

# Efficacy of 25% Glucose in Pain Alleviation During Retinopathy of Prematurity (ROP) Screening: A Randomized Controlled Trial

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**Abstract-** Retinopathy of prematurity (ROP) remains a painful examination, despite the common application of local anesthetic eye drops. This study aimed at examining the analgesic effects of 25% glucose in a premature infant pain profile (PIPP) in the first eye examination of infants with ROP. This three-group, randomized clinical trial was conducted from March to February 2017. One oral dose of 25% glucose solution (1 cc/kg) was administered one minute before the first examination of ROP. Mydriatic and anesthetic eye drops were locally instilled in the eyes before the examination for each group. Then, comparisons were made with the control group, which did not receive oral glucose (B), as well as the group which received 1 ml/kg of distilled water (C). The main investigator, who was blinded to the groups, evaluated pain using PIPP at one minute before, during, and one and five minutes after the procedure (ethics code: IR.TUMS.MEDICINE.REC.1396.3130). The baseline characteristics were comparable between the groups. During the procedure, the group receiving oral 20% glucose showed significantly lower PIPP scores ( $13.8 \pm 1.39$ ) compared to the other groups (group B:  $15.95 \pm 1.27$  and group C:  $15.10 \pm 1.19$ ) ( $P=0.001$ ). The positive effects persisted for five minutes in this group after the procedure ( $7.6 \pm 1.26$ ), compared to the other groups ( $P=0.034$ ). During and after ROP screening, oral 25% glucose in combination with local anesthetic eye drops can cause a significant reduction in pain.

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**Keywords:** Premature; Retinopathy of prematurity; Pain measurement; Oral 25% glucose; Premature infant pain profile (PIPP) scale

## Introduction

In preterm infants, recurrent painful events may change pain tolerance, perception, and threshold in subsequent exposure to painful events, with possible unfavorable effects on the neurodevelopmental process (1,2).

In retinopathy of prematurity (ROP), the ophthalmologic examination is considered an excruciating procedure, requiring frequent assessments until completely vascularizing the entire retina. According to recent protocols, the use of local anesthetic eye drops before eye examinations, besides the use of non-pharmacological analgesic techniques during ROP screening, is recommended (3-5).

Despite these effective measures, evidence shows that newborns still experience moderate pain (6). Different concentrations of glucose and sucrose for pain

management have been previously studied during eye examinations (7-9). However, evidence on their use is inconclusive.

No non-pharmacological protocols as national guidelines were available for pain management during ROP screening during the present study. Also, due to the inaccessibility of sucrose, we determined the analgesic effects of 25% glucose on pain relief in the first ROP examination in newborns with gestational age (GA)  $\leq 32$  weeks.

## Material and Methods

This three-group, prospective, randomized clinical trial was conducted from March 2017 to February 2017 in the NICU of a level-III hospital. We aimed to study the efficacy of 25% glucose in pain management during ROP examination. The Ethics Committee of Tehran University

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of Iran approved this study (IR.TUMS.MEDICINE.REC.1396.3130).

The inclusion criteria were as follows: 1) preterm infants (GA  $\leq$ 32 weeks), and 2) the first ROP examination in this clinical trial. On the other hand, the exclusion criteria were: 1) preterm infants on opioid analgesics or anticonvulsants; 2) contraindications to oral feeding; 3) need for mechanical ventilation support during the procedure; and 4) congenital disorders. During the first ROP examination, the subjects were randomly divided into three groups: group 1 (oral 25% glucose solution), group 2 (control group), and group 3 (distilled water). Pupil dilation was initiated 60 minutes before the procedure. Tropicamide 0.5%, as well as phenylephrine HCl 2.5%, was injected at five- to ten-minute intervals (three times) in order to induce pupil dilation.

The infants' facial expressions change as pain develops in ROP examination. Their facial expressions were captured on a video camera by the research nurse (blinded to grouping) at the following intervals: one minute before the examination, during the examination, and one minute and five minutes after the examination. Moreover, the same nurse evaluated the physiological variables (e.g., oxygen saturation and heart rate) on the monitor. These changes were evaluated using PIPP (The Premature Infant Pain Profile) and rated as follows: mild, moderate, and severe (<6, 6-12, >12, respectively). The validity and reliability of PIPP have been confirmed in Iran.<sup>10</sup> PIPP score is considered the most reliable and valid tool for pain assessment of premature infants during procedures. This tool assesses the variation of vital signs (highest heart rate and lowest O<sub>2</sub> saturation) and behavior state, and three facial actions (brow bulge, eye squeeze, and nasolabial furrow).

For each group, after administering 1 ml/kg of distilled water or oral 25% glucose into the injector, the research nurse sealed it with foil before handing it to the nurse responsible for ROP examinations. The nonpharmacologic solution was orally administered by the assisting nurse in the injector one minute before ROP examination and immediately after PIPP assessment.

### Statistical analysis

Chi-square test, as well as one-way ANOVA, was used to determine the homogeneity of demographic variables in the groups. Differences between the groups were also studied using repeated-measures ANOVA before and after the eye examination. The significance level was set at 0.05, and SPSS v. 15 (SPSS Inc., USA) was used for all statistical analyses.

### Results

A total of 60 VLBW infants were divided into the intervention and control groups (20 newborns per group). The eligible VLBW newborns had similar demographic characteristics in the groups (Table 1).

According to the results of Scheffe's post hoc test, the group receiving oral glucose during the procedure had significantly lower PIPP scores; this difference continued even for five minutes after the procedure (Table 2).

However, the groups were not significantly different regarding the PIPP scores at other intervals. The ANOVA test also showed a significant difference regarding the mean score of pain at the recorded intervals between the groups.

**Table 1. The clinical and demographic characteristics of the three groups**

Variant	Oral glucose (A)	Control group (B)	Distilled water (C)	P
Gestational Age	28.9±2.5	29.1±1.99	29.20±2.14	0.951
Weight	1170.9±291.3	1223.5±267.8	1111.0±239.92	0.553
Apgar min 1	3.3±2.2	4.15±1.72	4.00±1.76	0.497
Apgar min 5	6.8±1.22	6.90±1.16	7.00±0.81	0.992
Sex	Female	4(40)	9(55)	5(50)
	Male	6(60)	11(45)	5(50)
Delivery Method	Vaginal	2(20)	4(20)	2(20)
	cesarean	8(80)	16(80)	8(80)

**Table 2. Comparison of Mean Pain Scores by Time and Intervention Group during the Retinopathy of Prematurity Examination**

Variant	Oral glucose(A)	Control group(B)	Distilled water(C)	P
Pain 1 minute before the examination	8.10±0.99	8.05±1.09	7.80±1.39	0.815
Pain During Examination	13.8±1.39	15.95±1.27	15.10±1.19	0.001
Pain 1 minute after examination	8.20±1.68	9.35±1.26	8.20±1.68	0.099
Pain 5 minutes after the examination	7.60±1.26	8.55±0.88	7/60±1.26	0.034

## Discussion

In preterm infants with ROP, the ophthalmologic examination can be a painful procedure, causing stress, besides psychological and physical distress (3,6). Despite the application of local anesthetic eye drops, it still remains a painful examination (3). The use of proparacaine for ROP screening is suggested for pain relief. In recent research, non-pharmacological pain relief methods during ROP screening, such as non-nutritive sucking, swaddling (11), and use of dextrose (8), sucrose (9), and breast milk (12), have been suggested. In this regard, Samra (6) and Sun (13) evaluated the pain-relieving effects of oral sucrose in ROP screening.

The majority of previous studies have examined the effects of 24% sucrose solution, whereas, in another study, 33% sucrose was assessed (14). Findings have been contradictory in terms of the administered volume, administration time, and the number of doses. The majority of previous studies have shown that pain decreases during ROP examination (15). On the other hand, in several studies, the significant pain relief impact of sucrose or oral glucose was not confirmed (3,6,16).

This study evaluated the analgesic effects of 25% glucose in preterm infants, using a PIPP scale in the first eye examination for ROP. The groups were not significantly different regarding the demographic characteristics. Comparison of the pain scores showed that the scores of group A (oral 25% glucose) significantly decreased during and after examinations, compared to the other groups. Although oral glucose has an established pain-relieving effect among infants, the underlying mechanism of this effect is not known yet (17). Indirect endogenous opioid or dopamine release has been speculated to be the mechanism of action (18).

The ROP-associated pain is attributed to the speculum insertion causing deep pain (high PIPP score). Therefore, proparacaine might not be able to relieve this pain (6). However, oral 25% dextrose could relieve the pain of heel lance and venipuncture, which can cause moderate pain (19); consequently, 25% dextrose could not reduce pain in ROP screening (PIPP score >12). In our study, it seems that oral use of 25% glucose in combination with local anesthetic eye drops can reduce pain significantly during and after ROP examination.

Dolgun *et al.*, in their study, examined the effects of infant swaddling, besides sucrose and breast milk, on pain perception during ROP examination. The mean pain scores of the control group were higher than those of the sucrose and breast milk groups after the ROP

examination; however, the difference was insignificant. (20) This finding maybe because of the lower volume of solution or breast milk used in their study.

In the present study, one drop of oxybuprocaine 0.4% (local analgesic) was immediately administered before ROP examination as pain management. It seems that routine use of oral glucose and perhaps increased dose and concentration of glucose or continuous administration of a pacifier in combination with local analgesic drops may decrease pain severity during ROP examinations.

Oral 25% glucose in combination with locally anesthetic eye drops could significantly decrease pain during and after ROP screening. It is recommended to use oral 25% glucose for this purpose.

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