Procedure

Tests were performed without changing the environments in which the babies were being cared for in the NICU, between 9:00–10:00 a.m., within 1–2 h of feeding, while they were lying supine in their crib or in the incubator. The pre-test behavioural state of the individual babies was observed to be sleeping lightly or awake and resting quietly. Before skin preparation, the probes of the monitors were put on the baby's chest and hand and baseline of heart rate (HR), respiratory rate (RR) and transcutaneous oxygen saturation (SaO_2) was recorded; 2 ml of test solution was then syringed into the mouth for 1 min. The solution was given mainly on the anterior part of the tongue to best promote the taste perception. Two minutes later, the heel was exposed, cleaned with a sterile swab and gently squeezed. One investigator then pricked the heel on the

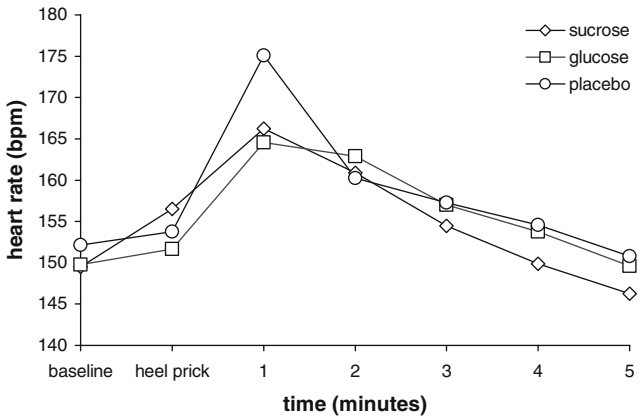

Fig. 1 Mean heart rate (bpm) at 1-min intervals for the entire study of the sucrose, glucose and placebo groups

side with a disposable micro-lancet, collected the blood with a micropipette, fixed an adhesive plaster and repositioned the foot. Because the method of performing blood samples may affect the pain response, all tests were performed by the same person, standardising the procedure and recording the time spent squeezing. During the test, no part of the baby's body was touched except for the foot from which the blood sample was drawn, and no word was spoken. One heel prick was enough for each baby, and no other intervention was made after the blood-taking process.

Measurements

Physiological responses to the painful stimulus were recorded by the changes in HR, RR and SaO_2 measurements. HR and RR were established using standard cardiorespiratory monitors, and oxygen saturation was monitored using a pulse oximeter (BCl-mini-torr plus). The moment at which the heel was pricked by the lancet was registered as the 0th minute, and the HR, RR and SaO_2 values were recorded after each minute (at the 1st, 2nd, 3rd, 4th and 5th minutes).

Behavioural responses to the pain were assessed by using the Neonatal Facial Coding System (NFCS) score and the duration of crying [16]. The NFCS assesses the presence of each of the following facial actions: bulging brow, eyes squeezed shut, deepening of the naso-labial furrow, open lips, vertical mouth stretching, horizontal mouth stretching, lip pursing, a tautly cupped tongue, and shivering at the chin. The facial reactions were analysed 2 min before the heel was pricked (baseline), at the moment the heel was pricked (0th minute), and at each minute for the next 5 minutes (at the 1st, 2nd, 3rd, 4th, 5th minutes). In the case of the defined actions occurring, 1 point was given for each (a total of 9 points), and 0 points were given if no action was observed.

Crying was defined as a high-pitched vocalisation. The duration of the first cry was taken to be the crying time, starting immediately after the heel lancing and continuing until the first lull that lasted 5 s. The total crying time, on the other hand, was taken to be the time that passed starting from the moment the first crying sound was heard and lasting until total silence was reached. When measuring the total crying time, no pauses of more than 2 s were included.

The facial reaction was videotaped using a Sony DR-TR10E Handycam (with a real-time counter) to record and play back the videotapes. The videotape records were later analysed by two observers who were not aware of which solution was used. Each observer assessed the data independently and could not communicate their findings to the other. The observers were trained with the NFCS method and interobserver reliability was 95% [12].

Statistical analysis

The results of physiological variables and pain scores are expressed as mean (± standard deviation, SD). The total crying time and the duration of the first cry are given as median and interquartile range (IQ). Statistical analysis was performed using a computer statistics package (SPSS, Chicago, IL, USA) using analysis of variance with a repeated measures design used for comparison of sequential samples. The differences in the duration of crying time and

Table 1 Changes in heart rate (*HR*, bpm) during the heel prick, and 5 min later in the sucrose, glucose and placebo groups

Time (min)	Sucrose group		Glucose group		Placebo group		f	*P**
	HR[a]		HR[a]		HR[a]			
Baseline	149	(15.2)	150	(19.5)	152	(14.9)	0.381	0.687
0 (heel prick)	157	(15.4)	152	(15.3)	154	(16.8)	1.050	0.365
1	166	(17.6)	165	(17.5)	175	(20.8)	6.127	0.007
2	161	(15.8)	163	(17.5)	160	(24.4)	0.451	0.642
3	154	(14.1)	157	(17.5)	157	(20.0)	1.329	0.283
4	150	(18.0)	154	(18.5)	154	(19.4)	1.382	0.270
5	146	(13.7)	150	(16.6)	151	(21.9)	0.535	0.593

**P* values based on the results of the repeated measures analysis of variance among the three groups
[a] Values were expressed as mean (± SD)

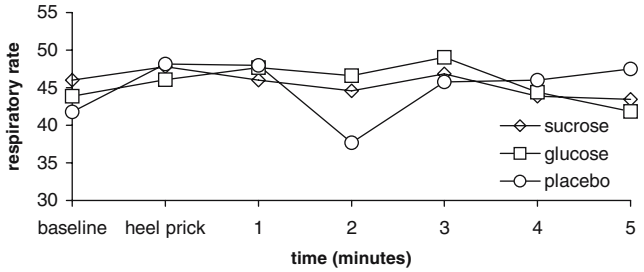

Fig. 2 Mean respiratory rate at 1-min intervals for the entire study of the sucrose, glucose and placebo groups

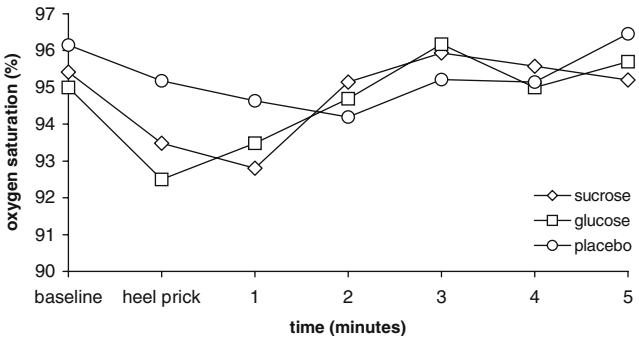

Fig. 3 Mean oxygen saturation at 1-min intervals for the entire study of the sucrose, glucose and placebo groups

blood collection were analysed using the Friedman test. The reason for choosing this statistical method was to normalise the skewedness of the variable. P values < 0.05 were considered significant.

Results

Characteristics of the study group

Thirty-one preterm infants were enrolled in the study (16 girls, 15 boys). The mean (± SD) birth weight of the babies was 1,401 g (406; range 670–2,400); gestational age was 30.5 weeks (2.7; range 26–36); at the time of the procedure, the weight was 1,524 g (352; range 900–2,450); postmenstrual age was 32.3 weeks (1.5; range 29–36); and postnatal age was 20 days (16; range 5–45).

Physiological responses to pain

Heart rate measurements

The HR measurements of the sucrose, glucose and placebo groups are shown in Fig. 1 and Table 1. HR did not significantly differ among the sucrose, glucose and placebo groups before heel prick (baseline). However, the painful stimulus caused a significant increase in HR in the 1st, 2nd and 3rd minutes after the painful procedure compared with baseline in all three groups ($P<0.05$ for all).

The highest HR in all groups was observed in the first minute. When the three groups were compared, the heart rate of the placebo group was higher than sucrose and glucose and analysis of the variance showed that heart rates were significantly different ($P=0.007$). No significant differences were observed between the sucrose and glucose groups.

Respiratory rate measurements

The RR measurements of the sucrose, glucose and placebo groups are shown in Fig. 2 and Table 2. The RR did not significantly differ among the groups before heel lancing (baseline) and slightly increased after the painful stimulus in all groups, but this increase was not significant at any time compared with the rest of RR measurements. There were no significant differences among the groups.

Oxygen saturation measurements

The SaO_2 measurements of the sucrose, glucose and placebo groups are shown in Fig. 3 and Table 3. The level of SaO_2 did not significantly differ among the sucrose, glucose and placebo groups before heel lancing (baseline). SaO_2 slightly decreased during the first 2 min after the

Table 2 Changes in respiratory rate (*RR*) during the heel prick, and 5 min later in the sucrose, glucose and placebo groups

Time (min)	Sucrose group		Glucose group		Placebo group[a]		f	*P**
	RR[a]		RR[a]		RR[a]			
Baseline	46	(13.6)	44	(11.0)	42	(14.4)	1.096	0.361
0 (heel prick)	48	(12.9)	46	(17.3)	48	(15.5)	0.673	0.525
1	46	(16.3)	48	(16.2)	48	(13.5)	0.394	0.681
2	45	(14.6)	47	(16.5)	38	(12.8)	1.247	0.317
3	47	(15.8)	49	(12.4)	46	(11.4)	0.060	0.942
4	44	(15.5)	44	(10.7)	46	(14.9)	0.236	0.793
5	43	(16.0)	42	(13.6)	47	(15.8)	0.417	0.668

**P* values based on the results of the repeated measures analysis of variance among the three groups
[a] Values were expressed as mean (± SD)

Table 3 Changes in oxygen saturation (SaO_2) during the heel prick, and 5 min later in the sucrose, glucose and placebo groups

Time (min)	Sucrose group		Glucose group		Placebo group		f	*P**
	SaO_2[a]		SaO_2[a]		SaO_2[a]			
Baseline	95	(3.4)	95	(3.6)	96	(3.5)	1.032	0.371
0 (heel prick)	93	(4.8)	92	(6.3)	95	(3.6)	1.820	0.183
1	93	(4.9)	93	(3.9)	95	(3.7)	1.244	0.311
2	95	(3.5)	95	(5.2)	94	(3.9)	0.797	0.464
3	96	(3.8)	96	(4.0)	95	(3.0)	0.906	0.417
4	95	(4.2)	95	(4.2)	95	(4.4)	0.851	0.439
5	95	(4.2)	96	(3.9)	96	(2.3)	0.303	0.742

**P* values based on the results of the repeated measures analysis of variance among the three groups
[a] Values were expressed as mean (± SD)

painful stimulus in all groups. In the placebo group, differences were significant in the first and the second minutes compared to baseline values (P=0.043 and P=0.046 respectively). The level of SaO2 reached the baseline value at the second minute in the sucrose and glucose groups; however, it reached the baseline value at the 5th minute in the placebo group. When the SaO_2 values are compared among groups, no significant changes were observed. The mean levels of SaO_2 were not found to be less than normal in any of the groups.

Behavioural responses to pain—NFCS score

In 25 (84%) of the babies, a minimum of 2 and a maximum of 8 of the facial actions as defined in NFCS were observed. There were 6 babies (16%) with a 0 score, of which 3 were in the sucrose group, 2 were in the glucose group, and 1 was in the placebo group. While the mean NFCS score was 0 at rest (baseline), it increased rapidly after the heel lancing in all three groups, and the highest value was found at the moment the painful stimulus was given (0th minute), and then it slowly decreased. Changes in NFCS scores are presented in Fig. 4 and Table 4. The NFCS score was significantly higher in the placebo group compared with the sucrose and glucose groups at the 4th and 5th min (P=0.009 and P=0.046,respectively). No significant differences in the NFCS scores existed between the sucrose and glucose groups.

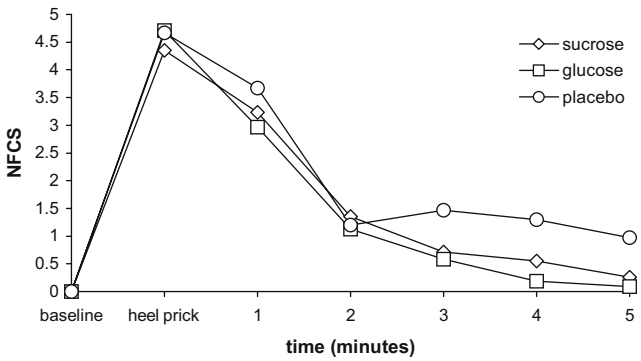

Fig. 4 Mean neonatal facial actions system (*NFCS*) scores in 1-min intervals for the entire study of the sucrose, glucose and placebo groups

Crying characteristics

In 25 processes out of a total of 93 tests performed on 31 babies, none of the babies cried (27 %). Of these 25 processes, 9 were performed on the sucrose group while 8 were carried on the glucose and 8 on the placebo groups. The median durations of the first cry and total crying time are shown in Table 5. The total crying time and the duration of the first cry was found to be shortest in the sucrose group. The duration of the first cry and total crying time were significantly longer in the placebo group compared with the sucrose and glucose groups (P=0.005 and P=0.007 respectively). No significant differences were observed between the sucrose and glucose groups. When individual phases of squeezing the heel (blood collection) were compared among groups, no differences were observed.

Discussion

Orally giving a sucrose solution before minor, painful procedures like heel lancing or venipuncture is known to have an analgesic effect on term and preterm neonates. This pain relief is presumably mediated by the activation of endogenous opioids by the sweet taste; this explanation is supported by the fact that the effect can be blocked by naltrexon, an opioid antagonist [7, 25, 27]. Comparison of the analgesic effects of sucrose given orally or intragastrically has concluded that the latter has no analgesic effect [24]. This finding has also supported the fact that the effect of the sucrose has begun by the sense of taste, before the absorption. The analgesic efficacy of 30% sucrose and 30% glucose was found to be similar in term neonates [9].

Painful stimuli in neonates are generally associated with diaphragmatic splinting, forced expiratory movements

Table 4 The neonatal facial coding system scores (*NFCS*) in the sucrose, glucose and placebo groups

Time (min)	Sucrose group		Glucose group		Placebo group		χ^2	*P**
	NFCS score[a]		NFCS score[a]		NFCS score[a]			
0 (heel prick)	4.3	(2.7)	4.7	(2.5)	4.7	(2.6)	1.117	0.572
1	3.2	(3.2)	3.0	(3.3)	3.7	(2.9)	0.306	0.858
2	1.3	(2.2)	1.1	(2.1)	1.2	(2.0)	1.849	0.397
3	0.7	(1.9)	0.6	(1.4)	1.5	(2.6)	0.974	0.614
4	0.5	(1.7)	0.2	(0.5)	1.3	(2.0)	9.455	0.009
5	0.3	(1.3)	0.1	(0.3)	1.0	(1.0)	4.714	0.046

**P* values based on the results of the repeated measures analysis of variance among the three groups
[a] Values were expressed as mean (± SD)

(crying), tachycardia, and hypertension secondary to sympathetic activation. Reaction to pain can be assessed by monitoring physiologic variables such as heart rate, respiratory rate, blood pressure and transcutaneous blood gases in the neonatal period [19]. The opioid analgesics cause a decrease in the heart rate by reducing sympathetic activity; similarly, the sense of sweet taste slowed down the heart rate as a result of the increase in the vagal tonus, which was induced by the stimulated endogenous opioid system, at the same time as the decrease in crying [15]. A significant calming effect of sucrose on the pain reaction of term infants to a heel lance, measured as an increase in their heart rate, has been shown by Blass and Hoffmeyer [5]. In our study, heel lancing was observed to cause an increase in HR in preterm babies. This increase was significant in the first 3 min—the immediate response to acute pain—and was found to be highest in the first minute in all groups. The highest HR in the placebo group was significantly higher compared with the sucrose and glucose groups; there was no difference between the sucrose and glucose groups. Our findings support the hypothesis that the effects of the sucrose and glucose solutions in reducing the sympathetic activity might be similar.

Although there was a slight increase in the RR of all the babies after the painful stimulus, the difference was not significant. When the SaO_2 changes were assessed, in the placebo group the decrease in SaO_2 was significant at the first and the second minutes compared with baseline values. It is known that physiological responses to painful stimuli may be individually different, and especially in small and sick babies, the physiological indicators are influenced more after the painful stimulus [30]. The slight decrease in SaO_2 and the slight increase in RR show that these physiological indicators were influenced by painful stimuli. Yet, the SaO_2 and RR values were within the normal limits in all groups. These results suggest that the heel prick might not lead to so much stress that it affects the oxygenisation in healthy preterm babies.

The detection and quantification of pain in newborns and infants is difficult due to the limited means of communication. The generally accepted way is to assess the response to pain by facial expressions and body movements using various methods, and to examine the characteristics of crying like intensity and duration. As defined by Craig and Grunau [11, 17], the NFCS is a scale that can reflect the intensity of the pain and that can discriminate between the responses given to painful and painless interventions. Shown to be reliable among observers, this method is accepted as a sensitive test for evaluating the behavioural responses to pain of term and preterm babies. Having the facial actions, as defined in the NFCS, observed after the painful stimulus in 84% of our study group proves that this method is valuable for evaluating the procedural pain response. On the other hand, having the 5 (83%) out of 6 cases with no defined facial actions, according to the NFCS, in the sucrose and glucose groups supports the idea that the sweet solutions raise the pain threshold in premature infants. In the placebo group, the NFCS score was significantly higher in the fourth and fifth minutes. That the NFCS values did not differ when comparing the sucrose and glucose solutions shows that the effects of both solutions are similar. Skoogsdal et al. [28] compared the analgesic effect of glucose in different concentrations (10%, 1 ml, 0.1 g vs. 30%, 1 ml, 0.3 g) with breast milk contain-

Table 5 Duration of first cry, total crying time and blood collection time after heel prick in the sucrose, glucose and placebo groups

Time (s)	Sucrose group		Glucose group		Placebo group		χ^2	*P**
First cry	3	(1–7)	6	(1–8)	18	(12-25)	10.963	0.005
Total crying time	25	(5–50)	43	(10–57)	60	(35–75)	10.067	0.007
Blood collection time	60	(40–75)	59	(45–71)	60	(45–67)	0.804	0.669

**P* values based on the result of Friedman test among the three groups

ing disaccharide lactose and proved that glucose at the concentration of 30% produced significantly stronger pain relief. In their study, the effects of the solutions were analysed by measuring HR, facial actions and the duration of crying as responses to heel lancing, similar to our study. Carbajal et al. [10] also has shown, by using the DAN (*Douleur Aigue Nouveau-ne*) scale, that glucose given in small amounts (30%, 0.3 ml, 0.09 g) before subcutaneous injection reduced the behavioural response to pain in small premature infants. In our study, the total duration of crying in the sucrose group was shortest, whereas the total duration of crying in the placebo group was significantly longer than in the sucrose and glucose groups. Like the NFCS results, the crying response of the babies has shown that the analgesic and calming effects of sucrose and glucose were similar.

A systematic review of the literature on the analgesic effect of sucrose shows that the optimal dose of sucrose to reduce pain in term and preterm babies is not yet clearly established [29]. This raises the question of whether or not giving more sucrose/glucose during the acute phase of pain would be more effective. More concentrated sweet solutions such as 30% sucrose or glucose seem to have a better analgesic effect. However, the use of concentrated sucrose or glucose may be criticised in light of their high tonicity and the risk of development of necrotising enterocolitis in preterm infants. No immediate adverse effects have been reported after various concentrations and volumes in a single oral dose of sucrose or glucose in the literature. There is no precise knowledge on the safety of carbohydrates if administered in repeated doses. In all cases, the staff should be aware of the potential adverse effects of sucrose solution due to hereditary fructose intolerance.

In conclusion, we have shown that sucrose and glucose given orally to premature infants before a painful stimulus reduces the changes in HR in the acute phase of the pain and shortens the duration of crying. In our study, while the facial actions of the babies receiving sucrose or glucose reached calmness and rest in the fourth and fifth minutes after the painful stimulus, no calmness was observed in those who received placebo. Although no gastrointestinal complications were seen in the babies who were administered carbohydrates, we believe that investigations are needed to determine what the lowest sucrose or glucose doses are for safely providing analgesia in preterm infants with fewer gestational weeks.

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