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*Original Article*

# The Effect of Sucrose on the Control of Pain Secondary to Retinopathy of Prematurity Screening: Randomised Controlled Trial

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**Abstract** ***Introduction:*** Pain control during interventions may be able to prevent long term impact of pain on infants' neurodevelopmental outcome. We would like to examine the efficiency of sucrose intake on pain control during retinopathy of prematurity examination. ***Methods:*** Sixty-four infants were included in the study between December 2010 and September 2011. They were randomised into three groups as repeated doses of 0.2 ml distilled water, repeated doses of 0.2 ml sucrose, and single dose of 0.6 ml sucrose group. Premature infant pain profile, peak heart rate, oxygen saturation ($SpO_2$), and characteristics of crying were evaluated during eye examination. ***Results:*** The only significant difference of median pain scores was on the left eye at 30 seconds [7.5 (11), 8 (12), 9 (9) in repeated low doses and single high dose of sucrose, and placebo group, respectively] (p=0.015). Heart rate and $SpO_2$ (p=0.67 and p=0.21) were not different between groups. Crying time was shorter (p=0.028) and severity of crying was lower (p=0.009) in groups that received sucrose compared with placebo. ***Discussion:*** Sucrose may lead to sucking, swallowing and decrease crying by stimulating taste sensation, thus may result in misinterpretation of the subjective parameters of pain score, considering that it has no influence on objective criteria of pain.

**Key words** Pain; Prematurity; Retinopathy; Sucrose

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## Introduction

Infants are exposed to many painful procedures for diagnostic and therapeutic purposes in the intensive care unit. Inadequate pain relief may result in increased pain sensitivity over time and altered responses to pain later in life.[1,2] Autonomic pathways for pain processing develops basically from mid to late gestation, and suboptimal inhibitory mechanisms play a major role in increased pain sensitivity.[3] Repetitive pain during the neonatal period may cause permanent or long-term changes in the immature brain.[4,5] It is therefore important to take precautions for pain relief, early diagnosis of pain sensation and provide effective therapy.

Screening for retinopathy of prematurity (ROP), is one of the invasive painful procedures conducted in the neonatal intensive care unit, is performed at postnatal age four to six weeks in order to diagnose and provide treatment early for one of the major causes of blindness in childhood, and its examination is recommended with certain intervals

depending on the stage of the ROP.[6] Recent studies have shown transient changes in blood pressure, heart rate, respiratory rate, and oxygen saturation during highly painful ROP screening.[3,7-10] There is a need for reducing pain secondary to ROP examination in a safe and effective way in premature infants. Recent studies on various minor and major interventional procedures have focused on reliable and easy-to-perform non-pharmacological methods in providing pain relief; however, there are limited studies on the efficiency of these methods in the ROP examination. In addition, these limited studies are highly heterogeneous due to different study designs.[11-16] Therefore, the present study evaluated the effect and side effect profile of repeated low doses or relatively high single dose of sucrose which is one of those non-pharmacological agents that acts by activating lingual sweet taste receptors and releasing endogenous opioids in providing pain relief during ROP screening in premature babies.[3]

## Methods

This study was designed as a prospective, randomised, double-blinded, placebo-controlled study, and conducted between December 1, 2010 and August 31, 2011 after obtaining approval from the ethics committee at Zeynep Kamil Maternity and Children's Training and Research Hospital, Neonatology Unit, Turkey. Being a tertiary center in its region, the patient population of our hospital consists of high-risk and complicated neonates and mothers who require multidisciplinary care, and our patients often include the neonates of mothers with inadequate antenatal care. The Neonatology Unit is a 60 bed unit accepting only inborn infants with approximately 1500 annual admissions. Twenty-five percent of admissions were very low birth neonates. The premature infants, who underwent first ROP examination and who met the criteria as outlined by the American Academy of Pediatrics, were enrolled in the study after parental informed consent was obtained.[6] The infants that received invasive or noninvasive mechanical ventilator support during first ROP screening, and systemic analgesics or sedative agents during the procedure, infants with intracranial haemorrhage and those having asphyxia, infants that underwent cardiopulmonary resuscitation and those with congenital anomaly were excluded from the study. The infants were divided into three groups; 0.2 ml distilled water (placebo) given by mouth using a syringe two minutes before, during, and after the procedure with two minute intervals (n=21) (Group 1); 0.2 ml sucrose 24% given by mouth using a syringe two minutes before, during, and after the procedure with two minute intervals (n=22) (Group 2); infants that received 0.6 ml sucrose 24% given by mouth using a syringe two minutes before the procedure, and applied empty syringe during, and after the procedure with two minute intervals (n=21) (Group 3). Both of the solutions were colorless. The interventions were drawn into syringes which were covered by identical label to prevent inspection of the contents of the syringe and keep the study as double-blinded. Empty syringe was applied after the single dose of sucrose as placebo instead of distilled water to prevent the impulses for sense receptors in group 3. The infants were randomly assigned to one of the three groups using a computer generated randomisation program. A nurse who administered the interventions provided by the pharmacy opened sealed envelopes with instructions on infant group assignment. The babies were fasted for two hours before and after ROP examination considering the side effects of analgesics and mydriatics. The ophthalmologic examination was performed by a single ophthalmologist (MKG). Mydriasis was produced by administering tropicamide (0.5%) and phenylephrine HCl (2.5%) drops twice 60 minutes before ROP examination with 10-minute intervals. Topical local anesthetic drops (Proparacaine; Alcaine® drops 0.5%) were applied in all infants 30 seconds before ROP examination. Each infant was equipped with an oxisensor connected to a Nelcor pulse oximeter (Ovidien RMS). All the infants were video-recorded during ROP screening. Video recordings and pulse oximeter recordings were displayed on a single screen. Left eye was examined firstly followed by the right eye. Detecting the presence and severity of pain accurately constitutes a challenge in infants, who are unable to express pain sensation. The premature infant pain profile (PIPP) score which was one of these scoring systems for overcoming this problem was set as the primary outcome measure. PIPP scoring system consists of three behavioural indicators (brow bulge, eye squeeze, and nasolabial furrow), two physiological indicators (heart rate, oxygen saturation), and two contextual variables (gestational age and behavioural state) that are used to assess pain.[17] Scores can range from one to twenty-one. PIPP scores under seven indicate no pain, scores between seven and 12 are indeterminate, and scores above 12 indicate significant pain.[17] The frequency of tachycardia (>180 bpm), bradycardia (<100 bpm), desaturations (<85% for 10 seconds), crying time (minute), and the degree of cry (1 to 5 points) were set as the secondary outcome measures. The primary and secondary outcome parameters at baseline before examination, immediately after administration of local

anesthetic drops, at 30 seconds, 60 seconds, and two minutes after placement of the speculum for both eyes, and at four minutes for right eye by watching video records were evaluated by the same investigator (OSP) who was blinded to the subject assignment. The possible side effects of sucrose like gastrointestinal intolerance (increased gastric residuals, abdominal distention), apnoea, or requirement of mechanical ventilation were monitored within 12 hours after ROP examination. The effects of different doses of sucrose in providing pain relief during ROP screening, the association of the possible effect with the dose and administration frequency and duration of the effect, and side effects of sucrose were evaluated. Furthermore, it was also investigated if PIPP score that contain subjective behavioural parameters in the evaluation of pain was correlated to more objective parameters such as heart rate and oxygen saturation ($SpO_2$).

### *Statistical Methods*

NCSS (Number Cruncher Statistical System, Utah, USA) 2007 Statistical Software was used in the statistical analysis. The variables were expressed as mean, standard deviation, median, ranges, and the categorical variables were expressed as frequency and percentage. The assumption of normality for continuous variables was checked using the Shapiro-Wilks test. Oneway Anova test was used to compare normally distributed variables, and Turkey HDS test was used in post hoc analysis of them. In addition, Kruskal Wallis test was used to compare the variables between groups which were not distributed normally, and Mann Whitney U test was used in post hoc analysis of these variables. Pearson Chi Square test was used in comparing qualitative data.

G*Power (v3.1.7) statistical program was used in power analysis. A pilot study which composed of fifteen infants per group with similar findings was conducted prior to the main study. The power of the study was expressed as 1-β (β=Type II error). Means and standard deviations of the results were referenced. While assuming a three-point difference in PIPP scores between two groups was clinically significant, the effect size (d) was calculated as 0.937 for achieving 80% power for $\alpha$=0.05. As a result, minimum number of infants was determined as 20 per group.

## Results

Seventy-six neonates were assessed for eligibility. The neonates that received invasive or noninvasive mechanical ventilator support during the first ROP screening (n=2), and systemic analgesics or sedative agents (n=1) during the procedure, and those having asphyxia (n=2), neonates with congenital anomaly (n=2), and neonates for which their parents did not provide informed consent (n=3) were excluded from the study. Sixty-six neonates were randomised. Neonates with intracranial haemorrhage (n=1) in group 1, and those that underwent cardiopulmonary resuscitation (n=1) in group 3 were excluded after randomisation. A total of 64 patients were included in the study.

Time of the eye examination between group 1 and group 2 was the only significant difference in demographic features of the groups (Table 1).

The PIPP score of the left eye at 30 seconds was significantly lower in the 0.6 ml single dose of sucrose group (group 3, n=21) and repeated dose of 0.2 ml sucrose group (group 2, n=22) compared to placebo group (group 1, n=21) (p=0.015) (Table 2) (Figure 1). The PIPP scores were not statistically different between low and relatively high dose sucrose groups. There was no significant difference between the groups in terms of the PIPP scores of the right eye (Table 2). There was also no significant difference between the three groups in terms of peak heart rate and $SpO_2$ ($p>0.05$) (Table 2).

During the examination, oxygen demand increased in four patients in the placebo and 0.6 ml single dose sucrose groups and three patients in the 0.2 ml repeated dose sucrose group.

The crying behaviour of the infants during ROP screening was summarising in Table 3. Crying duration was shorter (p=0.028) and severity of crying was lower (p=0.009) in groups receiving sucrose compared with placebo. Also, crying behaviour difference between low and high dose sucrose, was not statistically significant ($p>0.05$).

After the examination, none of the patients had possible side effects of sucrose monitored within 12 hours.

## Discussion

Repetitive painful stimuli increase pain sensitivity by affecting pain threshold.[18] Therefore; we included only the infants who would undergo ROP screening for the first time in order to standardise pain sensitivity in this study. Finally, low or relatively high dose sucrose administration reduced PIPP scores, and crying behaviour at 30 seconds of ROP examination; however, no effect was observed on the peak heart rate and $SpO_2$ that are more objective criteria for pain perception, and the observed effect was not sustained with the administration of repeated low doses of sucrose during

examination. Sucrose concentration, doses, administration time, and frequency vary between the studies (Table 4). In a consensus statement for the prevention and management of pain in the newborn, using pacifier with 0.1-0.4 ml 12%-24% sucrose for preterm infants is recommended as a pain relief measure.[19] In Cochrane review, even small doses of sucrose as 0.05 ml was effective in pain control during heel lance or venipuncture.[20] Also, there were studies that determined lower PIPP scores in the sucrose group with a dose application of 0.1 or 0.2 ml 24% than control group during ROP screening.[13,16] ROP examination is more painful than venipuncture or heel stick, and caution should be taken when comparing studies undertaken on procedures involving different areas of the body which may have different pain sensitivity.[16] Furthermore, the long term adverse effect of sucrose intervention is not clear, yet. So, we aimed to find optimal minimum dose for pain control during ROP screening, and preferred to study the efficacy of the repeated 0.2 ml or single 0.6 ml 24% sucrose doses. As a result, although both low and relatively high dose administration of sucrose decreased PIPP score at 30 seconds of the examination, there was no significant difference in the efficacy of sucrose on PIPP scores between low and relatively high dose sucrose group. It was observed that of all studies, those where the sucrose and placebo groups were combined with other non-pharmacological methods reported the potent effects of sucrose to decrease PIPP score,[3,12,13,16] except the one by Rush et al (Table 4).[15] However, in the latter study sucrose has been administered 15 minutes before the examination. Whereas sucrose should be administered approximately two minutes before the procedure, in order to maximise its analgesic effects. Parallel to the results of all these studies, the sucrose and the placebo isolated or combination to nipple, four groups were compared by Boyle et al and the sucrose alone found to be ineffective in reducing PIPP score while it is effective when combined with the nipple.[14] In our study, in order to demonstrate the independent effect of sucrose we wanted to use sucrose alone. Similarly, Grabska et al, did not combined the sucrose with other methods and reported that the sucrose was ineffective to reduce the PIPP score.[11] The dosage of sucrose in our study was low compared to Grabska et al's, but our sample size was larger.

The hypothesis that repeated lower doses may be more effective than single dose is another part that requires consensus. Johnstone et al did not recommend the use of multiple repeated doses of sucrose for preterm neonates less than 32 weeks of age.[21] On the other hand, a Cochrane review reported a study that determined low and repeated doses of sucrose increased analgesia in minor interventions, and this

**Table 1** Demographic features of the groups that underwent first retinopathy of prematurity screening

| | Group 1 (n=21) | Group 2 (n=22) | Group 3 (n=21) | P |
|---|---|---|---|---|
| Male, n (%) | 10 (47.6) | 7 (31.8) | 12 (57.1) | 0.241[a] |
| Birth weight (grams), mean±SD | 1215±376 | 1242±337 | 1194±319 | 0.106[b] |
| Gestational age (weeks), mean±SD | 29.8±3.1 | 29.5±2.5 | 30.3±2.2 | 0.598[b] |
| Postconceptional age (weeks), mean±SD | 34.2±2.9 | 33.4±1.8 | 34.5±1.9 | 0.262[b] |
| APGAR score (1st minute), median (range) | 7 (6) | 6 (5) | 5 (7) | 0.240[c] |
| APGAR score (5th minute), median (range) | 9 (4) | 8 (4) | 8 (4) | 0.481[c] |
| Antenatal steroid users, n (%) | 10 (47.6) | 16 (72.7) | 14 (66.7) | 0.210[a] |
| Time of eye examination (days), mean±SD | 28.8±4.6 | 24.2±6.2 | 25.7±6.0 | 0.034[c]* (G 1-2)[c]; 0.029 |
| Invasive mechanical ventilation, n (%) | 14 (66.7) | 15 (68.2) | 14 (66.7) | 0.993[a] |
| Duration of mechanical ventilation (days), median (range) | 8.5 (40) | 5.0 (13) | 4.5 (27) | 0.256[c] |
| Noninvasive ventilation, n (%) | 6 (28.5) | 7 (31.8) | 7 (33.3) | 0.943[a] |
| Duration of supplemental oxygen by incubator or hood (days), mean±SD | 13±12.8 | 10.8±9.5 | 9.2±8.4 | 0.481[c] |

Group 1, Sterile water; Group 2, Repeated doses of 0.2 ml sucrose; Group 3, Single dose of 0.6 ml sucrose

G1-2, Group 1 vs Group 2

[a]Pearson Chi Square test; [b]Oneway ANOVA test; [c]Kruskal Wallis test (post hoc Mann Whitney U test); *p<0.05

**Table 2** Peak heart rate, oxygen saturation, and pain scores of the infants during first retinopathy of prematurity screening

| Parameter | Group | Baseline | After Alcaine® | Left eye 30 sec | Left eye 60 sec | Left eye 2 min | Right eye 30 sec | Right eye 60 sec | Right eye 2 min | Right eye 4 min |
|---|---|---|---|---|---|---|---|---|---|---|
| Heart rate (bpm), mean±SD | 1 | 145±16 | 136.±19 | 145±23 | 141±23 | 143±20 | 143±25 | 141±20 | 137±20 | 139±21 |
| | 2 | 135±22 | 137±18 | 139±22 | 135±30 | 143±19 | 144±22 | 140±25 | 140±22 | 142±21 |
| | 3 | 147±18 | 150±16 | 148±20 | 140±23 | 152±19 | 141±26 | 146±25 | 135±27 | 139±21 |
| ***P*** [a] | | **0.130** | **0.056** | **0.386** | **0.755** | **0.225** | **0.918** | **0.674** | **0.803** | **0.925** |
| $SpO_2$ (%), mean±SD | 1 | 96±4 | 95±4 | 93±5 | 95±3 | 96±3 | 94±4 | 95±5 | 96±4 | 97±3 |
| | 2 | 97±3 | 95±6 | 94±7 | 94±7 | 94±7 | 94±6 | 92±8 | 96±5 | 96±5 |
| | 3 | 96±4 | 97±4 | 94±5 | 92±12 | 94±8 | 92±9 | 94±7 | 96±5 | 97±3 |
| ***P*** [a] | | **0.790** | **0.466** | **0.645** | **0.463** | **0.526** | **0.648** | **0.473** | **0.932** | **0.901** |
| PIPP, median (range) | 1 | 3.0 (5) | 3.0 (6) | 9.0 (9) | 7.0 (10) | 4.5 (11) | 7.0 (12) | 5.0 (12) | 3.0 (11) | 3.0 (9) |
| | 2 | 3.0 (5) | 3.5 (9) | 7.5 (11) | 6.0 (13) | 5.0 (11) | 7.,0 (12) | 5.5 (10) | 4.0 (8) | 4.0 (8) |
| | 3 | 3.0 (5) | 3.0 (11) | 8.0 (12) | 6.0 (10) | 6.0 (10) | 6,0 (10) | 5.0 (13) | 3.0 (7) | 2.0 (4) |
| ***P*** [b] | | **0.204** | **0.782** | **0.015*** (G1-2; 0.007) (G1-3; 0.021) | **0.712** | **0.647** | **0.707** | **0.630** | **0.812** | **0.270** |

Group 1, Sterile water; Group 2, Repeated doses of 0.2 ml sucrose; Group 3, Single dose of 0.6 ml sucrose.
G1-2,Group 1 vs Group 2; G1-3, Group 1 vs Group 3.
PIPP, premature infant pain profile; [a]Oneway ANOVA test (post hoc Turkey HSD test); [b]Kruskal Wallis test (post hoc Mann Whitney U test); *p<0.05

**Table 3** Crying behaviour of the infants during first retinopathy of prematurity screening

| | Group 1 (n=21) | Group 2 (n=22) | Group 3 (n=21) | P | Post Hoc |
|---|---|---|---|---|---|
| Left eye | | | | | |
| Degree of cry, median (range) | 4.0 (4) | 2.0 (5) | 3.0 (4) | 0.009* | G1-2; 0.002 G1-3; 0.018 |
| Duration of cry (minutes), median (range) | 4.0 (4) | 2.0 (5) | 3.0 (4) | 0.028* | G1-2; 0.003 G1-3; 0.046 |
| Right eye | | | | | |
| Degree of cry, median (range) | 4.0 (4) | 3.0 (5) | 3.0 (5) | 0.286 | NS |
| Duration of cry (minutes), median (range) | 4.0 (4) | 2.0 (5) | 3.0 (5) | 0.183 | NS |

Group 1, Sterile water; Group 2, Repeated doses of 0.2 ml sucrose; Group 3, Single dose of 0.6 ml sucrose
G1-2, Group 1 vs Group 2; G1-3, Group 1 vs Group 3.
NS: Non significant; *p<0.05

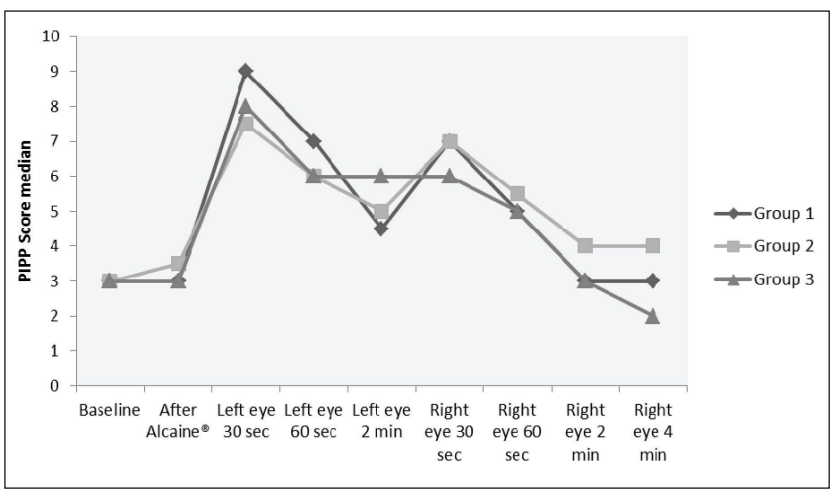


**Figure 1** The premature infant pain profile (PIPP) scores during the first retinopathy of prematurity screening.

**Table 4** The studies that evaluated the efficiency of sucrose in secondary pain prophylaxis during the retinopathy of prematurity screening

| Number of cases | Evaluated groups | Sucrose concentration & dose | Administration time according the procedure & frequency | ROP examination of pain | Evaluated parameters | Time for the evaluation | Result |
|---|---|---|---|---|---|---|---|
| 32 (Grabska et al) | - Sucrose<br>- Sterile water | 24%<br><1 kg=0.12 gr<br>1-1.5 kg=0.24 gr<br>1.5-2 kg=0.36 gr<br>2 kg>0.48 gr | - Once<br>- Before two minutes | Repeated | PIPP, PHR, $SpO_2$, blood pressure, respiratory rate, crying time | Before procedure, during and after procedure | Only differenc was lower $SpO_2$ in the sucrose group than placebo |
| 23 (Gal et al) | - Swaddle +sucrose<br>- Swaddle +sterile water | 24% (2 ml) | - Examining in the arms<br>- Before two minutes | First | PIPP score | 1 and 5 minutes before procedure, during procedure, and 1 and 5 minutes after procedure | PIPP scores were higher in the placebo group during procedure, no difference after procedure than control group |
| 30 (Mitchell et al) | - Sucrose +nipple<br>- Sterile water +nipple | 24% (0.1 ml) | - During the procedure, three times with two minutes intervals | Repeated | PIPP score | Before procedure after local anesthetic administration, 30, 60, 90, and 120 seconds during examination | PIPP scores were lower during procedure in the sucrose+nipple group than control group |
| 40 (Boyle et al) | - Sterile water<br>- Sucrose<br>- Sterile water +nipple<br>- Sucrose +nipple | 33% (1 ml) | - Before two minutes | Repeated | PIPP score | When speculum is first placed on the eye | No difference between sterile water and sucrose groups. PIPP scores lower in groups containing nipple than others |
| 30 (Rush et al) | - Control group<br>- Swaddle +nipple +sucrose | 24% (saturated gauze pad) | - Swaddle+ sucrose 15 minutes before<br>- Cuddle 15 minutes before and after | Repeated | $SpO_2$, PHR, respiratory rate, crying time | 30 minutes before proparacaine apply, 5 minutes before procedure and at three time points during procedure, 5 minutes after procedure | No difference between groups |
| 40 (Osullivan et al) | - Sterile water +swaddle +nipple<br>- Sucrose +nipple +swaddle | 24% (0.2 ml) | - Before two minutes | First | N-PASS score, PHR, $SpO_2$ | When speculum is first placed on the eye and while scleral examination is performed | N-PASS score was lower in the sucrose group than control group |
| 64 (Dilli et al) | - Sucrose +nipple<br>- Sterile water +nipple | 24% (0.5 ml/kg) | - Before two minutes | First | PIPP, PHR, $SpO_2$, blood pressure, respiratory rate, crying time | When speculum is first placed on the eye | PIPP score and crying time were lower in the sucrose+nipple group than control group |

N-PASS, Neonatal Pain, Agitation and Sedation Scale; PHR, peak heart rate; PIPP, premature infant pain profil; $SpO_2$, oxygen saturation

effect lasted for approximately four minutes.[20] However, favoruable effects of repeated low doses of sucrose were not determined in our study.

Pain assessment is a necessary part of neonatal pain management, as an indication for initiating therapy, as well as assessing its effectiveness. However, the presence and severity of pain accurately constitute a challenge in infants, who are unable to express pain sensation. Many scoring tools have been developed to overcome this problem. We preferred to use PIPP scoring tool due to the fact that it combines behavioural and physiologic variables, has utility in premature and mature infants, and can be used to monitor neonatal pain on a routine basis in many neonatology units. Nevertheless, many signs used in these assessment tools require the subjective evaluation by observers. So, we investigated if PIPP score that contain also subjective behavioural parameters in the evaluation of pain was correlated to more objective parameters such as heart rate and $SpO_2$. However, the favoruable effect of sucrose on PIPP score and also on crying behaviour was not observed on the peak heart rate and $SpO_2$ that are more objective criteria for pain perception. We suggest that sucrose may trigger sucking, licking, and swallowing behaviour due to the stimulation of taste sensation, and this may affect subjective behavioural parameters (e.g. brow bulge, eye squeeze, and nasolabial furrow) of PIPP scoring by affecting facial expression and cause misinterpretation. Sucrose may influence crying behaviour which may be resulted from starving in addition to pain by stimulating taste receptors.

We did not observe any side effect associated with repeated low or relatively high and single dose sucrose in the short-term follow-up period. However, the effects of sucrose on long-term neurodevelopmental outcomes remain unknown.[3] Our study did not evaluate long-terms effects of sucrose. It is one of the limitations of the study. In addition, the present results cannot be generalised to extremely preterm and sick infants due to inclusion of only stable infants in the present study. The future studies designed with higher doses of sucrose and larger sample size, evaluating physiological markers in combination with biochemical indicators of pain response are required to determine the exact and independent effect of sucrose on pain control during ROP examination.

In conclusion, though the sucrose implementation seems to have positive effect on crying behaviour and reducing the PIPP score, without proving the effects on objective criteria investigated in this study, further studies are needed for sucrose to recommend it in routine use in pain control during ROP examination.

## Conflict of Interest

None

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