

Original Article

Can Oral Sucrose Reduce the Pain and Distress Associated with Screening for Retinopathy of Prematurity?

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CONCLUSION:

Oral [S] was not effective in reducing pain/distress from the ROP screening exam. Alternative strategies should be considered to achieve adequate pain relief.

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OBJECTIVE:

Infants undergoing eye exams to screen for retinopathy of prematurity (ROP) demonstrate physiologic and behavioral manifestations of pain and distress. Oral sucrose has analgesic properties that might reduce these effects.

AIM:

To determine the efficacy of oral sucrose in reducing the pain/distress of eye exams for ROP.

METHODS:

A total of 32 infants about to undergo ROP screening exams received either oral sucrose [S] ($N=16$) or sterile water [C] ($N=16$) in a randomized, prospective and blinded fashion. Outcome measures included HR, RR, O₂ saturation, BP, pain (premature infant pain profile) and percent of time spent crying during the eye exam.

RESULTS:

The groups were similar in GA (weeks) (28 ± 1.6), BW (kg) (1.04 ± 0.26), postnatal age (days) 50.8 ± 20.3 , and study weight (kg) 1.88 ± 0.40). Both groups demonstrated significant increases in HR, BP, and pain score in response to the exam. Infants in both groups spent the majority of time actively crying during the exam ([S] $53 \pm 35\%$ vs [C] $63 \pm 31\%$). Infants receiving [S] showed a small but significant drop in O₂ saturation. No significant differences were seen between groups in physiologic or behavioral responses to the eye exam.

INTRODUCTION

Screening eye exams for retinopathy of prematurity (ROP) are recommended in infants with birth weight less than 1.5 kg or gestational age under 28 weeks.¹ Extremely premature infants (<28 weeks) usually require serial exams during their NICU stay to assess disease progression/regression and retinal vascular maturation. Previous studies have identified adverse effects of the ROP screening exam secondary to either the mydriatic drops² — typically a sympathomimetic combined with an anticholinergic or cycloplegic — or the exam itself.³ Effects of mydriatics include increased BP² and delayed gastric emptying.⁴ The exam produces elevated BP and HR, decreased O₂ saturations and increased measures of pain.³ Despite this information, there appears to be scant attention paid to methods to minimize these effects. A review of the literature yielded a paucity of studies targeting relief of pain/distress from the ROP exam.^{5,6}

Studies of oral sucrose in neonates have documented its analgesic properties speculated to occur through the release of endogenous opiates triggered by sweet taste.⁷ Recent published guidelines from the AAP's Section on Pain, recommended considering the use of sucrose in NICU patients undergoing a wide variety of procedures.⁸ We postulated that oral sucrose would reduce measures of pain/distress in premature infants undergoing this exam.

MATERIALS AND METHODS

Subjects

The study was conducted in the NICUs at Connecticut Children's Medical Center and John Dempsey Hospital, both level III units. Patients scheduled to undergo ROP screening were eligible unless they had any of the following exclusions: on mechanical ventilation, known neurologic deficit, or receiving analgesic therapy. The study was IRB approved and written parental informed consent was obtained.

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Eye Exam

Study personnel included two pediatric ophthalmologists from the same group with similar practice styles. All babies were examined in a similar fashion. Mydriatics used were tropicamide 0.5% and phenylephrine 2.5% one drop in each eye and repeated 5 minutes later. Infants also received the topical anesthetic tetracaine just prior to the exam. The exam was performed following adequate pupillary dilatation (approximately 30 minutes after mydriatic drops). Infants were swaddled and offered a pacifier then examined using indirect ophthalmoscopy and scleral depression.

Study Design

This was a prospective randomized, blinded and placebo-controlled study. Syringes of either 24% sucrose or sterile water were provided by the pharmacy in sealed envelopes after randomization. Sucrose dosing was adjusted according to study weight: <1 kg — 0.5 cm³ (0.12 g); 1 to 1.5 kg — 1.0 cm³ (0.24 g); 1.5 to 2 kg — 1.5 cm³ (0.36 g); >2 kg — 2.0 cm³ (0.48 g).

The infant's nurse delivered the solution either directly into the mouth or via a nipple 2 minutes prior to the onset of the eye exam. The study ended 2 minutes after the completion of the eye exam.

Outcome measures: HR, RR, and O₂ saturations were continuously measured and recorded on the bedside monitor. Values at 1-minute intervals were averaged for each study period. BP was intermittently measured by cuff. The premature infant pain profile⁹(PIPP) was measured intermittently by the same observer. The percent of the exam which the infant was crying was calculated using an audiotape recording.

Statistical Analysis

Groups were compared using *t*-tests and ANOVA. A *p*-value of <0.05 was considered significant. Sample size estimate (15 patients in

each group) was based on an anticipated 50% reduction in crying time and HR acceleration.

RESULTS

A total of 32 patients (16 in each group) were studied. There were no differences between the groups in the following clinical characteristics: gestational age (weeks) (28±1.6), birth weight (kg) (1.04±0.26), postnatal age (days) 50.8±20.3, study weight (kg) 1.88±0.40) or gender (males 50%). Physiologic outcome variables for both groups are shown in Table 1. Baseline measures (HR, RR, O₂ saturation, BP) and PIPP scores were the same. Significant increases in HR, BP and PIPP scores were seen in both groups during the eye exam (*p*<0.01), however no differences were noted between the sucrose and placebo groups. Infants receiving sucrose (but not placebo) had a small but significant reduction in O₂ saturation after dosing, which persisted during the exam but returned to baseline by 2 minutes postexam (*p*<0.05). Infants in both groups spent a majority of time crying during the exam with no difference noted between groups.

SIGNIFICANCE

This study confirms previously noted adverse effects of the ROP screening exam in premature infants. Infants in both groups had significant elevations in HR, BP, and pain (PIPP) during the eye examination, which included insertion of a lid speculum and depression of the sclera. Further, infants spent the majority of the 2 to 3 minutes exam actively crying. These findings, in conjunction with a lack of demonstrable efficacy for oral sucrose, suggest that such maneuvers commonly employed for ROP screening result in

Table 1 Physiologic Outcome Measures for Study Groups

Variable	Study group	Baseline	Postmydriatics	Poststudy drug	During eye exam	Post-eye exam
HR	S	163±9	160±15	158±10	175±22*	158±9
	P	168±13	161±11	166±16	181±16*	164±16
RR	S	51±8	54±9	49±10	48±12	59±17
	P	52±14	57±15	51±7	46±8	57±8
O ₂ Sat	S	96±4	97±1.5	95±4 [†]	93±5 [†]	98±2
	P	98±2	97±1.7	97±3	96±3	98±3
MBP	S	50±7	53±15	—	62±15*	53±13
	P	47±8	48±8	—	69±18*	57±17
PIPP	S	4±2	—	—	14±3*	4±2
	P	4±2	—	—	14±3*	5±2
Crying time (%)	S	—	—	—	53±35	—
	P	—	—	—	63±31	—

Numbers are mean±SD.

HR: heart rate; RR: respiratory rate; O₂ sat: O₂ saturation; MBP: mean blood pressure; PIPP: premature infant pain profile; S: sucrose group; P: placebo group.

*During eye exam vs all others *p*<0.01.

[†]Poststudy drug and during eye exam vs all others *p*<0.05.

significant pain/distress. These results are similar to findings of Laws et al.,³ who noted significant increased HR during the exam, and Slevin et al.,⁶ who noted motor stress responses and crying. In contrast to previous studies demonstrating a rise in systemic BP following mydriatic drops,² no significant increases were seen in the current study. This discrepancy may be explained by differences in specific preparations, dosing, or important patient characteristics (e.g. postnatal age). Mydriatics and eye examination have also been associated with delayed gastric emptying and feeding intolerance in premature infants,⁴ a problem not addressed in the current study.

Sucrose in the dose employed did not reduce the stress or pain associated with the ROP exam. The efficacy of sucrose for infants undergoing painful procedures has recently been reviewed.⁷ Doses of sucrose as little as 0.012 to 0.12 g were effective in reducing HR and PIPP scores in term and preterm infants undergoing heel lance or venipuncture. Higher doses of sucrose (up to 0.48 g) have been more efficacious in studies of term infants. The optimal analgesic dose of sucrose remains to be determined and may be procedure specific.

In the current study, infants did not seem to benefit from oral sucrose despite doses as high as 0.48 g. It is likely that the degree of discomfort from forceful lid retraction, and scleral depression cannot be ameliorated by the relatively mild analgesic effect of oral sucrose. Oral sucrose has been well tolerated in several studies. The most common adverse effect reported has been choking and/or transient O₂ desaturation⁷ a finding confirmed in the current study and likely a result of uncoordinated suck/swallow in premature infants.

The results of this study should be interpreted in light of its limitations. The sample size ($N = 32$) was small since the study was powered to detect large (50%) differences in HR acceleration and crying time. In response to the exam, the sucrose group showed a smaller rise from baseline in mean BP (17 vs 44%) and less time spent crying (53 vs 63%) than control but these differences were not significant. Although larger studies might detect more subtle benefits from oral sucrose, the adverse responses noted in the sucrose-treated infants still support the need for additional strategies for intervention. The time from instillation of mydriatic eye drops to study drug delivery (2 minutes prior to eye exam) was variable (20 to 40 minutes) since multiple patients were studied sequentially on the same "eye screening" day. This could potentially confound results focused on the physiologic responses to the drops (which were not seen) but is unlikely to affect responses to the subsequent study drug or eye exam.

Studies on methods to reduce the pain and distress from ROP screening are limited. Saunders et al.⁵ compared the topical

anesthetic (proparacaine HCL 0.5%) with saline control in 55 infants undergoing ROP screening. No differences were noted in HR, RR, BP, transcutaneous oxygen, or cry. Slevin et al.⁶ studied the effects of positioning/containment on stress responses to the ROP exam. They randomized 38 infants to either nesting with soft padded boundaries supporting the body and limbs or a standard blanket without boundaries. Infants in the nested group demonstrated fewer motor movements typically associated with distress (flailing) and reduced crying compared with controls. We are not aware of any additional behavioral or pharmacological studies to reduce pain or distress from the ROP exam. This is surprising since screening for ROP is included in a list of painful procedures commonly performed in the NICU in a recent consensus statement from the International Evidence-Based Group for Neonatal Pain.⁸

This study adds further data to document the stress and pain response to ROP screening. In light of the lack of efficacy of oral sucrose demonstrated in the current report, additional studies to assess the utility and safety of more potent pharmacological interventions to reduce the pain and distress of ROP screening are warranted.

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