ORIGINAL ARTICLE

Sucrose and non-nutritive sucking for the relief of pain in screening for retinopathy of prematurity: a randomised controlled trial

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Background: Screening is necessary for infants at risk of retinopathy of prematurity. Despite local anaesthetic drops, infants find eye examinations distressing, displaying behavioural and physiological changes indicating acute pain. Oral sucrose and non-nutritive sucking reduce pain responses associated with invasive procedures.

Objective: To evaluate the use of oral sucrose and/or pacifier for reducing pain responses during eye examinations.

Methods: Forty infants <32 weeks gestation or <1500 g birth weight, in two neonatal units, were randomised to one of four interventions administered two minutes before their first screening examination: 1 ml sterile water as placebo (group 1, n = 10), 1 ml 33% sucrose solution (group 2, n = 10), 1 ml sterile water with pacifier (group 3, n = 9), or 1 ml 33% sucrose solution with pacifier (group 4, n = 11). Examinations were videotaped. Two observers, blind to the intervention, assessed recordings. Pain responses were scored using the premature infant pain profile (PIPP).

Results: The groups were similar in gestation, birth weight, and age at examination. Mean PIPP scores were 15.3, 14.3, 12.3, and 12.1 for groups 1, 2, 3, and 4 respectively. Analysis of variance showed a significant difference in PIPP score between groups ($p = 0.023$). Infants randomised to pacifiers scored lower than those without pacifiers ($p = 0.003$). There was no difference between groups receiving sucrose and those receiving water ($p = 0.321$).

Conclusions: Non-nutritive sucking reduced distress responses in infants undergoing screening for retinopathy of prematurity. The difference in response was large enough to be detected by a validated assessment tool. No synergistic effect of sucrose and pacifier was apparent in this group.

Retinopathy of prematurity, if untreated, is a leading cause of blindness in infants born prematurely.[1] In infants with progressive disease, laser therapy is effective in preventing further deterioration.[2] Evidence based guidelines for screening have been produced.[3] In accordance with these recommendations, infants at the Royal Infirmary of Edinburgh and Birmingham Heartlands Hospital born at gestations below 32 weeks or with birth weight of less than 1500 g undergo screening.

During eye examinations, babies clearly display well defined pain responses.[4] Infants undergoing screening examination have usually progressed from the initial acute problems associated with prematurity. They are often no longer receiving intensive care and rarely have a requirement for regular analgesic medication. Although local anaesthetic drops are administered before eye examination, most infants score highly on validated pain scores such as the premature infant pain profile (PIPP)[5 6] during examination. There is therefore a need to identify a safe and effective way of providing procedural pain relief.

Sucrose and non-nutritive sucking are the most widely studied non-pharmacological interventions for pain relief in infants.[7–11] Analgesic effects of sucrose and non-nutritive sucking are thought to be mediated by both endogenous opioid and non-opioid receptors. A Cochrane Review concluded that oral sucrose reduces procedural pain in neonates.[7] It has been shown to decrease pain responses in infants undergoing heelstick[10] or venepuncture.[8 9 11] A wide range of doses has been investigated. Doses of less than 0.12 g appear to be ineffective, and little increase in effect has been shown with doses greater than 0.5 g.[7 11] In this group of babies undergoing a brief, but acutely painful examination, the use of sucrose with or without a pacifier might be expected to attenuate pain responses. This study was designed to investigate the effectiveness of sucrose with or without non-nutritive sucking as an analgesic for this procedure.

STUDY DESIGN AND SUBJECTS

This was a prospective, randomised, placebo controlled study. All infants recruited to the study met the criteria for screening for retinopathy of prematurity on the basis of birth weight and/or gestational age. Babies receiving mechanical ventilation and those receiving nothing by mouth were excluded from the study. Any infant receiving concurrent alternative analgesic medication was also excluded. Babies receiving continuous positive airways pressure via nasal prongs who were judged to be stable and comfortable on this form of airway support were not excluded. Randomisation was performed using sealed opaque envelopes. The study solutions were prepared by members of staff who were otherwise not involved with the study.

Only the first screening examination for each baby was considered. This was to overcome potential confounding effects that might occur if a baby were to anticipate a procedure following previous exposure to the same painful stimulus. Eye examinations in both centres were carried out by one of two experienced ophthalmologists. Ethical approval was granted by each of the two local research ethics committees, and written parental consent was obtained.

Table 1 Characteristics of infants by randomised group (1–4)

	1	2	3	4
Intervention	Water alone	Sucrose alone	Water + pacifier	Sucrose + pacifier
Number	10	10	9	11
Gestational age (weeks)	27 (24–30)	29 (25–34)	30 (27–31)	29 (24–31)
Birth weight (g)	1000 (755–1550)	1030 (810–1570)	1300 (820–1610)	1210 (650–1910)
Age at examination (days)	45 (40–70)	43 (26–70)	41 (38–45)	42 (29–49)

Values are given as median (range).

SAMPLE SIZE AND POWER CALCULATION

Behavioural responses were observed, and PIPP scores performed in a group of 18 babies who were undergoing screening examination according to the usual unit protocol. The mean (SD) PIPP score in this group was 16.1 (1.7).

On the basis of these results a power calculation indicated that a sample size of seven per group would be required to allow 80% probability of detecting a three point difference in PIPP score with significance at the 5% level.

METHODS

Infants were randomised to receive one of the following four interventions two minutes before the start of one of the screening eye examinations. The start of the examination was defined as the time of administration of local anaesthetic eye drops.

- Group 1: 1 ml sterile water given by mouth using a syringe
- Group 2: 1 ml sucrose 33% given by mouth using a syringe
- Group 3: 1 ml sterile water given by mouth using a syringe and pacifier put into the mouth
- Group 4: 1 ml sucrose 33% given by mouth using a syringe and pacifier put into the mouth

Investigators, staff, and parents were blind to the identity of the study drug, but could not be blinded to the use of the pacifier.

Each infant was videorecorded during the examination and until two minutes after completion of the examination. Examination of the first eye only was used for recording of the PIPP score. It was not possible to include the second eye in the analysis, as the view was inevitably obscured by the examining ophthalmologist. Baseline physiological data were collected before the start of the examination. Maximum heart rate and minimum oxygen saturation values were noted during the procedure for later inclusion in the scoring of the PIPP. Two observers experienced in the use of the PIPP analysed all videotapes. Inter-observer reliability was >90%. PIPP scores were recorded for each infant.

RESULTS

Forty infants were included in the study (group 1: n = 10; group 2: n = 10; group 3: n = 9; group 4: n = 11). The median (range) gestational age at birth and birth weight for the whole group were 29 (24–34) weeks and 1105 (650–1910) g respectively.

Table 1 summarises the characteristics for the four study groups. The randomised groups were similar with regard to gestational age at birth, birth weight, and age at time of eye examination.

Mean (SD) PIPP scores were 15.3 (1.9), 14.3 (1.6), 12.3 (2.9), and 12.1 (3.4) for groups 1, 2, 3, and 4 respectively. Figure 1 shows error bars indicating the mean scores for the four groups. One way analysis of variance showed a significant difference between the four groups (p = 0.023). Further analysis to determine where the major differences between groups lay was carried out using the independent samples *t* test for equality of means. Comparison of all infants receiving sucrose (n = 21) versus all infants receiving placebo (n = 19) revealed no significant difference between the groups (p = 0.321; 95% confidence limits −0.92, 2.74). However, analysis comparing infants who sucked on a pacifier (n = 20) with those who did not (n = 20) showed significantly lower scores in infants receiving a pacifier (p = 0.003; 95% confidence limits −4.23, −0.96).

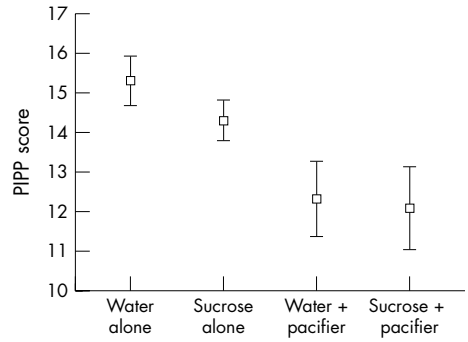

Figure 1 Premature infant pain profile (PIPP) scores. Data are mean and SEM.

DISCUSSION

In this group of infants, the highest PIPP scores were observed in those receiving water only, suggesting that intervention with either pacifier or sucrose has a pain relieving effect. Scores of infants receiving pacifiers were lower than those who did not, suggesting that non-nutritive sucking may be more effective than sucrose. There was a trend towards lower scores in the group receiving both sucrose and pacifier. However, the magnitude of the effect was not significant. Carbajal *et al*[12] showed similar results for infants undergoing venepuncture, although synergistic effects have been described for other procedures.[13]

Our study used a single dose of sucrose. In a study[14] that used pacifiers and repeated doses of sucrose or water, reduced pain scores were observed in infants receiving sucrose. It is possible that, had we given repeated doses, a greater positive effect may have been seen with sucrose.

Stress and pain responses associated with eye examination have been highlighted previously.[15 16] Although researchers have considered the use of sucrose and pacifier in retinopathy screening, to our knowledge, no previous study has compared responses of infants receiving one or both.

Results of recent studies in this field have been conflicting. Gal *et al*,[17] in a crossover study, showed a positive effect of sucrose on PIPP score during placement of the lid speculum. Others suggest that, although sucrose is effective at reducing pain responses to minor procedures, it may not be appropriate for the degree of pain associated with eye examination. Grabska *et al*[18] studied babies who were swaddled, had

What is already known on this topic

- Ophthalmological examination appears to be a painful procedure for infants
- Non-nutritive sucking and sucrose reduce pain responses in infants undergoing invasive procedures

What this study adds

- The use of a pacifier with or without sucrose reduces pain responses in infants having screening examinations for retinopathy of prematurity

pacifiers, and were randomised to receive sucrose or placebo as an adjunctive pain relieving intervention. They were unable to demonstrate a difference between the two groups. Rush *et al*[16] also found no benefit with comfort measures including the use of sucrose and pacifier. They speculate that lack of effect may be related to the length of eye examination, compared with other shorter procedures.

No adverse effects have been identified with single doses of sucrose. Johnston *et al*[19] observed worse neurodevelopmental outcomes in infants who had received repeated doses. However, repeated use over prolonged periods of time and long term effects of sucrose have not been adequately evaluated. Given this current uncertainty, the use of a pacifier alone, which appears to be equally or more effective, may be preferred by some clinicians and parents. For breast feeding infants where there is reluctance to offer a pacifier, sucrose alone may offer an alternative.

We suggest that the single or combined use of a pacifier and sucrose is effective in reducing pain responses in babies having ophthalmological examinations, and the use of these simple pain relieving interventions should be considered.

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