

Comparing the Efficacy of Oral Sucrose and Acetaminophen in Pain Relief for Ophthalmologic Screening of Retinopathy of Prematurity

Fatemeh Seifi¹, Ali Peirovifar², Manizheh Mostafa Gharehbaghi^{3,*}

¹Department of pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran

²Department of Anesthesiology, Tabriz University of Medical Sciences, Tabriz, Iran

³Pediatric Health Research Center, Department of pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran

*Corresponding author: gharehbaghimm@yahoo.com

Received March 12, 2013; Revised April 09, 2013; Accepted April 11, 2013

Abstract Retinopathy of prematurity (ROP) is a potential cause for visual impairment in preterm newborn infants with gestation age 32 weeks or less and birth weight less than 1500 gram. There are several studies that reported physiologic and behavioral responses to painful and stressing screening examination. This study was conducted to compare the efficacy of sucrose and acetaminophen in pain control during eye examination in premature infants. A prospective randomized clinical trial was carried out in a tertiary level NICU. One hundred twenty preterm infants were randomly allocated in to 3 groups. Group A received oral acetaminophen 15mg/kg 30 minutes before eye examination and 0.2ml sterile water, given by mouth using a syringe, during examination; group B 0.2ml sucrose 25% and group C 0.2ml sterile water given by mouth using a syringe during examination. Ophthalmologic examinations were recorded by videotape. Pain score was determined by using PIPP during first 45 seconds and at last 45 seconds of eye examination. There was no significant difference between groups regarding gestation age, birth weight and age at examination. The mean PIPP score at first 45 sec were 12.9 ± 2.4 , 9 ± 2.1 and 13.7 ± 1.6 for groups A, B, and C respectively ($p < 0.001$). It was 12.3 ± 2.4 , 11.2 ± 3 and 12.1 ± 2.6 at last 45 sec of examination in groups A, B, and C respectively $P = 0.12$. Two patients had apnea during first 12 hours after examination and both of them were in group C. In our study, using sucrose was associated with reduced pain score in neonates undergoing screening for ROP at beginning of eye examination but not at the last seconds of examination.

Keywords: retinopathy of prematurity, pain, preterm neonates, PIPP

1. Introduction

Retinopathy of prematurity (ROP) is a potential cause for visual impairment in preterm newborn infants with gestation age 32 weeks or less and birth weight less than 1500g. Early detection and treatment of developing ROP have been shown to be effective in prevention of blindness [1]. Screening of ROP with a serial indirect ophthalmologic examination until the infant became low risk for this disease is essential. There are several studies that reported physiologic and behavioral responses or adverse reactions to painful stressing screening examination [2-7]. Repeated exposure to pain in preterm infants may have long term consequences on the neurological and behavioral development [8,9]. Pain assessment is basic for its management [10]. Inability of neonates to verbalization makes this pain assessment and management subjective. Pain assessment is usually based on physiologic and behavioral factors. There are several validated and reliable pain scoring systems [11]. The premature infant pain profile (PIPP) is a behavioral measure of pain for premature infants that developed at the Toronto and McGill universities in Canada [12].

Several strategies, including pharmacologic and non pharmacologic methods, have been used for prevention of pain during procedures. Sucrose is one of the most commonly used non-pharmacologic interventions for pain control in infants [13,14,15]. Analgesic effect of sucrose is thought to be mediated by stimulation lingual sweet taste receptors and release of endogenous opioids. Paracetamol (N-acetyl-P-aminophenol) is an antipyretic and analgesic agent that is less potent than opioids with fewer side effects. It acts by inhibiting the cyclooxygenase (COX) enzymes in the brain and it is useful for mild to moderate pain in infants and neonates which can administered by oral, rectal or intravenous route [16,17]. The absorption half life for oral elixir preparation is 0.21 h with a lag time of 0.42 h that is further delayed in premature neonates (2h) in first few days of life [18].

Since there is not a universal strategy for pain reduction during eye examinations, this study was conducted to compare the efficacy of oral sucrose and acetaminophen for pain reduction in ROP screening eye examinations.

2. Materials and Methods

A randomized controlled clinical trial was carried out in a tertiary level neonatal intensive care unit (Al Zahra Hospital, Tabriz, Iran) from October 2011 to October 2012. One hundred twenty two preterm infants, gestational age less than 32 weeks, were enrolled in this study. Ethic committee of Tabriz University of Medical Sciences approved the study. Written informed consent was obtained from the parents. Infants receiving mechanical ventilation at time of ROP screening or receiving sedatives or narcotics, infants with severe birth asphyxia (APGAR score ≤ 3 at 5 minutes) and neonates with major congenital anomalies were excluded from this study. Neonates were allocated in three groups with a computer based randomization process according to their ophthalmologic examination sequence and by sealed opaque envelopes. Infants were enrolled only once in this study. Mydriatics used before eye examination were homatropine 2% and phenylephrine 2.5% one drop in each eye and repeated 5 minute later. Infants received topical tetracain 1% just prior to eye examination. Eye examinations were carried out following adequate pupillary dilatation (30 minutes after mydriatic drops) by same experienced ophthalmologist. Acetaminophen was administered to infants in group A orally 15mg/kg 30 minutes before examination and 0.2ml sterile water during initiation of eye examination to achieve blindness at assessing. Patients in group B received 0.2ml sucrose 24% solution by mouth using a syringe during the initiation of eye examination. Sterile water 0.2ml was given as placebo to neonates in group C. No pacifier was used and oral drugs were given by mouth using a syringe in all studied neonates. ROP screening examinations were recorded by videotape. Physiologic parameters including heart rate, respiratory rate and base line SpO₂ were determined in all patients prior to eye examination and during examination and every 5 minutes until 20 minutes after examination using pulse oxymeter and a nurse who was blind to the study groups. Two neonatologists experienced in the use of PIPP scoring and blind to the intervention groups determined pain score by 30-sec observation of neonates' responses in videotape at starting eye examination and during last 45 seconds of eye examination. Data were analyzed using the Statistical Package for Social Science Software (SPSS) version 16.0. Variables were expressed in percentages and mean \pm standard deviation. Data were analyzed with Chi-square test and one way analysis of variance (ANOVA). The difference was considered significant for *p. value* less than 0.05.

3. Results

One hundred twenty two infants who underwent ROP screening eye examination were included in this study. One neonate in group C and one infant in group B were excluded because of impaired video tape recording and covering of neonates' face with examiner's hand that makes pain assessing impossible. Sixty four infants (53%) were male. The mean gestation age of studied infants was 27.6 \pm 2 weeks and their birth weight was 986 \pm 249 gr. APGAR score at 1 minute and 5 minute were 5.3 \pm 2 and 7.4 \pm 1.6 respectively. The mean age of neonates at study was 39 \pm 11.7 days and their weight was 1238 \pm 316 gr. There was no significant difference between groups

regarding gestation age, birth weight and age at examination (Table 1).

There was history of assisted ventilation in 20 (48.8%), 16 (40%) and 11 (28.2%) of patients in groups A, B and C respectively ($p=0.22$). Surfactant replacement therapy was done in 29 (70.7%), 26 (65%) and 25 (64.1%) neonates in groups A, B and C respectively $p=0.91$. The mean PIPP scores in three groups are showed in Table 2. The duration of examination was 2-3 minutes in all neonates. Two patients had apnea during first 12 hours after examination and both of them were in group C.

Table 1. Characteristics of neonates in 3 groups

	Group A (n=41)	Group B (n=40)	Group C (n=39)	P value
Gender, male n(%)	21(51.2)	21(52.5)	22(56.4)	0.89
Labor, C/S, n (%)	13(31.7)	13(32.5)	20(51.3)	0.12
Birth weight, gr*	921.5 \pm 220.6	1028.5 \pm 258.1	1013.7 \pm 260.5	0.11
Gestation age, wk*	27.4 \pm 1.9	27.9 \pm 1.9	27.4 \pm 2.2	0.53
Apgar score				
1 minute*	5.2 \pm 2.4	5.3 \pm 2.2	5.5 \pm 2.2	0.84
5 minute*	7.3 \pm 1.7	7.3 \pm 1.6	7.6 \pm 1.4	0.70
Antenatal corticosteroid, n(%)				
2 doses	21(51.2)	20(50)	15(38.5)	0.59
One dose	15(36.6)	14(35)	20(51.3)	
no	5(12.1)	6(15)	4(10.2)	

Note: Group A: Acetaminophen 15mg/kg

Group B: Sucrose 0.2ml

Group C: sterile water 0.2ml

* Mean \pm Standard Deviation

C/S: Cesarean section

Table 2. Pain assessment in studied groups

	Group A (n=41)	Group B (n=40)	Group C (n=39)	P. Value
PIPP ₁ score	12.9 \pm 2.4	9 \pm 2.1	13.7 \pm 1.6	<0.001
PIPP ₂ score	12.3 \pm 2.4	11.2 \pm 3	12.1 \pm 2.6	0.12
Number of eye examination				
First	23(56.1)	21(52.5)	26(66.6)	0.45
Second	18(43.9)	19(47.5)	13(33.3)	

PIPP1 PIPP score in first 45 seconds of examination

PIPP2 PIPP score in last 45 seconds of examination

4. Discussion

Patients that received sucrose had significantly lower PIPP score compared with acetaminophen or sterile water treated groups at the beginning of eye examination but not at its termination. These findings indicate that sucrose does not abolish pain responses during ROP examination in preterm infants. There are several studies comparing different doses and routes of sucrose administration with sterile water. Sullivan and coworkers [19] assessed sucrose and sterile water combined with non nutritive sucking and swaddling in total 40 infants undergoing primary eye examination. They used neonatal pain agitation and sedation scores (N-PASS) and found fewer infants with episodes of desaturation or bradycardia in sucrose group. They concluded that pain scores remained consistently high and appropriate pain relief for ROP remains a challenge. Gal studied 23 infants and showed short term reduced pain score in sucrose group immediately after examination [20]. The optimal dose of sucrose in pain control is not determined. The reported doses differ from 0.05- 0.5ml of sucrose 24% (0.012-

0.12g) to 2ml (0.48g) sucrose. In a study of 32 infant, efficacy of sucrose was compared with sterile water. Both groups demonstrated significant pain score (14 ± 3) in response to eye examination during insertion of a lid speculum and depression of the sclera [21]. Their studied infants don't benefit from high dose (0.48g) sucrose. They used the solution 2 minutes prior onset of eye examination but we used sucrose simultaneously with eye examination. PIPP score in our study is very close to Mitchell results that used local anesthetic eye drops as part of the routine eye examination procedure and three doses of sucrose 24% at 2 minutes intervals before and during eye examination [22]. A recent Cochrane review showed that single doses of oral sucrose reduce crying, facial grimacing and motor activity in term and preterm infants during minor painful procedures [23]. The effects of repeated doses of sucrose have examined in a few studies [24,25,26,27]. In one study, preterm infants with greater exposure to sucrose (>10doses in 24 hours) had poorer motor and attention development at ages 36 and 40 weeks [24]. A very low incidence of short term adverse events including hyperglycemia, oral infections, necrotizing enterocolitis, intra-ventricular hemorrhage and death reported [24,25,26,27]. In agreement with previous studies [28], the pain score was not reduced in patients treated with acetaminophen. Acetaminophen is useful for mild to moderate pain and is not helpful for painful eye examination. We have not any superiority of this pharmacologic pain control over non pharmacologic methods and acetaminophen use is not recommended routinely before eye examination.

5. Conclusion

In our study, using sucrose was associated with reduced pain score in neonates undergoing screening for ROP at beginning of eye examination but not at the last seconds of examination.

This result demonstrates that sucrose is relatively effective for reducing pain during eye examination that is believed to be more painful than heel sticks. It is suggested that repeated doses or higher volume of sucrose may be more effective than single dose. We have not used repeated doses of sucrose and pain score was higher at the termination of eye examination. It is recommended future studies with large number of patients and using higher volume of sucrose or repeated doses during eye examination to determine the optimum dose of sucrose for pain control during this painful procedure.

Acknowledgments

The authors would like to thank research vice chancellor of Tabriz University of Medical Sciences and children's Health Research Centre for providing the funding for the study. We thank Dr Eftekhari Milani AA, Mrs Sabuhi R, Mrs Nikzad H and Mrs Karamooz M for their assistance in research performance. We also gratefully acknowledge the work done by the staff at the neonatal intensive care unit and neonatal unit, Al-Zahra hospital, Tabriz, Iran.

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