Original Article

Efficacy of Oral Dextrose versus Acetaminophen versus Placebo on Pain Relief during Retinopathy of Prematurity Eye Examinations: A Randomized, Double-Blind Controlled Clinical Trial

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Abstract

Purpose: To assess the effect of oral dextrose versus acetaminophen versus placebo in pain relief in retinopathy of prematurity (ROP) examination.

Methods: In this prospective randomized, double-blind controlled clinical trial study performed in the ophthalmology clinic of Shafa Hospital (referral hospital for eye disease), Kerman, Iran, 105 premature neonates with birth weight ≤2000 g and gestational age between 28 and 34 weeks were studied. Pain score measurement with Premature Infant Pain Profile-Revised (PIPP-R) during ROP examination in three intervention groups, acetaminophen group (15 mg/kg oral acetaminophen), dextrose group (one cc of oral dextrose 50%), and placebo group (one cc of distilled water), was done.

Results: Out of 105 infants, 33 infants received acetaminophen drops, 35 infants received dextrose drops, and 37 infants received placebo. The mean pain score of the group receiving acetaminophen was 11.39, dextrose 12.17, and placebo 11.54. The acetaminophen group had a lower average PIPP-R score. This difference was not significant between the three groups ($P = 0.38$).

Conclusions: Acetaminophen and dextrose in comparison with distilled water did not show a significant difference in reducing neonatal pain during ROP examinations. However, the PIPP-R score in the acetaminophen group was lower compared to the other groups.

Keywords: Acetaminophen, Dextrose, Infant, Retinopathy of prematurity

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Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder caused by incomplete retinal vascularization.[1,2] Low gestational age (GA) and birth weight (BW) are important risk factors for ROP among preterm neonates.[3] The rising trend of preterm births can lead to ROP and preventable childhood blindness globally.[1,4] The sequela of ROP can be prevented with appropriate screening and early diagnosis.[5] Various screening criteria are based on GA, BW, and postnatal age (PNA).[6] ROP screening is a painful and uncomfortable procedure and can have detrimental effects such as bradycardia on newborns, highlighting the importance of pain control in these vulnerable babies.[7] This painful procedure can result from eyelid speculum

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or scleral indentation. Infants cannot report pain as adults do, so their physiological behavioral expressions are observable manifestations, examples being heart rate (HR) and facial changes, respectively.[8,9]

There are some pharmacological and nonpharmacological alternatives to overcome this issue. Restricting infants' movements, providing maternal milk, a calm environment, sucrose, and glucose with or without nonnutritive sucking can be considered nonpharmacological approaches.[10] The age of infants at the time of the examination may influence some nonpharmacological approaches.[8] On the other hand, opiates, benzodiazepines, ketamine, local and topical anesthetics, along with acetaminophen, and dextrose are pharmacological options.[8,11]

To manage pain during ophthalmic examination for ROP screening and management, many studies have been conducted. As an illustration, there is evidence suggesting that topical anesthetic agents can be beneficial in reducing pain at the time of examination.[12] A systematic review concluded that sucrose effectively reduced pain during this type of eye examination.[13] There are some studies on the analgesic effect of dextrose during eye examination of premature babies. Kataria *et al*. found that oral dextrose does not have a prominent effect in pain alleviation of preterm neonates and suggested more studies with multiple doses along with other interventions.[2] While there are many studies about approaches to reduce preterm infants' pain during an eye examination, acetaminophen is the most common agent for managing mild-to-moderate pain.[14] According to some studies, a low dose of acetaminophen has neuroprotective effects.[14,15]

As the need for ROP screening is increasing, finding a good analgesic agent to reduce pain is necessary. In addition to ROP screening, neonates may need other invasive, painful procedures until they heal, gain weight, or are discharged from the hospital.[16] Because of inconsistent findings of the effectiveness of acetaminophen and dextrose in the current literature, we chose to perform a controlled study to investigate the efficacy of oral dextrose and acetaminophen in pain reduction during the first eye examination for ROP screening in preterm infants.

Methods

This study is a prospective double-blinded randomized controlled trial at Shafa Medical Education Center (The only referral center in Kerman for ROP examination) in 2020. Inclusion criteria for screening premature neonates were (1) BW ≤2000 g and (2) GA between 28 and 34 weeks as was protocol in the national program.

Exclusion criteria included any routine use of sedative medications, congenital anomalies, and neurological disorders. Informed consent was obtained from parents or guardians for participation in this research. All raw data were anonymously obtained from the ROP clinic of Shafa Hospital Medical Education center, and it was used for research purposes only.

The Ethics Research Committee of Kerman University of Medical Sciences approved this study with ID number IR.KMU.REC.1399.262 and the Iranian Registry of Clinical Trials approved this study with ID number IRCT20210710051836N1. It was compliant with the principles of the Declaration of Helsinki. Enrolled patients were divided into three groups based on their age: 28–30 weeks, 30–32 weeks, and 32–34 weeks. Furthermore, they were distributed equally but randomly in three groups of either acetaminophen, dextrose 50%, or control groups. In the acetaminophen group, patients received 15 mg/kg of oral acetaminophen; in the dextrose group, 1 cc of 50% dextrose was given. The control group was given one cc of distilled water (placebo) by mouth using a syringe. The screening was performed on Sundays from July 2020 to December 2020 by the same researchers. The infants were placed on the examination bed in the supine position, and they were swaddled, and parents were allowed to be in the examination room. The examiners did not use topical anesthesia to avoid bias in the study. The eye speculums were inserted. The examination sequence commenced with the right eye and subsequently proceeded immediately to the left eye. The average duration of each examination ranged from 75 to 80 s in all subgroups. Pain assessment was conducted during the examination of both eyes. Some unique loops were used for indentation. The examination was conducted using Heine indirect ophthalmoscopy along with the VOLK pan retinal 20 D lens. The researchers and parents were unaware of the order of blocks and infants who would receive acetaminophen, dextrose, or placebo. This blinding was done by a trained nurse. Before the start of the examination, another nurse administered acetaminophen (60 min prior), placebo, and dextrose (2 min prior) for neonates randomly. To score pain, the Premature Infant Pain Profile-Revised (PIPP-R), which is a standard and multi-dimensional tool for behavioral, physiological (HR and oxygen saturation [SpO2]), and contextual (GA and baseline behavioral state [BBS]) indicators, was used. This tool is also helpful for short-term procedures such as ROP screening. In our research, we utilized the PIPP-R table and scoring instructions by Stevens *et al*., which can be found in Table 1.[17] Each item of PIPP-R has four scales (0, 1, 2, and 3), and a total score is obtained based on the sum of seven PIPP-R items to indicate pain intensity. The maximum total score is 21 for preterm infants. Before starting the examination, HR, SpO2, GA, and BBS were determined. Behavioral items are categorized into three facial actions: brow bulge, eye squeeze, and nasolabial furrow. These behavioral items were scored [Table 1] based on the duration of these facial actions in seconds. One of the researchers measured and documented all these items (HR, SpO2, GA, and BBS) before speculum insertion for baseline and then 30 s after speculum removal. The reason why GA and behavioral state are evaluated using the PIPP-R scoring system after the procedure involving speculum placement in the eyes is that it triggers changes of some infants in physiological and/or behavioral variables as a response to that painful stimulus. Demographic features (BW, GA and PNA, weight at the time of examination, gender, and type of delivery [TD]) were documented for each infant.

Descriptive and inferential statistics were used to analyze the data. The conclusions of analyzed demographic variables are provided in Table 2. *P value* (α) and test power (1-β) were 0.05 and 0.8, respectively. The infants were assigned to one of the three groups (acetaminophen, dextrose, and placebo) through block randomization by Random Allocation Software 2.0.

Results

A total of 140 infants underwent ROP screening during our study, 105 infants had the inclusion criteria, and their parents consented to be included.

Table 2 shows the details of the demographic variables. As Table 2 illustrates, there is no significant difference between the groups of study concerning gender, TD, and PNA.

Differences among dextrose oral solution, acetaminophen drop, and placebo group concerning reducing pain during retinopathy screening examination among premature neonates were not statistically significant [Table 3]. However, comparing mean scores between the three groups confirmed that the acetaminophen group showed a lower pain score. There were no statistically significant differences between the three groups (acetaminophen, dextrose, and placebo) [Figure 1].

Discussion

This study compared the effect of acetaminophen versus oral dextrose solution versus placebo on reducing the pain of retinopathy screening examinations among premature neonates. The results of this study illustrated that there were no significant differences in overall pain score among the three groups.

Some studies have suggested that acetaminophen with one of its metabolites can activate the cannabinoid system and help in its analgesic activity.[18]

In a clinical trial, Macke explored the effect of acetaminophen in reducing pain during circumcision and postprocedure. A total of 60 newly born neonates received 10 mg/kg acetaminophen or placebo 1 h before circumcision. The results showed that HR and crying time did not differ significantly between the two groups.[19] Badiee and Torcan showed that 50 mg/kg paracetamol usage for 90 min before heel prick had no effect on PIPP-R score among premature neonates.[20] Although acetaminophen can effectively reduce pain, in these two studies, similar to our study, acetaminophen did not affect pain alleviation. Unlike Badiee and Macke's studies, we examined the effects of acetaminophen and dextrose in reducing pain with bigger sample sizes.

Table 1: The Premature Infant Pain Profile: Revised

Infant indicator	Indicator score				Infant indicator score
	0	+1	+2	+3	
Change in HR (bpm) baseline	0–4	5–14	15–24	>24	
Decrease in oxygen saturation (%) baseline	0–2	3–5	6–8	>8	
Brow bulge (s)	None (<3)	Minimal (3–10)	Moderate (11–20)	Maximal (>20)	
Eye squeeze (s)	None (<3)	Minimal (3–10)	Moderate (11–20)	Maximal (>20)	
Nasolabial furrow (s)	None (<3)	Minimal (3–10)	Moderate (11–20)	Maximal (>20)	
Subtotal score*					
GA (weeks + days)	>36	32–35 weeks, 6 days	28–31 weeks, 6 days	<28 weeks	
Baseline behavioral state	Active and awake	Quite and awake	Active and sleep	Quiet and sleep	
Total score**					

*Subtotal for physiological and facial indicators. If subtotal score >0, add GA and behavioral state indicator scores, **Total score: Subtotal score + GA score + behavioral state score. Stage 1: To evaluate vital signs such as HR, oxygen saturation, and behavioral state in infants, it is recommended to observe them while they are at rest for a duration of 15 s, Stage 2: It is advisable to keep an eye on infants for 30 s after the procedure and examine any modifications in their vital signs, Stage 3: If the subtotal score is >0, then the score for corrected GA and behavioral state will be taken into account, Stage 4: Finally, to obtain the total score, we need to add the subtotal score to the behavioral state score. GA: Gestational age, HR: Heart rate

Table 2: The demographic characteristics

Variables	Group I (acetaminophen)	Group II (dextrose)	Group III (placebo)	*P*
GA (weeks), mean±SD	31.88±1.24	31.10±1.89	31.71±1.56	0.103
BW (g), mean±SD	1719.39±252.16	1565.71±278.56	1604.86±265.89	0.052
Gender, *n* (%)				
Male	19 (34.5)	19 (34.5)	17 (30.9)	0.6
Female	14 (28)	16 (32)	20 (40)	
TD, *n* (%)				
Cesarean	26 (31)	26 (31)	32 (38.1)	0.42
Vaginal birth	7 (33.3)	9 (42.9)	5 (23.8)	
PNA (days), mean±SD	32.39±2.86	32.83±3.97	32.38±3.18	0.82

GA: Gestational age, BW: Birth weight, TD: Type of delivery, PNA: Postnatal age, SD: Standard deviation

Table 3: Comparing the level of pain across the three groups

	Group	*n*	Mean of pain score	*P*
Total PIPP-R	Acetaminophen	33	11.394	0.386
	Dextrose	35	12.171	
	Placebo	37	11.541	
	Total	105		

PIPP-R: Premature Infant Pain Profile-Revised

Limited studies have been performed on the role of paracetamol in pain mitigation during ophthalmic examination for ROP. In a randomized clinical trial study by Seifi *et al*. on 120 premature neonates hospitalized in a NICU, the babies were assigned to three groups. Group A received 15 mg/kg of oral acetaminophen 30 min before the eye examination, plus 0.2 mL of sterilized water. Group B was given 0.2 mL sucrose 25%, and Group C 0.2 mL sterilized water through an oral route using a syringe at the time of examination. The pain score was determined using the PIPP-R scoring system during the first 45 s and the last 45 s of the eye examination. There was no significant difference between the two groups regarding pregnancy age, BW, and age at the time of examination. The results of their study showed that the usage of sucrose was effective in pain mitigation among neonates who underwent ROP examination at the beginning of the eye examination (but not in the last seconds of examination). They found that patients who received sucrose had a significantly lower PIPP-R score than patients who received acetaminophen or sterilized water.[21] The study had the most remarkable similarity to ours in terms of methodology, and its results were also in line with ours. However, our study used pure acetaminophen and dextrose, and acetaminophen was given 60 min before the examination. It could be postulated that the pain intensity resulting from the retina examination of neonates is so severe that acetaminophen does not affect its mitigation. Despite acetaminophen ineffectiveness in examined studies, only one study by Kabataş *et al*. showed a single dose of oral paracetamol effect on pain mitigation during retinopathy examination of premature neonates in 2016. In that study, 114 neonates were included for retinopathy screening of premature neonates and underwent an eye examination. Before the examination, local anesthesia (0.5% proparacaine drop) was used for all neonates. In the intervention group (group 1, $n = 58$), 15 mg/kg of neonatal body weight oral paracetamol was administered 60 min before the examination. In the control group (group 2, $n = 56$), 15 mg/kg of neonatal body weight sterilized water was poured into the infants' mouths through an opaque syringe. The findings showed that the PIPP-R score was significantly lower in the intervention (acetaminophen) group after placing the speculum.[14] The results of that study did not concur with ours. Although the acetaminophen dose was similar to our study, the effect of acetaminophen is not fully clear.

There is a neonatal infant pain scale (NIPS) to evaluate pain based on six behavioral indicators. One of the benefits of NIPS is its easy use without additional equipment.[22]

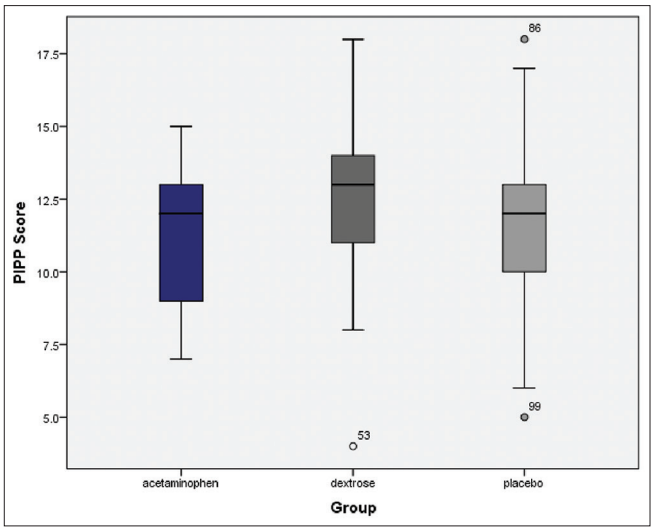

Figure 1: Total of Premature Infant Pain Profile-Revised scores between the groups. PIPP-R: Premature Infant Pain Profile-Revised

In some studies, the efficacy of tetracaine in releasing pain during some painful procedures, including laser and photorefractive keratectomy therapy, is confirmed;[23] in this study, we did not use tetracaine drop to avoid bias. Finally, in future studies, we can use the NIPS tool and tetracaine instead of PIPP-R and dextrose or acetaminophen to examine releasing pain in ROP eye examination.

This study presents several limitations. First, a larger number of neonates within each subgroup would enhance the precision of our conclusions. In addition, the limitation regarding the number of observers who assessed pain is noteworthy. The PIPP-R is a multidimensional pain assessment tool that includes physiological, behavioral, and contextual indicators of pain. Behavioral indicators are particularly vulnerable to observer bias, as they can be subjective and difficult to interpret. When a single observer assesses pain using the PIPP-R, there is a risk that their own biases may influence their interpretation of the behavioral indicators. To mitigate the potential for observer bias when using the PIPP-R, it is necessary to use multiple observers to assess pain and quantify inter- and intraobserver variability. This can help to identify any systematic biases in the scoring. In our study, we were unable to use multiple observers to assess pain due to resource constraints. However, we acknowledge that this is a limitation of our study, and we plan to address this in future research.

In conclusion, our prospective randomized controlled trial revealed that the effects of acetaminophen and dextrose to reduce neonatal pain do not differ from distilled water; however, the acetaminophen group had a lower PIPP-R score. These results provide essential clinical information for the care of premature neonates that require ophthalmic care.

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Conflicts of interest

There are no conflicts of interest.

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