Oral Sucrose Improves Analgesia During Retinopathy of Prematurity Screening

Ryan R Ramoutar (✉ ryan_ramoutar@hotmail.com)

Leicester Royal Infirmary <https://orcid.org/0000-0001-7050-5379>

Anil J Singh

East and North Hertfordshire NHS Trust

Charikleia Papandreou

East and North Hertfordshire NHS Trust

Research Article

Keywords: analgesia, Retinopathy of Prematurity, Premature Infant Pain Profile

Posted Date: July 14th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-642733/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Purpose

To determine whether sucrose provides significant analgesia during Retinopathy of Prematurity (ROP) screening

Methods

This was a prospective, randomized, single masked audit. The examinations were performed by a single examiner. Forty-five (45) neonates were separated into two groups; Group 1 received oral sucrose while Group 2 received oral sucrose and non-nutritive suckling (NNS) at the discretion of the attending nurse. Pain was assessed using the Premature Infant Pain Profile (PIPP) score and recorded at baseline, immediately following lid speculum, at 3 minutes and 6 minutes following lid speculum insertion.

Results

The mean baseline PIPP score was 0.5. Fifteen (15) neonates (33%) received NNS. The mean PIPP scores at speculum insertion in both groups (Group 1: 7.24, Group 2: 5.50) were observed to be higher than at baseline and lower in Group 2 than in Group 1. In both groups, the scores at 3 minutes (Group 1: 4.70, Group 2: 4.20) and 6 minutes (Group 1: 4.50, Group 2: 4.70) were observed to be higher than at baseline, lower than at speculum insertion, but not significantly different to each other.

Conclusions

Lid speculum insertion during ROP screening appears to be a significantly painful event. ROP examinations should be conducted with a combination of topical analgesia and sucrose and NNS for greatest pain-relieving effect.

Introduction

Worldwide, about 10% of births occur preterm (before gestational age 37 full weeks).[1] Preterm birth is the most common cause of neonatal death,[2] and the second most common cause of death in children younger than 5 years.³[3] Prematurity also has associated comorbidities, one of which is Retinopathy of prematurity (ROP).

ROP is a leading cause of childhood preventable blindness in middle-income countries [4]. Ophthalmologic examination with binocular indirect ophthalmoscopy is considered to be the gold standard to detect ROP. This has been shown to be a painful procedure which causes stress and physical debilitation. It is thought that this can occur during use of the eyelid speculum or scleral indentation during ophthalmoscopic examination [5-9]

In the United Kingdom, the Royal College of Ophthalmologists guidelines state that all babies less than thirty two weeks gestational age or less than 1,501g birthweight should be screened, while all babies less than thirty-one weeks gestational age or less than 1,251g birthweight must be screened for ROP. [10] The use of local anesthetic eye drops before an eye examination is a partially effective therapeutic procedure. [11]

Our study set out to measure the effect of pain relieving measures during ROP examinations at the East and North Hertfordshire NHS Trust. The aim was to determine the efficacy of our most frequently used pain relieving procedure; titrated oral sucrose combined with non-nutritive sucking (NNS). The effect of any additional pain relieving intervention such as swaddling was also measured. We used the Premature Infant Pain Profile (PIPP) score to measure this in our study.

The Premature Infant Pain Profile is a validated pain scale used for infants of gestational age 37 weeks or less. [12] (Figure 1) Based on a tiered approach to analgesia in the neonate, examination of ROP falls between Tiers 1 and 2 on the 5-tiered scale, suggesting that non-pharmacologic and topical anaesthesia should be used. [13] (Figure 2) [14] Sucrose, along with non-nutritive suckling (NNS) and swaddling has been found to be effective in some studies reducing pain in Retinopathy of Prematurity examination, [15] although others showed no adjunctive effect of sucrose with NNS and swaddling. [16]

Patients And Methods

The Principles of the Declaration of Helsinki were adhered to. Ethical approval was sought from the East and North Hertfordshire NHS Trust but was deemed to not be required. This was a prospective, randomized, single masked audit which recruited patients for 3 consecutive months. The inclusion criteria were all infants born at < 32 weeks gestation or <1501g birth weight who underwent screening examinations for ROP.

Exclusion criteria were sucrose intolerance, sucrase-isomaltase deficiency, fructose intolerance, glucose-galactose malabsorption and muscle relaxed neonates. Forty-five patients met the study criteria and were all included in the study.

Pain assessment was completed by a neonatal nurse experienced in assessing neonatal pain scores. This nurse was blinded to the examination and any pain relieving measure employed during the procedure. The examination technique was standardised and carried out by a single examiner with 10 years' experience in ROP examinations. The technique included instillation of topical anaesthetic, insertion of a lid speculum and scleral indentation. Pain was assessed by the Premature Infant Pain Profile (PIPP) by an experienced neonatal nurse blinded during the pain relieving and comforting measures that were employed during the examination. The PIPP score was recorded at baseline and immediately following speculum insertion, at 3 minutes and 6 minutes respectively. This time frame was chosen because the analgesic effect of sucrose lasts 6-8 minutes. Oral Sucrose 0.5 ml was administered 2 minutes prior to the insertion of the lid speculum.

NNS was administered at the discretion of the attending nurse if the neonate demonstrated increasing signs of distress during the examination more than 1 minute after the sucrose bolus. To minimise bias from the systemic analgesic effect of sucrose, only pain scores from the first eye examined were included in the study data.

We divided the patients into two groups. Group 1 received only sucrose and Group 2 received sucrose and NNS. In both the sucrose only group (Group 1) and the sucrose and NNS group (Group 2), we compared the PIPP scores at baseline, speculum insertion, and 3 and 6 minutes post sucrose administration. Data was compared within each group and then we compared the groups to each other.

Results

The mean baseline pain score in both groups was 0.5. The mean length of examination was 7 minutes. The average range was 5 – 9 minutes. The median length of the examination was 6 minutes. Non-nutritive sucking (NNS) was applied to 33 % (n= 15) of neonates.

Group 1 (n=30)

In Group 1 (sucrose only); the mean speculum insertion PIPP score was observed to be 7.24 compared to baseline (0.50).

At three minutes, the mean PIPP score was 4.70 compared to base line (0.5).

Comparing the speculum insertion (7.24) and three-minute (4.70) scores, a large, and likely significant difference was observed.

At six minutes, the mean PIPP score was 4.50 compared to baseline (0.50), but did not appear to be significantly different from the three-minute score (4.70). (Figure 3)

Group 2.

In Group 2 (sucrose and NNS); the mean speculum insertion PIPP was 5.50 compared to baseline (0.50).

At three minutes, the mean PIPP score was 4.20 compared to base line (0.50). Comparing the speculum insertion (5.50) to three-minute (4.20) score, a likely significant difference exists.

At six minutes, the mean PIPP was 4.70 compared to baseline but not likely to be significantly different from the three-minute (4.20) score. (Figure 4)

Group 1 and Group 2 comparison.

When comparing Group 1 (sucrose only) with Group 2 (sucrose and NNS), the mean PIPP scores at speculum insertion were observed to be 7.24 vs 5.50 respectively.

At three minutes, the Group 1 mean PIPP was 4.70 vs Group 2 mean PIPP score of 4.20.

The six-minute mean PIPP scores were 4.50 in Group 1 and 4.70 in Group 2. The differences in the three-minute and six-minute scores were not likely to be statistically significant.

At ten minutes post examination, the mean pain score was 1.32 for the sucrose-only group and 1.25 for the group with adjunctive NNS. (Table 1 and Figure 5)

Table 1.

	SUCROSE (n=30)	SUCROSE +NNS (n=15)
BASELINE	0.5	0.5
SPECULUM INSERTION	7.24	5.50
3 MIN	4.70	4.20
6 MIN	4.50	4.70
10 MIN	1.32	1.25

Oxygen desaturation was reported in 20% of the neonates. This was self-resolving. No other adverse events were documented during the examination.

Discussion

Our results strongly suggests that insertion of the lid speculum is a significantly painful stimulus during the screening examination because pain scores were maximum at that point in both groups. We do not think that the pain score was confounded by scleral indentation as scleral indentation was not performed until after the first minute of the examination. Scleral indentation was started by the second or third minute of the examination as this was the standard method used by the examiner.

The three-minute pain scores were similar in both groups; 4.70 without NNS and 4.20 with NNS. In both groups, pain scores were likely significantly lower at three minutes compared to speculum insertion and we attribute this to the analgesic effect of the sucrose. In both groups, oral sucrose with and without NNS appear to significantly reduce pain scores at three and six minutes. However, the PIPP scores appeared to be significantly higher at speculum insertion, without NNS. Our results suggest that during the period of scleral indentation from minute-two to minute-six, additional NNS did not have any effect on the three and six-minute PIPP scores. Further evaluation is required to determine the precise cause or causes of this, and these may be addressed following publication of the recently concluded stressROP clinical trial. [17]

No untoward effects of the administration of sucrose were observed. Our study has shown that the combination of sucrose and NNS is more effective than either method alone and we now use both measures in our screening examinations. We feel this provides significantly reduced pain as measured in our PIPP scores, which is better for the neonates being examined. Single and repeated doses of sucrose

have not been found to have adverse effects on the neonate, [18,19] and it is our recommendation that ROP examinations should be conducted with a combination of Tier 2 (topical) and Tier 1 (Sucrose and NNS) analgesia for the greatest pain relieving effect.

Declarations

FUNDING

NOT APPLICABLE

CONFLICTS OF INTERESTS/COMPETING INTERESTS

NOT APPLICABLE

AVAILABILITY OF DATA AND MATERIAL

NOT APPLICABLE

CODE AVAILABILITY

NOT APPLICABLE

ETHICS APPROVAL

SOUGHT BUT WAS NOT REQUIRED

CONSENT TO PARTICIPATE

NOT APPLICABLE

CONSENT FOR PUBLICATION

NOT APPLICABLE

References

1. Goldenberg RL, Culhane JF, Iams JD, Romero R: Epidemiology and causes of preterm birth. Lancet. 2008; 371: 75-84
2. Lawn JE, Gravett MG, Nunes TM, Rubens CE, Stanton C: GAPPS Review Group Global report on preterm birth and stillbirth (1 of 7): definitions, description of the burden and opportunities to improve data. BMC Pregnancy Childbirth. 2010; 10: S1
3. Liu L, Johnson HL, Cousens S et al. for the Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012; 379: 2151-2161

4. Retinopathy of prematurity: clinical aspects. Fielder AR, Reynolds JD *Semin Neonatol.* 2001 Dec; 6(6):461-75.
5. Belda S, Pallas CR, De la Cruz J, Tejada P. Screening for retinopathy of prematurity: is it painful. *Biol Neonate.* 2004;86(3):195–200.
6. Rush R, Rush S, Ighani F, Anderson B, Irwin M, Naqvi M. The effects of comfort care on the pain response in preterm infants undergoing screening for retinopathy of prematurity. *Retina.* 2005;25(1):59–62.
7. Rush R, Rush S, Nicolau J, Chapman K, Naqvi M. Systemic manifestations in response to mydriasis and physical examination during screening for retinopathy of prematurity. *Retina.* 2004;24(2):242–5.
8. Laws DE, Morton C, Weindling M, Clark D. Systemic effects of screening for retinopathy of prematurity. *Br J Ophthalmol.* 1996;80(5):425–8
9. Allegaert K, Casteels I, Tibboel D. Pain management during eye examinations for retinopathy of prematurity: what about procedural adaptations to blunt the pain response. *Acta Paediatr.* 2010;99(4):488–9.
10. Guideline for the Screening and Treatment of Retinopathy of Prematurity. Royal College of Ophthalmologists. May 2008
11. Dempsey E, McCreery K. Local anaesthetic eye drops for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity. *Cochrane Database Syst Rev.* 2011;9:CD007645.
12. Stevens B, Johnston C, Petryshen P, et al. Premature infant pain profile: development and initial validation. *Clin J Pain.* 1996;12(1):13–22
13. Norina Witt, Seth Coynor, Christopher Edwards, and Hans Bradshaw A Guide to Pain Assessment and Management in the Neonate *Curr Emerg Hosp Med Rep.* 2016; 4: 1–10
14. Witt, N., Coynor, S., Edwards, C. *et al.* A Guide to Pain Assessment and Management in the Neonate. *Curr Emerg Hosp Med Rep* **4**, 1–10 (2016)
15. O'Sullivan A, O'Connor M, Brosnahan D, et al. Sweeten, soother and swaddle for retinopathy of prematurity screening: a randomised placebo controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 2010;95(6):F419–F422.
16. Boyle EM, Freer Y, Khan-Orakzai Z, et al. Sucrose and non-nutritive sucking for the relief of pain in screening for retinopathy of prematurity: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 2006;91(3):F166-F168. doi:10.1136/adc.2005.087668
17. United States National Institutes of Health Clinical Trials NCT04408807
18. Gaspardo CM, Miyase CI, Chimello JT, Martinez FE, Martins Linhares MB. Is pain relief equally efficacious and free of side effects with repeated doses of oral sucrose in preterm neonates? *Pain.* 2008 Jul;137(1):16-25. doi: 10.1016/j.pain.2007.07.032. Epub 2007 Sep 12. PMID: 17854995.
19. Shreshtha Banga, Vikram Datta, Harmeet Singh Rehan, Bhanu Kiran Bhakhri, Effect of Sucrose Analgesia, for Repeated Painful Procedures, on Short-term Neurobehavioral Outcome of Preterm

Figures

Gestational Age	> 36 weeks	32-35 weeks	28-31 weeks	< 28 weeks
Behavioral State	Active awake Eyes open Facial movements	Quiet awake Eyes open No facial movements	Active sleep Eyes closed Facial movement	Quiet sleep Eyes closed No facial movements
Maximum heart rate	0–4 BPM increase	5–14 BPM increase	15–24 BPM increase	> 25 BPM increase
Minimum oxygen saturation	0–2.4% decrease	2.5–4.9 % decrease	5.0–7.4% decrease	> 7.5% decrease
Brow bulge	None 0–9% of time	Minimum 10–39% of time	Moderate 40–69% of time	Maximum > 70% of time
Eye squeeze	None 0–9% of time	Minimum 10–39% of time	Moderate 40–69% of time	Maximum > 70% of time
Nasolabial Furrow	None 0–9% of time	Minimum 10–39% of time	Moderate 40–69% of time	Maximum > 70% of time

Figure 1

The Premature Infant Pain Profile is a validated pain scale used for infants of gestational age 37 weeks or less.

A Tiered Approach to Analgesia in the Neonate

Figure 2

Based on a tiered approach to analgesia in the neonate, examination of ROP falls between Tiers 1 and 2 on the 5-tiered scale, suggesting that non-pharmacologic and topical anaesthesia should be used.

Figure 3

At six minutes, the mean PIPP score was 4.50 compared to baseline (0.50), but did not appear to be significantly different from the three-minute score (4.70).

Figure 4

At six minutes, the mean PIPP was 4.70 compared to baseline but not likely to be significantly different from the three-minute (4.20) score.

Figure 5

At ten minutes post examination, the mean pain score was 1.32 for the sucrose-only group and 1.25 for the group with adjunctive NNS.