Original Article

Comparison of the Effectiveness of Pharmacological and Non-Pharmacological Methods in Reducing the Pain of Retinopathy of Prematurity Examination

Maryam Khoshnoud Shariati[1], Afsar Dastanjani Farahani[2], Naeemeh Taslimi Taleghani[1], Farzaneh Palizban[1], Ali Naseh[1], Marzieh Maddah[1], Mahmoud Hajipour[3], Hamed Razi[4*]

[1]Clinical Research Development Center, Mahdiyeh Educational Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Adjunct Prof in Community Ophthalmology Research Center, National ROP Center of Excellence, Farabi Eye Hospital, Tehran, Iran
[3]Pediatric Gastroenterology, Hepatology and Nutrition Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Resident of Pediatrics, Mofid Children's Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: 19 February, 2024; Accepted: 13 March, 2024

DOI: 10.22037/nbm.v12i3.44696

Abstract

Background: Retinopathy of prematurity (ROP) is one of the common complications in premature neonates. ROP examination is one of the most important examinations for premature babies, which is associated with pain and can be very annoying. This study aimed to compare the effectiveness of pharmacological and non-pharmacological methods in reducing the pain of ROP examination.

Materials and Methods: This study was conducted as a double-blind, randomized control trial on 300 ROP examinations of patients who were hospitalized in the NICU department of Mahdieh Hospital in Tehran. The neonates were randomly selected into three groups, and ketamine 2mg/kg nasally, fentanyl two µg/kg nasally10minutes before an examination, and acetaminophen 2drop/kg orally 30 minutes before each examination were given to each neonate as two pharmacological groups. In the non-pharmacological group, infants received saddling-pacifier oral sucrose 25% 0.5cc 2 minutes before examination. Pain was assessed based on PIPP (premature infant pain index).

Results: The amount of pain after using oral sucrose was significantly lower than the ketamine-acetaminophen (P-value=0.011) and fentanyl-acetaminophen (P-value=0.027) groups, but there was not a statistically significant difference between the two groups of ketamine-acetaminophen and fentanyl-acetaminophen (P-value=0.953). The hypoxia was more prevalent in the ketamine-acetaminophen group (18.8%), and the least hypoxia occurred in the oral sucrose treatment group (7%) (P-value=0.028).

Conclusion: It is concluded that the effect of non-pharmacological drugs is greater than pharmacological drugs in reducing the pain of neonates during ROP examination. The effect of oral sucrose in reducing pain was more significant than ketamine-acetaminophen and fentanyl-acetaminophen. However, there was no significant difference between the two groups of ketamine-acetaminophen and fentanyl-acetaminophen.

Keywords: Acetaminophen, Prematurity, Retinopathy, Sucrose

***Corresponding Author:** Hamed Razi, Mofid Children's Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: +989212102967. Email: razihamed50@gmail.com, Orcid: 0001-9653-3327

Please cite this article as: Khoshnoud Shariati M, Dastanjani Farahani A, Taslimi Taleghani N, Palizban F, Naseh A, Maddah M, et al.

Comparison of the Effectiveness of Pharmacological and Non-Pharmacological Methods in Reducing the Pain of Retinopathy of Prematurity Examination. Novel Biomed. 2024;12(3):104-9.

Introduction

Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy that affects premature infants and is one of the leading causes of childhood blindness worldwide[1,2]. In 2010, about 184,700 of the 14.9 million premature babies were diagnosed with ROP, of whom 20,000 became blind or severely visually impaired[1,3].

In the United States, retinopathy of prematurity is the second most common cause of blindness in children after cerebral cortical blindness, and it is estimated that 14,000 to 16,000 babies suffer from different degrees of this disease every year, of which 1/100 to 1/500 need treatment and 400 to 600 babies become blind [4]. The incidence of ROP in Iran has been reported from 5.6% to 42%[5,6].

On average, each infant requires a series of examinations, which means that several hundred thousand ROP screening tests are needed annually [7]. Because the late diagnosis of the disease will lead to reduced vision and loss of vision in one or both eyes, the importance of timely screening of newborns becomes more apparent[8].

One of the painful examinations that premature babies face is the eye examination for screening of ROP. Although ROP examinations are an essential screening in premature babies, these examinations are not without complications. The International Evidence-Based Pain Group considered ROP examinations in the list of painful examinations in the NICU that cause behavioral changes[9]. These aggressive examinations may lead to short-term and long-term complications for these babies, such as adverse effects on the development of the central nervous system, emotional problems, attention disorders, hyperactivity, and defects in social skills[10].

One of the pain relief methods to prevent behavioral changes during eye examination is the use of pharmacological and non-pharmacological methods. Due to the unknown pharmacokinetic and pharmacodynamic effects of drugs in infants, it is challenging to use pharmacological methods in infants. Also, nowadays, many non-pharmacological techniques are available to relieve and control pain or behavioral changes[11,12]. Various interventions have been performed to reduce this pain response, but they have not been very effective[13,14]. So far, there have been various studies on the effect of pharmacological (such as ibuprofen) and non-pharmacological (such as breast milk) methods in reducing pain in infants during ROP examinations. However, the results of the studies are contradictory[15-17]. The purpose of this study was to investigate and compare the effectiveness of pharmacological and non-pharmacological methods in reducing the pain of ROP examination.

Methods

This study has received the ethical code from the ethical committee of Shahid Beheshti Medical University (IR.SBMU.RETECH.REC.1401.037). This study was conducted as a double-blind, randomized control trial in 300 cases of ROP examination in the NICU department of Mahdieh Hospital in Tehran. Patients were selected between the premature and low birth weight newborns (before 34 weeks of gestational age and lower than 2 kilograms) who were born in the hospital from January 2022 to June 2022.

Based on random sampling and the difference between the behavioral status score (PIPP) based on the study by Zeraati et al.[18], 100 people were selected in each group. At first, the parents were given an informed consent form about the need for and method of treatment. After the acceptance of the condition of the study, the eye examination candidates were enrolled in the study. The inclusion criteria were that being hemodynamically stable, being alert, being able to tolerate oral 25% sucrose, and passing at least one hour from feeding. The examination was done before the next feeding time. The exclusion criteria were an addicted mother's baby, taking sedative medication before the examination, connecting to a ventilator, and hemodynamic instability.

Newborns were examined by a trained ophthalmologist with sufficient experience in the field of premature newborns to investigate clinical retinopathy of prematurity. Indirect Ophthalmoscopy was performed during these examinations. Accurate fundoscopy and

peripheral retinal examination, pupil dilatation, speculum, and depressor were performed. Half an hour before the examination, one drop of Tropicamide 1%, 0.5% phenylephrine eye drops, and tetracaine drops were instilled in the eye according to certain intervals. About 15 minutes before the examination, the babies were randomly selected, and ketamine 2mg/kg nasally, fentanyl 2 µg/kg nasally, and acetaminophen 2 drops/kg orally were given to each patient by a nurse. Before pouring the ketamine and fentanyl drugs, the noses were suctioned and cleaned by pouring a drop of normal saline, and the drops were poured 5 minutes later.

In the non-pharmacological group, infants received a saddling pacifier and oral sucrose 25% 0.5cc two minutes before the examination. During and after the examination, the vital signs were monitored until 24 hours later. Scaling based on PIPP (premature infant pain index) was done by someone other than the patient's nurse without knowing the implementation method. Patients were randomly assigned to treatment groups, and the nurse responsible for performing the PIPP form was blinded to the treatment group.

Statistical Analysis: The mean, standard deviation, median, range, frequency, and percentage were used to describe the data. Shapiro-Wilk test was used to check the normal hypothesis of the main variable (pain level) and then to compare the average pain of the patients between the three study groups. A one-way ANOVA statistical test was used. Fisher's exact and chi-square tests were also used to check the significance of the frequency of clinical symptoms between groups. All analyses were done using SPSS 26.0 statistical software. In these analyses, $P<0.05$ is considered statistically significant.

Results

In this study, the effects of three treatment methods, ketamine-acetaminophen, fentanyl-acetaminophen, and oral sucrose, were compared in 300 cases of ROP examination. Descriptive statistics of pain level (0 is the least pain and 18 is the most pain) can be seen in Table 1.

The amount of pain after using oral sucrose-saddling-pacifier groups was significantly lower than the ketamine-acetaminophen (P=0.011) and fentanyl-acetaminophen (P=0.027) groups. However, there was no statistically significant difference between the ketamine-acetaminophen and fentanyl-acetaminophen groups (P=0.953).

Table 1. Pain level based on the treatment group**.**

Treatment group	Number	SD ± Mean
ketamine-acetaminophen	101	7.14±3.59
fentanyl-acetaminophen	99	7.0±3.72
Oral sucrose	100	5.69±3.39
Total	300	6.61±3.62

In Table 2, the frequency of clinical symptoms in patients was analyzed according to the treatment groups.

In Table 3, blood pressure and heart rate drop were analyzed among the groups. No significant statistical difference was observed between the groups (based on the chi-square test, P-value>0.05).

Discussion

In the current study, 300 ROP examinations were compared in three treatment groups: ketamine-acetaminophen, fentanyl-acetaminophen, and oral sucrose saddling-pacifier. There was a statistically significant difference between the groups regarding pain reduction. It was seen that the amount of pain after using an oral sucrose saddling pacifier was significantly lower than the ketamine-acetaminophen and fentanyl-acetaminophen groups. However, there was no significant difference between the ketamine-acetaminophen and fentanyl-acetaminophen groups. Regarding symptoms during the examination, it was seen that none of the patients receiving fentanyl-acetaminophen had apnea; 7.9% of people in the ketamine-acetaminophen group and 2% of people in the oral sucrose group experienced apnea. The most group with the decreased oxygen saturation was the ketamine-acetaminophen group (18.8%), and the lowest group was the oral sucrose group, with a rate of 7%. There was no statistically significant difference in the blood pressure and heart rate between the three groups.

Bulut et al. evaluated the effectiveness of oral ibuprofen and oral paracetamol (acetaminophen) in reducing pain during

Table 2. Clinical symptoms of patients in treatment groups**.**

Clinical symptoms		ketamine-acetaminophen	fentanyl-acetaminophen	Oral sucrose	P value
Apnea	No	93 (92.1%)	99 (100.0%)	98 (98.0%)	0.005
	Yes	8 (7.9%)	0 (0.0%)	2 (2.0%)	
Hypoxia	No	82 (81.2%)	89 (89.9%)	93 (93.0%)	**0.02**
	Yes	19 (18.8%)	10 (10.1%)	7 (7.0%)	
Need to ventilation	No	70 (69.3%)	60 (60.6%)	59 (59.0%)	0.26
	Yes	31 (30.7%)	39 (39.4%)	41 (41.0%)	
Chest tightness	No	93 (92.1%)	98 (99.0%)	99 (99.0%)	0.007
	Yes	8 (7.9%)	1 (1.0%)	1 (1.0%)	
Rash	No	100 (99.0%)	97 (98.0%)	99 (99.0%)	0.76
	Yes	1 (1.0%)	2 (2.0%)	1 (1.0%)	
Nutritional intolerance	No	100 (99.0%)	98 (99.0%)	99 (99.0%)	0.99
	Yes	1 (1.0%)	1 (1.0%)	1 (1.0%)	
Lethargy	No	93 (92.1%)	91 (91.9%)	97 (97.0%)	0.24
	Yes	8 (7.9%)	8 (8.1%)	3 (3.0%)	

ROP screening in premature infants. They observed that the mean N-PASS scores between the oral ibuprofen and oral paracetamol groups did not differ significantly, and there was no significant difference between the groups. There was no difference in the time of crying and occurrence of tachycardia/bradycardia and desaturation.

It was concluded that oral ibuprofen or paracetamol before ROP screening in preterm infants had similar analgesic effects and did not significantly reduce pain during eye examination[19]. In the current study, it was seen that there was no significant difference between the two groups of ketamine-acetaminophen and fentanyl-acetaminophen regarding pain reduction, and both reduced pain equally. Based on the present study and the study by Bulut et al., it can be said that the analgesic effect of pharmacological substances in reducing the pain of newborns during ROP examination is less than that of non-pharmacological drugs. Also, pharmacological drugs have the same effect in reducing pain because, according to our study and also the study of Bulut et al., these drugs did not significantly differ from each other, which means that these two studies were similar.

In Nayak et al.'s study, it was seen that the mean PIPP scores in three groups (breast milk, 10% dextrose, sterile water) were 11.8±2.8 versus 9.8±3.3 versus 10.2±2.9, respectively (p=0.18). Behavioral and physiological variables were similar in all three groups. It was concluded that breast milk, dextrose 10%, or sterile water that was administered orally before ROP screening in preterm infants had similar analgesic effects and did not significantly reduce pain during the procedure [20]. In the current study, it was seen that sucrose significantly reduced the pain score, which was different from the study of Nayak et al. This difference may be caused by the type of sugar used or genetic

Table 3. Blood pressure changes and decreased pulse of the patients based on the treatment**.**

Parameters	Severity	ketamine-acetaminophen	fentanyl-acetaminophen	Oral sucrose	P value
Changes in blood pressure	mild	71 (70.3%)	74 (74.7%)	82 (82.0%)	0.34
	moderate	26 (25.7%)	23 (23.2%)	15 (15.0%)	
	severe	4 (4.0%)	2 (2.0%)	3 (3.0%)	
Decreased pulse	mild	72 (71.3%)	64 (64.6%)	80 (80.0%)	0.10
	moderate	25 (24.8%)	33 (33.3%)	17 (17.0%)	
	severe	4 (4.0%)	2 (2.0%)	3 (3.0%)	

differences in pain threshold because in the present study, the sugar substance was sucrose, but in the study by Nayak et al., dextrose was used. Also, one of the other differences between the present study and Nayak et al.'s study was the difference in the sample size of the two studies. In the present study, the sample size was much larger than that of Nayak et al.

Sethi et al. compared the effectiveness of low-dose fentanyl infusion and oral sucrose 24% in optimal pain relief during laser treatment for ROP. Fifty-eight preterm infants with spontaneous breathing undergoing phototherapy were included in the study. Preterm infants were randomly divided into fentanyl infusion (1 µg/kg/h) or oral 24% sucrose (2 ml). It was seen that the proportion of time spent crying during the procedure was significantly lower in the fentanyl group. The mean PIPP-R score during the procedure was significantly lower in the fentanyl group. There were no differences in other outcomes between the two groups. The conclusion was that during laser for ROP, low-dose fentanyl infusion was more effective in reducing pain compared to sucrose [21]. In the current study, it was seen that the administration of oral sucrose had a better effect than fentanyl. This difference in the results can be explained by the difference in the kind of procedure Laser versus ROP examination and method of fentanyl administration in the two studies, and because in the current study, fentanyl was administered nasally. However, in the study by Sethi et al., fentanyl was administered by infusion. It seems that there is a need to investigate the two methods of sucrose administration and fentanyl infusion in future studies. However, based on these two studies and the fact that oral sucrose administration is more acceptable to the patient's parents as a non-invasive method, it can be said that oral administration of sucrose is more acceptable than fentanyl infusion.

The study by Dolgun et al. was conducted to investigate the effects of swaddling infants with oral administration of sucrose, swaddling with oral administration of breast milk, and swaddling with oral administration of distilled water (control) on the perception of pain in premature infants during the ROP examination. Data were obtained from 87 preterm infants (54% girls) who were less than 32 weeks of gestation and had a body weight of 1500 grams. There was no significant difference in the pain profile scores of premature babies in the three groups. The conclusion was that infant swaddling with oral administration of sucrose or breast milk was not more effective in reducing pain in preterm infants during ROP examinations than swaddling with oral administration of distilled water [22]. The findings of this study are in contrast with the current study, and this difference between the findings can be caused by the sample size or genetic differences in pain threshold. The sample size of the present study was much larger than the study of Dolgun et al. Based on our findings, sucrose is effective in reducing pain in infants during ROP examination.

Rosalie et al. evaluated the effectiveness of breast milk (EBM) on infant pain during ROP screening. It was concluded that oral EBM significantly reduced pain during and after ROP screening [23]. In the current study, breast milk was not investigated as a method. However, in future studies, the administration of breast milk can be compared with the administration of sucrose, and the combination of these two methods should be investigated.

Conclusion

The findings showed that the effect of non-pharmacological methods was greater than pharmacological methods in reducing the pain of newborns during the ROP examination. Based on our findings, the effect of oral sucrose in reducing pain was greater than the effect of ketamine-acetaminophen and fentanyl-acetaminophen. However, there was no significant difference between the ketamine-acetaminophen and fentanyl-acetaminophen groups. 7.9% of the ketamine-acetaminophen group and 2% of the oral sucrose group experienced apnea, and the episodes of de-saturation in the ketamine-acetaminophen group was the highest with 18.8% and in the oral sucrose treatment group was the lowest with 7%. Blood pressure and heart rate did not differ between the groups.

Acknowledgment

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

References

1. Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatric research. 2013;74(1):35-49.
2. Blencowe H, Moxon S, Gilbert C. Update on blindness due to retinopathy of prematurity globally and in India. Indian pediatrics. 2016;53:S89-S92.
3. Brown AC, Nwanyanwu K. Retinopathy of prematurity. StatPearls [Internet]: StatPearls Publishing. 2021.
4. Shulman RHMHJ. Retinopathy of prematurity: evolving concepts in diagnosis and management. 2015.
5. Ghaseminejad A, Niknafs P. Distribution of retinopathy of prematurity and its risk factors. Iranian journal of pediatrics. 2011;21(2):209.
6. Sabzehei MK, Afjeh SA, Farahani AD, Shamshiri AR. Retinopathy of prematurity: incidence, risk factors, and outcome. Archives of Iranian medicine. 2013;16(9):507.
7. Murphy SL, Mathews T, Martin JA, Minkovitz CS, Strobino DM. Annual summary of vital statistics: 2013–2014. Pediatrics. 2017;139(6).
8. Fierson WM, Capone Jr A, American academy of pediatrics section on ophthalmology aaoo, et al. Telemedicine for evaluation of retinopathy of prematurity. Pediatrics. 2015;135(1):238-54.
9. Mitchell AJ, Green A, Jeffs DA, Roberson PK. Physiologic effects of retinopathy of prematurity screening examinations. Advances in neonatal care: official journal of the National Association of Neonatal Nurses. 2011;11(4):291.
10. Allegaert K, Van Den Anker JN. Neonatal pain management: still in search of the Holy Grail. International journal of clinical pharmacology and therapeutics. 2016;54(7):514.
11. Hatfield LA, Chang K, Bittle M, Deluca J, Polomano RC. The analgesic properties of intraoral sucrose: an integrative review. Advances in neonatal care. 2011;11(2):83-92.
12. Hatfield LA, Murphy N, Karp K, Polomano RC. A systematic review of behavioral and environmental interventions for procedural pain management in preterm infants. Journal of Pediatric Nursing. 2019;44:22-30.
13. Dempsey E, McCreery K. Local anaesthetic eye drops for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity. Cochrane Database of Systematic Reviews. 2011(9).
14. Disher T, Cameron C, Mitra S, Cathcart K, Campbell-Yeo M. Pain-relieving interventions for retinopathy of prematurity: a meta-analysis. Pediatrics. 2018;142(1).
15. Bueno M, Yamada J, Harrison D, et al. A systematic review and meta-analyses of nonsucrose sweet solutions for pain relief in neonates. Pain Research and Management. 2013;18(3):153-61.
16. Dilen B, Elseviers M. Oral glucose solution as pain relief in newborns: results of a clinical trial. Birth. 2010;37(2):98-105.
17. Dilli D, İlarslan NEÇ, Kabataş EU, Zenciroğlu A, Şimşek Y, Okumuş N. Oral sucrose and non-nutritive sucking goes some way to reducing pain during retinopathy of prematurity eye examinations. Acta paediatrica. 2014;103(2):76-9.
18. Zeraati H, Shahinfar J, Vashani HB, Reyhani T. Effect of multisensory stimulation on pain of eye examination in preterm infants. Anesthesiology and pain medicine. 2017;7(1).
19. Bulut O, Tarak Bozkurt O, Arslanoglu S. Oral Ibuprofen Versus Oral Paracetamol in Pain Management During Screening for Retinopathy of Prematurity: A Prospective Observational Study. The Journal of Perinatal & Neonatal Nursing. 2022;36(3):305-11.
20. Nayak R, Nagaraj KN, Gururaj G. Prevention of pain during screening for retinopathy of prematurity: A randomized control trial comparing breast milk, 10% dextrose and sterile water. The Indian Journal of Pediatrics. 2020;87(5):353-8.
21. Sethi A, Sankar MJ, Kulkarni S, Thukral A, Chandra P, Agarwal R. Low dose fentanyl infusion versus 24% oral sucrose for pain management during laser treatment for retinopathy of prematurity—an open label randomized clinical trial. European Journal of Pediatrics. 2020;179(2):285-92.
22. Dolgun G, Bozlak Ş. Effect of nonpharmacologic pain control during examination for retinopathy of prematurity. Journal of Obstetric, Gynecologic & Neonatal Nursing. 2017;46(5):709-15.
23. Rosali L, Nesargi S, Mathew S, Vasu U, Rao SP, Bhat S. Efficacy of expressed breast Milk in reducing pain during ROP screening—a randomized controlled trial. Journal of tropical pediatrics. 2015;61(2):135-8.