ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2023.90775
Nam Kem Med J 2023;11(3):271-275

Can the Side Effects of Mydriatics Be Reduced with the ROP-bundle Protocol?

ROP-bundle Protokolü ile Midriyatiklerin Yan Etkileri Azaltılabilir mi?

Özlem ŞAHİN[1], Özmert M.A. ÖZDEMİR[2], Ebru Nevin ÇETİN[3], Kazım KÜÇÜKTAŞÇI[4], Hacer ERGİN[2]

[1]*University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Neonatal Intensive Care, İstanbul, Turkey*
[2]*Pamukkale University Faculty of Medicine, Department of Neonatal Intensive Care, Denizli, Turkey*
[3]*Pamukkale University Faculty of Medicine, Department of Ophthalmology, Denizli, Turkey*
[4]*Denizli Private Hospital, Clinic of Neonatal Intensive Care, Denizli, Turkey*

ABSTRACT

Aim: The mydriatics that used for pupil-dilation in the examination of retinopathy-of-prematurity (ROP) may cause some side-effects in the neurological, gastrointestinal, cardiovascular systems by absorption from the nasal mucosa, cornea, conjunctiva, skin. In order to minimize these side-effects, it's recommended to prepare mydriatics in appropriate concentrations, combinations, and to apply pressure on the naso-lacrimal canal by closing the eyes after the application. In this study, we aimed to evaluate the systemic side-effects in the early period of using 0.5% cyclopentolate-1% phenylephrine combination for pupil-dilatation before the ROP-examination and with the protocol we applied after drip in our unit.
Materials and Methods: Thirty-three ROP examinations of 17 cases were included in the study, which was planned retrospectively. After instillation of eye drops containing 0.5% cyclopentolate-1% phenylephrine combination in accordance with our ROP-bundle-protocol, the eye was closed, pressure was applied to the naso-lacrimal canal for 1-2 minutes, and the excess part that had leaked into the skin was wiped off. Oxygen saturation (SaO_2), the amount of oxygen given, blood pressure arterial (TA), heart rate were recorded before and after the drop at 10., 30., and 60. minutes. In addition, patients were followed up for 24 hours in dimensions of gastric-residue, distention, apnea and other side-effects.
Results: The mean-week of gestation, body weight of 17 newborns, 35.3% (6) of whom were boys, 64.7% (11) of girls, were found to be 27.6±3 weeks, 1025±389 g, respectively. In 33 evaluations made before and after mydriatic in 17 cases; distension developed in two cases, apnea in one, and pallor of the skin in one patient. Although there was a statistically significant difference only in SaO_2 and 60th minute systolic TA-measurements between pre- and post-treatment measurements, hemodynamic changes were not evaluated as clinically significant.
Conclusion: In-order-to reduce the side-effects that may develop due to mydriatics, it's necessary to standardize the practices before and after the ROP-examination, close follow-up of the cases after the ROP-examination in terms of early intervention.

Keywords: Retinopathy of prematurity, newborn, cyclopentolate, phenylephrine

ÖZ

Amaç: Prematüre retinopatisi (ROP) muayenesinde pupil dilatasyonu için kullanılan midriyatikler; nazal mukoza, kornea, konjonktiva ve deriden emilerek nörolojik, gastrointestinal ve kardiyovasküler sistemde bazı yan etkilere neden olabilmektedir. Bu yan etkilerin en aza indirilebilmesi için midriyatiklerin uygun konsantrasyon ve kombinasyonlarda hazırlanması, uygulama sonrasında gözlerin kapatılıp nazo-lakrimal kanal üzerine bası uygulanması önerilmektedir. Bu çalışmada, ünitemizde ROP muayenesi öncesinde pupil dilatasyonu amacıyla kullanılan %0,5 siklopentolat-%1 fenilefrin kombinasyonu ve damla sonrası ünitemizde uyguladığımız protokol ile erken dönemdeki sistemik yan etkileri değerlendirmeyi amaçladık.
Gereç ve Yöntem: Retrospektif olarak planlanan çalışmaya 17 olguya ait 33 ROP muayenesi dahil edildi. ROP-bundle protokolümüze uygun olarak %0,5 siklopentolat-%1 fenilefrin kombinasyonunu içeren göz damlalarının damlatılmasından sonra göz kapatılıp, nazo-lakrimal kanala 1-2 dakika süreyle bası uygulandı ve deriye sızan fazla kısmı silindi. Damla öncesinde ve sonrası 10., 30., 60. dakikalarda oksijen satürasyonu (SaO_2), verilen oksijen miktarı, tansiyon arteriyel (TA), kalp tepe atımı kaydedildi. Ayrıca hastalar 24 saat süreyle gastrik rezidü, distansiyon, apne ve diğer yan etkiler açısından takip edildi.

Address for Correspondence: Özlem ŞAHİN MD, University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Neonatal Intensive Care, İstanbul, Turkey
Phone: +90 505 373 77 65 **E-mail:** colkozlem@yahoo.com **ORCID ID:** orcid.org/0000-0001-9951-8624
Received: 30.05.2023 **Accepted:** 03.07.2023

©Copyright 2023 by Tekirdağ Namık Kemal University / Namık Kemal Medical Journal is published by Galenos Publishing House.
Licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

Bulgular: Çalışma kapsamında %35,3'ü (6) erkek ve %64,7'si (11) kız olmak üzere değerlendirilen 17 yenidoğanın ortalama gestasyon haftası ve vücut ağırlıkları sırasıyla 27,6±3 hafta ve 1025±389 gr saptandı. On yedi olguda midriyatik öncesi ve sonrası yapılan 33 değerlendirmede; iki olguda distansiyon, birinde apne ve bir olguda da deride solukluk gelişti. Tedavi öncesi ile sonrası ölçümler arasında sadece SaO_2 ve 60. dakika sistolik TA ölçümünde istatistiksel açıdan anlamlı bir farklılık saptansa da hemodinamik değişiklik bakımından klinik olarak anlamlı değerlendirilmedi. **Sonuç:** Midriyatiklere bağlı gelişebilecek yan etkilerin azaltılması amacıyla ROP muayenesi öncesi ve sonrasındaki uygulamaların standardize edilmesi, erken müdahale açısından ROP muayenesi sonrası olguların yakın izlemi gereklidir.

Anahtar Kelimeler: Prematüre retinopatisi, yenidoğan, siklopentolat, fenilefrin

INTRODUCTION

Premature births are an important public health problem all over the world. In recent years, developments related to neonatal intensive care in developing countries such as China, India and Turkey have caused some morbidities such as retinopathy of prematurity (ROP) to be seen more frequently in this group of premature babies, together with the increase in survival rates of premature babies. ROP, which is a common complication of preterm birth, is a pathology in which immature blood vessels in the retina are affected and which can cause severe visual impairment and even blindness. ROP, which affects approximately 80% of premature babies with a birth weight of less than 1000 g, is the most important cause of visual impairment in children under 5 years of age in developed countries. Its incidence is tried to be reduced with optimal oxygen use strategy, early diagnosis with ROP screening protocols, and appropriate treatments[1,2]. In order not to delay the treatment, screening examinations should be done on time, and adequate pupil dilation should be ensured before the ROP examination. Due to the possible side effects of eye drops used for mydriasis, different concentrations and combinations of phenylephrine, cyclopentolate, and tropicamide have been tried to provide both safe and adequate pupil dilation. The main reason for concern in the use of mydriatics is that 80% of the drops enter the nasolacrimal duct after ocular administration and pass into the systemic circulation via the nasal mucosa and their systemic effects occur[2-5]. Hypertension, hypotension, tachycardia, bradycardia, apnea, cardiopulmonary arrest, seizure, necrotizing enterocolitis (NEC), sepsis and even death may develop in patients in relation to cardiovascular, respiratory, central nervous system and gastrointestinal side effects due to the systemic effects of mydriatics[5-8]. Phenylephrine makes vasoconstriction and causes increase in blood pressure and tachycardia; anticholinergics cause temporary bradycardia followed by tachycardia, palpitations and arrhythmias[3].

In this retrospective study, we aimed to evaluate how the ROP bundle protocol, which we routinely applied in our unit, affected the short-term results after drop.

MATERIALS AND METHODS

The files of premature infants who underwent ROP examination in our 18-bed tertiary neonatal intensive care unit between May 2011 and January 2012 were retrospectively reviewed. Approval for the retrospective study was obtained from the Non-Interventional Clinical Research Ethics Committee of Pamukkale University (decision no: E.349665, date: 28.03.2023).

Selection and Definition of Cases

Considering the recommendations of the American Academy of Pediatrics and the American Academy of Ophthalmology, ROP screening was performed for all infants with a birth weight of ≤1500 g and/or a gestational week of ≤32 weeks and a birth weight of 1500-2000 g or a gestational age greater than 32 weeks, taking cardiopulmonary support, who were clinically unstable and who were thought to be at risk for ROP by the clinician[9].

Patients with congenital anomaly, cardiovascular instability and need for inotropes were not included in the study.

Technical Information

ROP examinations are carried out by the specialist ophthalmologist in our clinic regularly on the same days, more frequently when necessary, at the bedside.

One hour before the ROP examination, 1% phenylephrine-0.5% cyclopentolate combination for pupil dilation was applied three times in each eye at 0^{th}, 5^{th} and 10^{th} minutes. In order to minimize the passage of eye drops into the systemic circulation, the eye was closed after the procedure, pressure was applied to the lacrimal canal for 1-2 minutes, and the excess part of the drop that leaked into the skin was wiped with a sterile sponge. In patients with adequate pupil dilation with 1% phenylephrine-0.5% cyclopentolate, eye examinations were performed 60 minutes after the start of mydriasis by the same experienced ophthalmologist, independent of the study.

Before and after mydriatic administration, at the 10^{th}, 30^{th}, 60^{th} minutes, oxygen saturation (SaO_2), amount of oxygen delivered, arterial blood pressure, heart apex beat and gastric residue for 24 hours, abdominal distension, apnea, and skin pallor were evaluated. Hemodynamic changes were also evaluated before the ROP examination was performed.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social

Sciences for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. ANOVA test was used for repeated measurements and paired samples test was used for paired comparisons to evaluate the difference between pre-treatment and post-treatment measurement values. Cases with a p value less than 0.05 were considered statistically significant.

RESULTS

A total of 17 patients, including 6 boys (35.3%) and 11 girls (64.7%), were included in the evaluation within the scope of the study. The distribution of demographic and clinical data of infants is given in Table 1.

In 33 ROP examinations of 17 patients included in the study, the pre- and post-mydriatic evaluation revealed distension in two cases, apnea in one patient, and skin pallor in one patient after the drip (Table 2). Complications developed in the patients were not resistant and additional medical treatment was not required.

Table 1. Distribution of demographic and clinical findings of patients

n=17 case	n (%) or Mean±SD
Gender	
Male	6 (35.3)
Female	11 (64.7)
Gestational week	27.6±3
Body weight (gr)	1025.9±389.4
Adjusted age (week)	34.4±3.4
Type of birth	
NSVD	2 (11.8)
C/S	15 (88.2)
Apgar score (1st minute)	6.2±1.1
Apgar score (5th minute)	7.9±0.7
Time of examination (day)	49±17.8

SD: Standard deviation, NSVD: Normal spontaneous vaginal delivery, C/S: Cesarean section

Table 3 shows the distribution of clinical data measured at the pre-treatment and post-treatment 10th, 30th and 60th minutes of the babies included in the evaluation. In the table, considering the analyses of repeated measurements before and after the treatment, although there was a statistically significant difference only in the measurement of SaO_2, SaO_2 was within the target saturation range and there was no need for additional oxygen. When we made a double comparison between the pre-treatment and the 60th minute of the treatment, a significant increase in systolic blood pressure was found (p=0.019), but it was not at the border of hypertension and did not persist.

DISCUSSION

In our study, a low concentration of 1% phenylephrine-0.5% cyclopentolate combination was used for mydriatic effect before the ROP examination. In order to reduce the systemic absorption of the drug after the drop, the patient's eyelid was closed, the excess part that had leaked into the skin was wiped off, and pressure was applied to the nasolacrimal duct for 1-2 minutes. After this application, which we called the ROP-bundle protocol, it was determined that there were no serious systemic side effects and no significant deterioration in hemodynamic parameters that would affect the clinical condition of the baby.

After absorption of topically applied mydriatics through nasal mucosa, cornea or conjunctiva, they pass into the systemic circulation, and may cause some side effects such as increased blood pressure, bradycardia or tachycardia in the cardiovascular system; desaturation and apnea in the respiratory system; feeding intolerance, abdominal distention, ileus, NEC in the

Table 2. Distribution of complications after drops in patients

ROP examination (n=17)	n (%)
Apnea	1 (5.9)
Skin pallor	1 (5.9)
Distention (4th hour)	1 (5.9)
Distention (12th hour)	1 (5.9)

ROP: Retinopathy of prematurity

Table 3. Distribution of clinical findings of patients before and after treatment

Variables (n=33 measurements)	Pre-treatment	Post-treatment 10th minute	Post-treatment 30th minute	Post-treatment 60th minute	p value
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
SaO_2	**94.4±3.1**	**94.8±2.6**	**93.8±3.2**	**95.3±3.2**	**0.049**
FiO_2	31.5±16.1	31.5±16.2	31.6±16.8	31.7±14.3	0.936
HPB	147.1±12.7	149.4±15.1	148.8±14.4	149.5±13.4	0.743
Systolic blood pressure	66.8±12.5	69.6±12.8	68.3±13.5	71.7±14.3	0.051
Diastolic blood pressure	38±11	38.7±13	37.8±11.1	39.8±11.1	0.694

SD: Standard deviation, SaO_2: Arterial oxygen saturation, FiO_2: Fractionated oxygen concentration, HPB: Heart peak beat

gastrointestinal tract; and apnea and convulsions in the central nervous system. In order to prevent the passage of ocularly applied drugs into the systemic circulation, applications such as applying pressure to the nasolacrimal canal, wiping the excess part of the drop that leak into the skin, using the microdrop form, reducing the number and the frequency of drops are recommended[4,5,8,10].

In the meta-analysis published by Kremer et al.[3] in 2019, in which mydriatics were evaluated, it was stated that different concentrations and combinations were used, the lowest dose providing adequate pupil dilation in terms of efficacy and the most appropriate content was the combination of 1% phenylephrine-0.2% cyclopentolate (1-2 drops), and the safety profile would increase even more with low dose microdrop application, but more studies were needed for the evaluation of efficacy. In addition, the demonstration of that low-dose mydriatics have comparable efficacy with higher doses has led clinicians to use low doses for pupil dilation[3]. We were able to provide adequate pupil dilation for ROP examination in all our patients with 1% phenylephrine-0.5% cyclopentolate, which we applied in low concentration for mydriasis before the ROP examination.

Due to the fact that mydriatics available in the market are produced for adults, their higher concentrations and larger volume drop forms pose a risk in terms of side effects. In order to reduce complications, mydriatics are administered in neonatal units by diluting them to the targeted concentration, and measures are taken for drop size[3,8]. Elibol et al.[5], in their prospective study, compared clinical efficacy and systemic side effects of mydriatics by using microdrop (mean drop volume 5.6 µL) and standard drop (mean drop volume 35.4 µL) forms. Adequate pupil dilation in all patients and the mean blood pressure, which was significantly higher in the group in which standard drops were applied, suggested that reducing the droplet volume might reduce possible side effects. It was concluded that mydriatics should be dropped with a small diameter intravenous cannula until the use of microdrops in premature infants is standardized in well-designed studies. In our study, no planning could be made regarding the drop size of mydriatics.

Although two or three drops of mydriatics are generally recommended for adequate pupil dilation in ROP screening, a single drop is considered sufficient in outpatient examinations. In a study using 1% phenylephrine-0.2% cyclopentolate combination for ROP screening and comparing the effectiveness of different numbers of drops, 64 eye examinations were performed on 15 babies, and no significant difference was found between pupil sizes. It was stated that pupil dilation could be achieved with less than three drops, and even a single drop might be sufficient for most infants[11]. The Turkish Neonatology Society recommended that 2.5% phenylephrine-0.5% tropicamide should be administered 2-3 times with 5-minute intervals before the ROP examination[6]. In our study, we dropped mydriatics three times with a 5-minute interval and provided sufficient pupil dilation. Considering the studies conducted, we think that the number of drops can be reduced in practice, since adequate pupil dilation can be achieved, considering the side-effect profile.

Kremer et al.[3] reported a statistically a significant increase in mean blood pressure of 3.4-22.8% in eight studies, and a significant decrease in mean blood pressure of 1-17.1% in four studies. In our study, although there was a statistically significant increase in systolic blood pressure at the 60th minute after the drop, it was observed that it did not persist and it improved.

Vasoconstriction, which occurs with the effect of phenylephrine, disrupts the perfusion of the intestines, and anticholinergics reduce peristalsis and may cause nutritional intolerance, abdominal distention, ileus and NEC in the gastrointestinal tract[1,4,12]. In the study of Jiang et al.[1] published in 2016, it was reported that after phenylephrine and tropicamide, approximately 10% of NEC developed and there was an increase in upper gastrointestinal system bleeding. Bonthala et al.[11] showed that with 1% phenylephrine and 0.2% cyclopentolate, duodenal motor contractions were reduced approximately four times and gastric emptying was significantly delayed. In a randomized controlled study that compared three different drug regimens to evaluate gastrointestinal side effects, it was concluded that the combination of 1% phenylephrine-0.2% cyclopentolate provided adequate pupil dilation with minimal systemic side effects[13]. In the study conducted by Mitchel et al.[2] blood levels of mydriatics were evaluated in patients with GI involvement after 1% phenylephrine-0.2% cyclopentolate combination, and a positive correlation was found between cyclopentolate level and residue. In our study, after -1% phenylephrine-0.5% cyclopentolate, GIS involvement was not detected in two cases, except for abdominal distension.

Many case reports about the side effects of mydriatics have been reported: Apnea with 1% phenylephrine-0.2% cyclopentolate in two patients who underwent outpatient ROP examination[14]; periorbital pallor, which regressed spontaneously in both eyes after 2.5% phenylephrine-0.5% cyclopentolate drops within 20 minutes and was thought to occur due to the cutaneous absorption of vasoconstricting phenylephrine[10]; transient paralytic ileus with abdominal distention and feeding intolerance within hours in two cases after drop of 1% phenylephrine-0.2% cyclopentolate[15]. In our study, pallor in the periorbital region, which resolved spontaneously, developed in one patient, and apnea developed in one patient, which resolved with tactile stimulation. We

think that ROP examinations should be done in a place with intensive care conditions or resuscitation materials should be available in the examination room for the safety of the patients and for emergency response when necessary.

Study Limitations

The inability to use the microdrop form, the small number of patients, and the inability to compare the side effects of different concentrations of mydriatics are important limitations of our study.

CONCLUSION

Despite the widespread use of mydriatic eye drops used for targeted pupil dilation before ROP screening in neonatal units, there are great differences in practice and the optimal dose, number of drops, time between drops, time between examination and drops are not standardized. In this study, we observed that there may be an increase in systolic blood pressure, abdominal distension, apnea and pale skin in premature and very low birth weight babies despite the ROP-bundle protocol we applied to minimize side effects. We planned to add mydriatic drop volume reduction, which we could not do in our study, to our ROP-bundle protocol. In conclusion, further randomized, controlled, multicenter studies are needed to develop approaches to reduce the transmission of mydriatic drugs into the systemic circulation in premature infants, to establish and standardize appropriate protocols such as ROP-bundle.

Ethics

Ethics Committee Approval: Approval for the retrospective study was obtained from the Non-Interventional Clinical Research Ethics Committee of Pamukkale University (decision no: E.349665, date: 28.03.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.Ş., Ö.M.A.Ö., E.N.Ç., K.K., H.E., Design: Ö.Ş., Ö.M.A.Ö., E.N.Ç., K.K., H.E., Data Collection or Processing: Ö.Ş., Ö.M.A.Ö., Analysis or Interpretation: Ö.Ş., Ö.M.A.Ö., H.E., Literature Search: Ö.Ş., Ö.M.A.Ö., E.N.Ç., K.K., H.E., Writing: Ö.Ş., Ö.M.A.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Jiang JB, Zhang ZW, Zhang JW, Wang YL, Nie C, Luo XQ. Systemic changes and adverse effects induced by retinopathy of prematurity screening. Int J Ophthalmol. 2016;9:1148-55.
2. Mitchell A, Hall RW, Erickson SW, Yates C, Lowery S, Hendrickson H. Systemic Absorption of Cyclopentolate and Adverse Events After Retinopathy of Prematurity Exams. Curr Eye Res. 2016;41:1601-7.
3. Kremer LJ, Reith DM, Medlicott N, Broadbent R. Systematic review of mydriatics used for screening of retinopathy in premature infants. BMJ Paediatr Open. 2019;3:e000448.
4. Dincer E, Gonen I, Bornaun HA, Yasa B, Babayigit A, Kurum O, et al. Early Hemodynamic Effects of Mydriatic Eye Drops in Preterm Infants. Am J Perinatol. 2022.
5. Elibol O, Alçelik T, Yüksel N, Caglar Y. The influence of drop size of cyclopentolate, phenylephrine and tropicamide on pupil dilatation and systemic side effects in infants. Acta Ophthalmol Scand. 1997;75:178-80.
6. Koç E, Baş AY, Özdek Ş, Ovalı F, Başmak H. Turkish Neonatal and Turkish Ophthalmology Societies consensus guideline on the retinopathy of prematurity. Turk Pediatri Ars. 2018;53:S151-60.
7. Akın O, Erdeve Ö, Bolat A, Sarıcı SÜ. Prematüre Bir Bebekte Midriyatik Göz Damlası Kullanımına Bağlı Gelişen Akut Gastrik Dilatasyon ve İleus Tablosu. Turkiye Klinikleri J Pediatr. 2009;18:240-3.
8. Seliniotaki AK, Prousali E, Lithoxopoulou M, Kokkali S, Ziakas N, Soubasi V, et al. Alternative mydriasis techniques for retinopathy of prematurity screening. Int Ophthalmol. 2020;40:3613-9.
9. Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2006;117:572-6.
10. Sesham R, Puvanachandra N, Muthukumar P. Phenylephrine eye drops: a rare complication in preterm neonate. Arch Dis Child Fetal Neonatal Ed. 2014;99:F180.
11. Bonthala S, Sparks JW, Musgrove KH, Berseth CL. Mydriatics slow gastric emptying in preterm infants. J Pediatr. 2000;137:327-30.
12. Chew C, Rahman RA, Shafie SM, Mohamad Z. Comparison of mydriatic regimens used in screening for retinopathy of prematurity in preterm infants with dark irides. J Pediatr Ophthalmol Strabismus. 2005;42:166-73.
13. Vicente GV, Bahri M, Palafoutas JJ, Wang H, Mehta N. A randomized controlled trial to determine the lowest effective dose for adequate mydriasis in premature infants. J AAPOS. 2012;16:365-9.
14. Wood MG, Kaufman LM. Apnea and bradycardia in two premature infants during routine outpatient retinopathy of prematurity screening. J AAPOS. 2009;13:501-3.
15. Lim DL, Batilando M, Rajadurai VS. Transient paralytic ileus following the use of cyclopentolate-phenylephrine eye drops during screening for retinopathy of prematurity. J Paediatr Child Health. 2003;39:318-20.