# Early Hemodynamic Effects of Mydriatic Eye Drops in Preterm Infants

Emre Dincer, MD[1] Ilker Gonen, MD[2] Helen A. Bornaun, MD[3] Beril Yasa, MD[4] Aslan Babayigit, MD[5] Ozge Kurum, MD[6] Sadık E. Bayramoğlu, MD[7] Merih Cetinkaya, PhD[2]

[1] Division of Neonatology, University of Health Sciences, Zeynep Kamil Maternity and Children's Training and Research Hospital, Istanbul, Türkiye
[2] Department of Neonatology, Istanbul Basaksehir Cam and Sakura City Hospital, Istanbul, Türkiye
[3] Department of Pediatric Cardiology, University of Health Sciences, Kanuni Sultan Süleyman Research and Training Hospital, Istanbul, Türkiye
[4] Department of Neonatology, Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Türkiye
[5] Department of Neonatology, University of Health Sciences, Kanuni Sultan Süleyman Research and Training Hospital, Istanbul, Türkiye
[6] Department of Neonatology, Kanuni Sultan Suleyman Training and Research Hospital, İstanbul, Türkiye
[7] Department of Ophtalmology, University of Health Sciences, Kanuni Sultan Süleyman Research and Training Hospital, Istanbul, Türkiye, Istanbul, Türkiye,

Address for correspondence Emre Dincer, MD, Division of Neonatology, University of Health Sciences, Zeynep Kamil Maternity and Children's Training and Research Hospital, Op. Dr. Burhanettin Üstünel Cad. No:10, Üsküdar, İstanbul 34668, Türkiye (e-mail: dinceremre@yahoo.com).

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## Abstract

**Objective** Mydriatic eye drops used for retinopathy of prematurity (ROP) examination can cause systemic effects, and there are case reports of serious adverse effects in the literature. In this prospective study, we aimed to evaluate the early hemodynamic effects of mydriatic eye drops to understand the possible mechanisms of adverse effects.

**Study Design** Between December 2018 and March 2019, preterm babies less than 32 gestational weeks and who underwent ophthalmologic examination in our unit were included. The vital signs (heart rate, respiratory rate, oxygen saturation [$SpO_2$], and blood pressure values), cerebral and mesenteric tissue saturation by near-infrared spectroscopy (NIRS), and left ventricular functions of infants were recorded before and after applying mydriatic eye drops (2.5% phenylephrine and 0.5% tropicamide). The data were compared statistically. Strict adherence to prevent systemic absorption of the eye drops was applied.

**Results** Thirty-two mydriasis procedures were evaluated in 26 patients. The mean gestational age was $28.5 \pm 1.7$ weeks, and the mean birth weight was $943 \pm 233$ g. There were no significant differences in terms of vital signs of infants including heart rate, blood pressure, and oxygen saturation [$SpO_2$] levels before and after eye-drop application. In addition, NIRS values showed no significant differences between before and after measurements. No significant differences were detected at echocardiographic evaluation performed before and after mydriatic administration. No adverse reaction was observed in the study population during the study.

**Keywords**
- retinopathy of prematurity
- mydriasis
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**Conclusion** This is the first study that evaluated the early hemodynamic effects of mydriatic eye drops used for ROP screening by vital signs, NIRS, and echocardiographic evaluation. Mydriatic eye drops have no significant effect on early hemodynamic parameters including vital signs, NIRS, and echocardiographic findings in preterm infants. We suggest that a cautious approach for avoiding the systemic absorption of these agents may prevent the possible early systemic effects in this high-risk population.

## Key Points

- Mydriatic eye drops are commonly used for pupil dilatation before retinopathy of prematurity examination, and there are reports of serious adverse events caused by these drops.
- Due to the adverse events of eye drops, hemodynamic effects of these agents were investigated by clinical findings, near-infrared spectroscopy, and echocardiography.
- No significant early hemodynamic effect was observed so avoiding systemic effects may be prevented with precautions.

"Retinopathy of prematurity (ROP)" is a vasoproliferative disorder of the immature retina in premature infants which may cause severe visual impairment or blindness.[1] Early diagnosis and appropriate treatment of ROP may prevent vision loss and contribute to improved neurodevelopment and quality of life in premature babies.[2] Therefore, screening of preterm babies at risk for ROP is very important, as the survival of premature infants improves day by day.

According to the 2018 Turkish Neonatal Society ROP consensus guideline, all preterm infants with a gestational age of $\leq$32 weeks or a birth weight of $\leq$1,500 g should be screened.[1] Considering that around 23,000 infants are born at less than 32 gestational weeks each year, according to the Turkish Ministry of Health and Public Health Institute of Türkiye (unpublished data, 2015), it can be assumed that at least 100,000 ROP examinations have been performed in Türkiye annually. Hence, it is crucial to know the adverse effects of eye drops used during examinations and ROP examination itself which are frequently performed.[3]

Before ROP examination, the pupil must be dilated for optimal visualization of the retina and ROP staging, and it is recommended to apply 2.5% phenylephrine and 0.5% tropicamide 1 hour before the examination.[4]

Phenylephrine is a selective α1-receptor agonist (with a low β-receptor agonism) that has a sympathomimetic effect. Phenylephrine causes an increase in systolic and diastolic blood pressures and also cardiac output, a decrease in renal, splanchnic, and cutaneous vascular blood flow, and vasoconstriction in the pulmonary artery. On the other hand, tropicamide is a synthetic muscarinic antagonist with parasympatholytic and atropine-like anticholinergic effects. Therefore, these agents may have the potential to cause serious side effects in the presence of systemic absorption.[4–6]

Even though these medications are considered safe, bradycardia, hypertension, hypotonia, feeding intolerance, risk of aspiration, flushing, and paleness of the skin were reported as adverse effects after mydriatic eye-drop instillation.[3,7] In addition, there are also reports of more severe adverse reactions such as transient paralytic ileus,[8] fatal necrotizing enterocolitis,[9] bronchoconstriction,[10] pulmonary edema,[11] and even cardiopulmonary arrest.[12]

In this prospective study, we aimed to evaluate the early hemodynamic effects of mydriatic eye drops in preterm infants. The effects of these agents were evaluated by echocardiography and cerebral and mesenteric near-infrared spectroscopy (NIRS), in addition to the clinical findings.

## Materials and Methods

### Patient Enrollment

This prospective observational study was conducted in a 42-bed neonatal intensive care unit in a tertiary hospital with 1,500 annual admissions. Preterm infants who underwent ophthalmologic ROP examination between December 2018 and March 2019 were included in the study. Infants who have major congenital anomalies, cardiovascular instability, need for inotropic medication, and those who had deterioration during echocardiography were excluded from the study. The study was approved by Institutional Ethics Board, and parental informed consent was obtained for all patients.

ROP examinations are regularly scheduled on the same days in our clinic and performed more if required. To ensure that the same cardiologist evaluates the patients to prevent interobserver variability, only one patient was enrolled in a day and evaluated for the study.

### Retinopathy of Prematurity Screening

Following Turkish Neonatal Society recommendations, all preterm infants with a gestational age of $\leq$32 weeks or birth weight of $\leq$1,500 g, and also infants with gestational age of $>$32 weeks or birth weight of $>$1,500 g who received cardiopulmonary support, and preterm infants who were deemed risky for ROP development by attending clinicians were all screened for ROP.[1]

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### Procedure for Pupil Dilation

For pupil dilation for ROP examination, 2.5% phenylephrine and 0.5% tropicamide were used three times with 5-minute intervals 1 hour before the examination. To avoid the systemic absorption of the agents, pressure is applied on the nasolacrimal canal for 1 minute, and excessive drop is wiped after drop instillation in every procedure.

### Evaluation and Timeline

Before the mydriasis procedure began, the first recording of vital signs (heart rate, $SpO_2$, systolic blood pressure, and diastolic blood pressure), NIRS, and echocardiographic evaluations were performed. The drops were then instilled in both eyes on minutes 0, 5, and 10. After 10 minutes from the last drops (20 minutes after the first evaluation finished), the secondary evaluation of vital signs, NIRS values, and echocardiography were performed again.

The same pediatric ophthalmologist performed the ophthalmological examinations, regardless of the study, 60 minutes after the beginning of the mydriasis procedure.

### Pain

Nonpharmacological supportive precautions (pacifier with/without sucrose, minimizing eye-lid manipulation) were taken to minimize the pain response to drops.[13] However, babies could not be swaddled because ultrasonography and echocardiography were to be performed.

### Near-Infrared Spectroscopy Evaluation

Cerebral ($StcO_2$) and mesenteric ($StmO_2$) tissue oxygenation were recorded by NIRS through an INVOS Oximeter (Somanetics, Covidien, Mansfield, MA). Cutaneous sensors were applied on the forehead for $StcO_2$ and the infraumbilical area for $StmO_2$ 1 hour before the first evaluation. Stable $StcO_2$ and $StmO_2$ values just before the mydriasis procedure and 20th minute (that is assumed to be when systemic levels of mydriatic drops are maximum)[14] after the first drop instillation were recorded.

### Echocardiography

The same pediatric cardiologist performed echocardiographic measurements, and Vivid E BT12 (General Electrics, MA) was used for the echocardiographic evaluation.

The prewarmed gel was used for echocardiographic evaluation. The first evaluation was made just before the first-drop instillation. After the initial evaluation, the mydriasis procedure was initiated. The second evaluation was made at the 20th minute of instillation of the first drop. The timeline of the mydriasis procedure and patient evaluation is shown in ►Fig. 1.

The systolic and diastolic interventricular septal thickness (IVSs and IVSd, respectively) and systolic and diastolic left ventricular posterior wall thickness (LVPWs and LVPWd, respectively) were measured by M-mode echocardiography using the leading-edge-to-leading-edge method.[15] In addition, the left ventricular mass (LVM) was calculated with the formula derived by Devereux et al.[16] Daily caffeine doses of the patients were delayed for the evaluation to prevent systemic effects of caffeine therapy on hemodynamics.

### Statistical Analysis

For statistical analyses, the SPSS software version 20.0 was used. The variables were investigated using visual (histograms and probability plots) and analytical methods (Shapiro–Wilk test) to determine if they are normally distributed. Parametric results were expressed as mean ± standard deviations. Median values of nonparametric tests were reported with median and minimum–maximum values. Nonnormally distributed numerical and ordinal variables were compared with the Mann–Whitney *U*-test. The Student's *t*-test was performed for comparison of parametric variables.

## Results

During the study period, 98 preterm babies requiring ROP screening were hospitalized. Three patients were deceased before the first ROP examination. Three patients had cardiac anomalies (Two patients had ventricular septal defect and one had Fallot's tetralogy), and four patients were not enrolled in the study due to cardiopulmonary instability. As a result, 32 mydriasis procedures were evaluated in 26 patients who met the inclusion criteria during the study period (►Fig. 2). The mean gestational age was 28.5 ± 1.7 weeks, and the mean birth weight was 943 ± 233 g. The demographic data of the study population are shown in ►Table 1.

Although the heart rate and systolic blood pressure seemed to increase and diastolic blood pressure tended to decrease after eye drops, there were no significant differences in terms of vital signs, including heart rate, blood pressure, and $SpO_2$ levels of infants before and after eye drop's application. In addition, cerebral and mesenteric NIRS

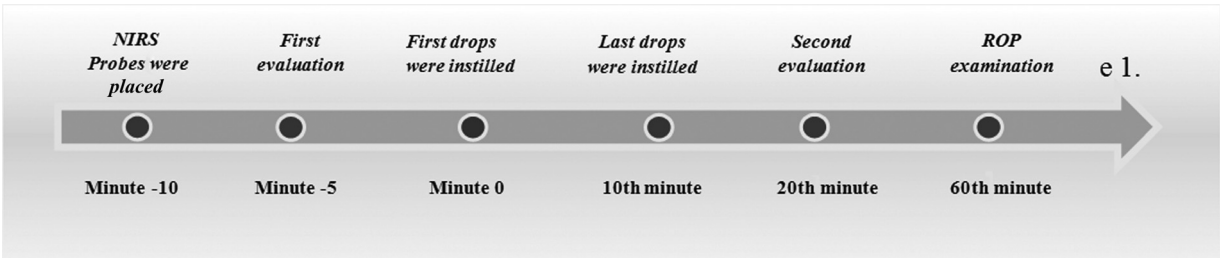



Fig. 1 Timeline for the mydriasis procedure and evaluation of the patients. NIRS, near-infrared spectroscopy; ROP, retinopathy of prematurity.

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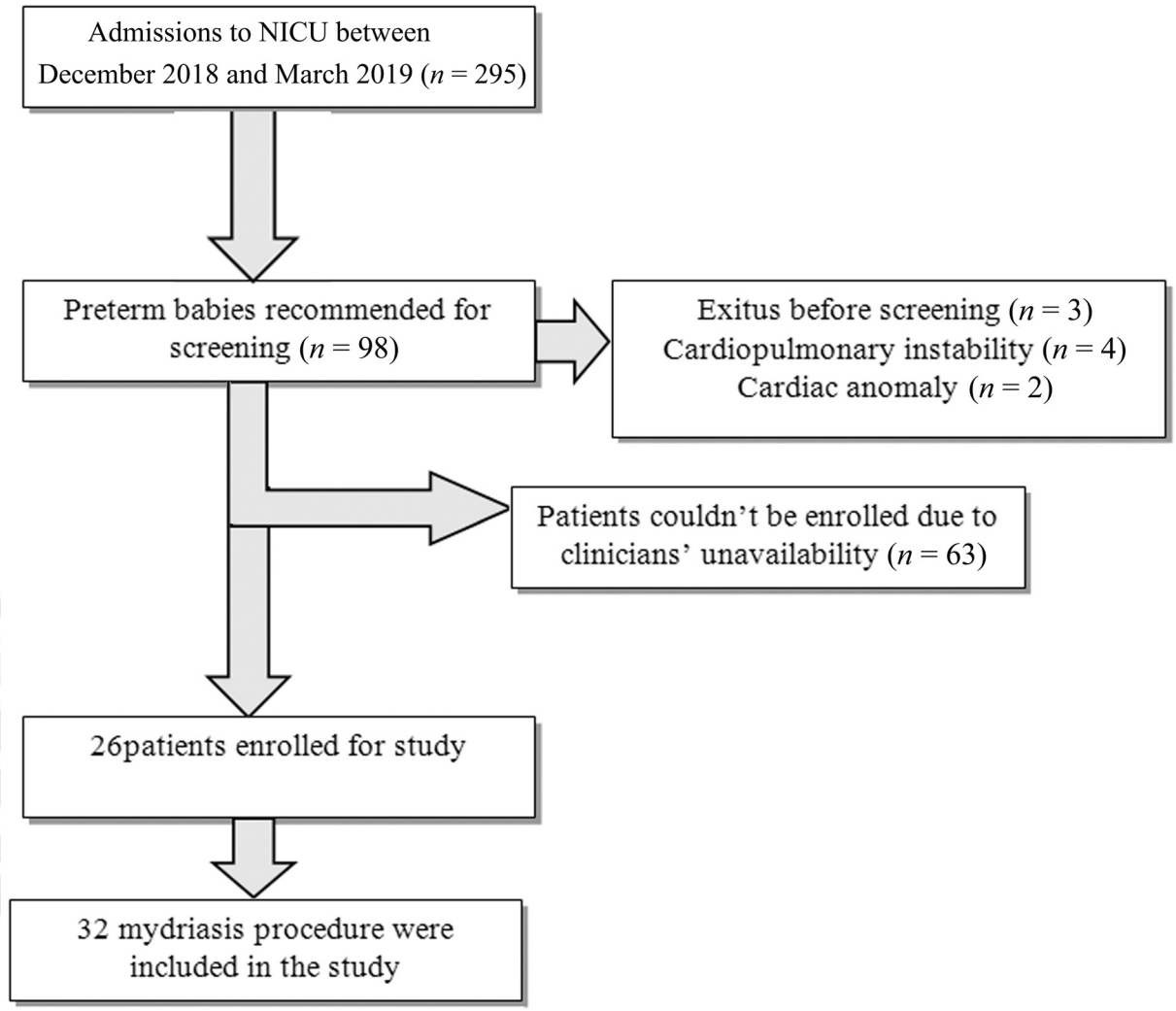



**Fig. 2** Patient enrollment according to inclusion/exclusion criteria. NICU, neonatal intensive care unit.

values showed no significant differences between the before and after measurements (►Table 2).

There was also no significant difference between echocardiographic measurements before and after the mydriatic administration. (Echocardiographic findings are depicted in ►Table 3) No adverse reaction was observed in the study population during the study.

**Table 1** Demographic data of the patients

| Demographic ($n = 32$) | Mean | Standard deviation |
|---|---|---|
| Birth weight (g) | 943 | 233 |
| Gestational age (wk) | 28.5 | 1.7 |
| Actual weight on examination day (g) | 1312 | 294 |
| Chronological age[a] (d) | 29.4 | 3.6 |
| Gender (*n*) | Female: 17<br>Male: 15 | |

[a]Values not normally distributed were given with median and interquartile range and marked with.

## Discussion

In this present study, which evaluated the vital signs, NIRS measurements, and echocardiographic findings of the preterm infants before and after mydriatic eye-drop instillation for the first time in literature, we found no significant differences in all these parameters. In this regard, we suggest that mydriatic drops used for ROP screening in premature babies may not cause systemic effects if appropriate precautions are taken.

Pupillary dilation depends on the stimulation of the sympathetic nerves and excitation of the radial fibers of the iris. For optimal mydriasis, a combination of parasympatholytic and sympathomimetic drops is recommended. However, these drugs may cause systemic adverse effects in case of systemic absorption. Phenylephrine is a selective α-adrenergic receptor agonist and potent vasoconstrictor that causes increased blood pressure, systemic vascular resistance, and reflex bradycardia in parenteral administration.[3,8] On the other hand, tropicamide is a short-acting atropine-like anticholinergic drug with a parasympatholytic effect on pupillary muscles. Five types of muscarinic receptors are

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**Table 2** Vital signs and NIRS values before and after mydriatic drop application

| | Before eye-drop application | ± SD | After eye-drop application | ± SD | *p* |
|---|---|---|---|---|---|
| | Mean | | Mean | | |
| Heart rate/min | 146.1 | 10.3 | 149.7 | 15.2 | 0.133 |
| Systolic pressure (mm Hg) | 70.0 | 10.3 | 72.1 | 9.4 | 0.213 |
| Diastolic pressure (mm Hg) | 39.4 | 10.9 | 38.8 | 9.1 | 0.669 |
| Cerebral tissue oxygenation (%) | 69.5 | 7.6 | 69.1 | 9.6 | 0.722 |
| Mesenteric tissue oxygenation (%) | 58.5 | 9.8 | 59.4 | 10.5 | 0.536 |

Abbreviations: NIRS, near-infrared spectroscopy; SD, standard deviation.

present in various organs like the central nervous system (cortex, substantia nigra, hippocampus, and brain stem), heart, smooth muscle, and eyes. Therefore, even though tropicamide is accepted as a safe drug, it can cause systemic adverse effects like myasthenia-like syndrome.[3,7,17,18] There was no change in the cerebral oxygenation levels in preterm infants in the early period in our study.

Gastrointestinal system (GIS) side effects are primarily reported in the current literature. In addition to feeding intolerance and abdominal distention, serious side effects, such as transient paralytic ileus,[8] acute gastric dilation,[13] and necrotizing enterocolitis,[9] were also reported. Therefore, it can be suggested that these drops reduce gastrointestinal motility and mesenteric flow with their parasympatholytic sympathetic effect. In the study of Bonthala et al,[19] gastric emptying and GIS motility were shown to decrease after applying mydriatic drops with the manometric system. However, a combination of phenylephrine and cyclopentolate was used in this study. There was a slight but not significant increase in the mesenteric tissue oxygenation in our study after the mydriasis procedure. In addition, no GIS finding was developed in the study population. Therefore, safety precautions and close follow-up for possible GIS symptoms after ROP examination can be strongly recommended to minimize mydriatic drops' potential GIS side effects.[20]

Adverse effects of mydriatic drops in the cardiovascular system (CVS) are also frequently reported and many studies have been conducted on this subject. Phenylephrine may lead to systemic vascular resistance and blood pressure increment. In this regard, phenylephrine causes hypertension and reflex bradycardia in the case of systemic absorption. It also has β-agonist effects in very high doses,[5] so it does not have a tachycardic effect in low doses. Tropicamide has a lower affinity for systemic muscarinic receptors and not a significant receptor occupancy in plasma which explains why it has no reported vasopressor effect.[5,6] Alpay et al found a significant drop in heart rate after mydriatic drop instillation but no change in blood pressure.[3] While many studies report increment in the heart after mydriatic drops, Bolt et al had found no significant change with the same combination of 2.5% phenylephrine and 0.5% tropicamide.[21] There are also different results of the studies regarding effects on blood pressure. Alpay et al found no significant change in blood pressure levels after drop instillation and they concluded that different results of the studies might be

**Table 3** Echocardiographic measurement of the patients before and after mydriatic drop application

| Items | Before mydriasis procedure | ± SD | After mydriasis procedure | ± SD | *p* |
|---|---|---|---|---|---|
| | Mean | | Mean | | |
| IVSd (mm) | 5.89 | 2.09 | 6.03 | 2.14 | 0.285 |
| IVSs (mm) | 8.41 | 2.41 | 8.39 | 2.53 | 0.892 |
| LVIDd (mm) | 12.3 | 2.47 | 12.1 | 2.18 | 0.370 |
| LVIDs (mm) | 6.7 | 2.57 | 6.76 | 2.39 | 0.736 |
| LVPWd (mm) | 3.30 | 1.12 | 3.45 | 1.14 | 0.264 |
| LVPWs (mm) | 6.03 | 1.47 | 6.17 | 1.61 | 0.361 |
| EF (%) | 81.1 | 8.22 | 81.2 | 5.82 | 0.869 |
| SV (mL) | 3.76 | 3.78 | 3.03 | 1.38 | 0.276 |
| FS (%) | 47.7 | 7.99 | 47.4 | 5.96 | 0.753 |

Abbreviations: EF, ejection fraction; FS, fractional shortening; IVSd, diastolic interventricular septal thickness; IVSs, systolic interventricular septal thickness; LVIDd, left ventricular internal diameter end-diastole; LVIDs, Left ventricular internal diameter end-systole; LVPWd, diastolic left ventricular posterior wall thickness; LVPWs, systolic left ventricular posterior wall thickness; SD, standard deviation; SV, stroke volume.

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related to different care standards of units and conditions of the babies.[3] Similarly, there was no significant change in both heart rate and blood pressure levels in our study. However, in current literature, some studies reported changes in the heart rate and blood pressure levels due to mydriatic drops. Therefore, it may be suggested that these drops may cause cardiovascular effects if systemic absorption occurs. We think different systemic absorption levels, caused by drop sizes, drop instillation methods, and different precautions, may lie behind these conflicting results.[3,8,11,14,22]

To provide efficient mydriasis, eye drops need to be more concentrated than other solutions because of the short contact time with pupils and the solid protective barrier of the eye. Additionally, premature babies have thinner and immature skin barriers. Cutaneous barrier maturation happens after 1 to 2 weeks after birth regardless of gestational age; it is believed to be fully functional after 37 weeks of gestation.[5] On the other hand, insufficient drug metabolism also contributes to delayed clearance of topical medication if absorbed systemically.[8,14] Besides the skin, eye drops are primarily absorbed via nasal mucosa as nearly 80% of eye drop passes through the nasolacrimal duct. After the passage, the absorption also occurs through the oropharynx and GIS. Therefore, preventing the drop from passing through the nasolacrimal duct and overflowing to the surrounding skin is crucial. To achieve these, wiping excess fluid after instillation and occlusion of the nasolacrimal duct for 1 to 4 minutes are strongly advised, and these applications may reduce the systemic absorption by up to 4%.[8]

## Limitations

In our study, it is actually not clear whether prevention of systemic absorption resulted with no systemic adverse effects or the mydriatic agents do not affect the concerned systems. Therefore, evaluation of plasma levels of these drugs may clarify this situation in future studies. Even so, as it was also shown that these medications had adverse effects and precautions might reduce the systemic absorption, we think that our strict adherence to precautions provided lower systemic absorption of the drugs. On the other hand, in the current literature, our study is the first study to evaluate the mydriatic eye drops' systemic effects with a combination of echocardiography and NIRS. However, small sample size and only early evaluation represent the study's main limitations. Therefore, we suggest that studies with a larger number of patients and evaluation of organ blood flow in combination with Doppler studies with a more prolonged follow-up time may be more helpful in investigating the systemic effects of these medications.

## Conclusion

Preterm babies are a particular group of pediatric and neonatal medicine patients with immature and distinctive pharmacokinetics and pharmacodynamics. Therefore, it is crucial to minimize the adverse effects of medications and applications to this special group of patients. ROP examination is common in NICUs and eye drops used for mydriasis before examination have the potential for serious adverse effects but they can be prevented with a cautious approach. To the best of our knowledge, this is the first study that evaluated the early hemodynamic effects of mydriatic eye drops used for ROP screening by vital signs, NIRS, and echocardiographic evaluation. No significant hemodynamic changes in the early period after mydriatic eye drop administration was observed in our study. However, larger studies with longer evaluation periods are required to evaluate the late effects of these agents in preterm infants.

### Conflict of Interest

None declared.

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