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Impact of Mydriatic Drops and Pain on Systemic Responses During Retinopathy of Prematurity Screening

Prematüre Retinopatisi Taraması Sırasında Midriatik Damlaların ve Ağrının Sistemik Yanıtlar Üzerindeki Etkisi

[1]Gulay BILGIN,[2]Demet TEKCAN, [3]Mustafa Gurkan ERDOGAN, [4]Sirin GUVEN

[1]Eskisehir City Hospital, Department of Pediatric, Division of Pediatric Pulmonology, Eskisehir, Türkiye
[2]Selcuk University, Faculty of Medicine, Department of Pediatric, Division of Pediatric Allergy and Immunology, Konya, Türkiye
[3]Istanbul University, Faculty of Medicine, Division of Ophthalmology, Istanbul, Türkiye
[4]University of Health Science, Prof Dr Ilhan Varank Sancaktepe Training and Research Hospital, Department of Pediatric, Istanbul, Türkiye

Gulay Bilgin: https://orcid.org/0000-0001-6207-3748
Demet Tekcan: https://orcid.org/0000-0003-1864-5651
Mustafa Gurkan Erdogan: https://orcid.org/0000-0003-4155-0407
Sirin Guven: https://orcid.org/0000-0001-8727-5805

ABSTRACT

Objective: Retinopathy of Prematurity (ROP) presents a significant challenge for neonatal intensive care units (NICUs). Therefore, the study aims to investigate the impact of neonatal pain on the systemic and procedural side effects of ROP examinations and mydriatic drops, with the aim of enhancing screening safety.

Materials And Methods: This study, designed as a prospective descriptive investigation, included 70 preterm infants admitted to the NICU between August and November 2012. Patients were monitored during the examination and for 48 hours afterwards, focusing on vital signs and any side effects. The Neonatal Infant Pain Scale was applied to all patients. Statistical analysis was conducted using SPSS version 15.

Results: Adverse effects were absent in 41.4% of the infants. Flushing was observed in 22.9%, gastric residuals were noted in 10%, vomiting occurred in 8.6%, and a combination of flushing, apnea, and gastric residuals was seen in 2.9% of the infants. The pain group exhibited temporary increases in heart rate and body temperature, most notably within the first hour after the examination. There were no significant relationships between pain and blood pressure, oxygen saturation levels, or respiratory rates ($p>0.05$).

Conclusions: A comprehensive understanding of the adverse effects associated with mydriatic drops and the examination procedure is essential. During ROP screenings, infants should be closely monitored in standardized clinical settings, appropriate pain management strategies should be implemented, and caregivers must receive thorough education upon discharge.

Keywords: Mydriatic drops, neonatal intensive care units, neonatal pain, preterm infants, retinopathy of prematurity

ÖZ

Amaç: Prematüre retinopatisi (ROP), yenidoğan yoğun bakım üniteleri (YYBÜ) için önemli bir klinik sorundur. Bu çalışmada, ROP taramaları sırasında uygulanan midriyatik damlaların ve yenidoğanda oluşan ağrının, sistemik ve işlemle ilişkili bulgular üzerindeki etkileri değerlendirilmiş; böylece tarama güvenliğinin artırılması hedeflenmiştir.

Materyal ve Metot: Prospektif tanımlayıcı nitelikteki bu çalışmaya, Ağustos–Kasım 2012 tarihleri arasında YYBÜ'ye yatırılan 70 prematüre bebek dahil edildi. Tüm hastalar, ROP muayenesi sırasında ve sonrasındaki 48 saat boyunca, yaşamsal bulgular ve gelişebilecek yan etkiler açısından takip edildi. Ağrı değerlendirmesi için tüm bebeklere Yenidoğan Bebek Ağrı Ölçeği (NIPS) uygulandı. İstatistiksel analizler SPSS 15.0 programı ile gerçekleştirildi.

Bulgular: Bebeklerin %41,4'ünde herhangi bir yan etki gözlenmedi. %22,9'unda ciltte kızarıklık, %10'unda mide içeriği artışı, %8,6'sında kusma ve %2,9'unda ciltte kızarıklık, apne ve mide içeriği artışının birlikte görüldüğü belirlendi. Ağrı hisseden grupta, özellikle muayeneden sonraki ilk saatte kalp hızı ve vücut sıcaklığında geçici artış izlendi. Ağrı ile kan basıncı, oksijen satürasyonu ve solunum hızı arasında anlamlı bir ilişki saptanmadı ($p>0,05$).

Sonuç: ROP taramaları sırasında uygulanan midriyatik damlalar ve muayene işlemiyle ilişkili olumsuz etkilerin iyi anlaşılması büyük önem taşımaktadır. Bu süreçte bebeklerin standart klinik koşullarda yakından izlenmesi, etkili ağrı yönetimi sağlanması ve taburculuk öncesinde bakım veren kişilere yeterli eğitim verilmesi gereklidir.

Anahtar Kelimeler: Midriyatik damlalar, prematüre bebekler, prematüre retinopatisi, yenidoğan ağrısı, yenidoğan yoğun bakım üniteleri

Sorumlu Yazar / Corresponding Author:
Gulay Bilgin
Department of Pediatrics, Division of Pediatric Pulmonology, Eskisehir City Hospital, 71 Evler, Çevreyolu, 26080, Odunpazarı/ Eskisehir, Türkiye
Tel.: +905432280879
E-mail: gulaybas1010@yahoo.com

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INTRODUCTION

Retinopathy of Prematurity (ROP) poses a major concern in neonatal intensive care units (NICU) due to its potential to cause severe visual impairment or even permanent blindness if not detected and managed in time.[1] Despite the serious implications of this condition, appropriate screening and timely treatment can effectively prevent its progression. The initial screening for ROP typically begins between four to six weeks after birth, offering a critical window for early intervention.[2]

To facilitate the examination, pupil dilation is achieved using topical phenylephrine 2.5% and tropicamide 1%. While these drops are essential for ensuring a thorough evaluation, they pose potential risks. Documented side effects include tachycardia, bradycardia, apnea, hypertension, oxygen desaturation, cyanosis, vomiting, and increased gastric residual volumes.[3,4] However, despite several studies in the literature, it is still uncertain whether these effects stem from the systemic action of the mydriatic drops or the stress and discomfort associated with the examination itself.[4-6]

Neonates, especially preterm infants, have an immature nervous system, which affects their pain perception and response to external stimuli.[7,8] Studies suggest that ROP examination is a potentially painful procedure, and despite the use of local anesthetics, neonates exhibit physiological responses indicating pain and discomfort.[8,9] In particular, pain-related stress may contribute to systemic changes (e.g., instability in heart rate, blood pressure, and oxygen saturation levels), all of which have also been documented as potential side effects of mydriatic drops.[7,8,10]

This investigation aims to explore the systemic and procedural side effects associated with ROP examinations and the mydriatic drops used, with an emphasis on how neonatal pain influences these outcomes.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Umraniye Training and Research Hospital. (Date: 16.08.2012, decision no:2012-4). It was carried out in accordance with the Helsinki Declaration. Written informed consent was collected from the parents of babies.

Study Design and Setting: This prospective descriptive study was conducted between August 2012 and December 2012 at Umraniye Training and Research Hospital, involving 70 preterm infants who were monitored during follow-up in the clinic.

Inclusion and Exclusion Criteria: The study involved preterm infants born before 31 weeks or weighing under 1500 g at birth. Additionally, infants between 1500-2000 g with a gestational age above 31 weeks were included if they required respiratory or circulatory support.[2] Gestational age was determined using the modified Ballard score. Exclusion criteria included major congenital heart anomalies, sepsis, and dependence on mechanical ventilation.

Ophthalmologic Examination Procedure: ROP screening began at 4 to 6 weeks postnatally. Pupil dilation was induced by administering one drop of phenylephrine 2.5% and tropicamide 1% three times at 5-minute intervals. Pressure was applied to the lacrimal ducts during administration. Topical anesthesia was provided with proparacaine hydrochloride 0.5%. Examinations were performed using a binocular indirect ophthalmoscope with 20- and 28-diopter lenses. Following the use of a neonatal lid speculum, the anterior segment and fundus were examined. Findings were documented based on the International Classification of Retinopathy of Prematurity (ICROP) criteria.[11] A single retinal specialist performed all evaluations. Follow-ups occurred every 2 –4 weeks for infants without ROP and 1–2 weeks for stage 1–2 ROP.

Monitoring of Vital Signs and Side Effects: Vital signs, including temperature, blood pressure (BP), respiratory rate, oxygen saturation (sPO_2), and heart rate (HR), assessed at baseline, 1-, 24-, and 48-hours post-examination. In addition to vital signs, side effects (flushing, restlessness, gastric residuals, vomiting, apnea, and abdominal distension) were documented. Pain was assessed immediately after the examination with the Neonatal Infant Pain Scale (NIPS).[7,10,12] These scales evaluate behavioral and physiological indicators of pain (facial expression, crying, breathing pattern, limb movement, and autonomic responses). The NIPS score ranges from 0 to 7, with scores above 3 indicating the presence of pain.

Statistical Analysis: Data analysis was performed using SPSS (Statistical Package for Social Sciences for Windows) 15.0. The Kolmogorov-Smirnov test assessed normality. Descriptive statistics were presented as means, standard deviations, and frequencies. Student's t-test compared two independent groups, while paired-sample t-tests evaluated changes over time. Chi-square tests assessed categorical variables. A p-value <0.05 was considered significant.

RESULTS

Table 1 presents the demographic and baseline clinical characteristics of the study population. A total of 70 preterm infants were included, with 41 (58.6%) being male and 29 (41.4%) females. The mean gestational age was 31.44±2.64 weeks (range:24–34 weeks), and the mean age was 39.77±12.39 days

(range:27–75 days). The mean birth weight was 1851.76±512.88 g (range: 660–2720 g), and the mean current weight at the time of examination was 2357.10±708.87 g (range: 940–4500 g). The number of ROP examinations ranged from one or more, with 38 infants (54.3%) undergoing a single examination and 32 infants (45.7%) undergoing multiple examinations. The mean NIPS score one hour after the examination was 3.47±1.15 (range:2–6), with a median score of 4 (Table 1).

Table 2 illustrates the distribution of pain and adverse effects in the study population. Pain was present in 52.9% (n=37) of infants, while 47.1% (n=33) had no pain. Adverse effects included flushing (23.5%), gastric residuals (10.3%), restlessness (8.8%), vomiting (3.0%), and apnea (1.4%). Additionally, 42.5% of infants had no adverse effects. Some infants exhibited multiple adverse effects, with 2.9% experiencing a combination of flushing, apnea, and gastric residuals, 2.9% having both flushing and residuals, 2.9% showing flushing and apnea, 2.9% presenting gastric residuals and vomiting, and 2.9% having flushing with restlessness (Table 2).

Table 1. Demographic data and baseline clinical characteristics of the patients.

		Min-Max	Mean±SD (%)
Age (day)		27-75	39.77±12.39
Gestational age (week)		24-34	31.44±2.64
The number of examinations		1-5	1.70±0.95
Birth weight (g)		660-2720	1851.76±512.88
Current weight (g)		940-4500	2357.10±708.87
NIPS score (number)		2–6	3.47±1.15
			n (%)
Gender	Male		41 (58.6)
	Female		29 (41.4)
The number of examinations	1 time		38 (54.3)
	≥2 times		32 (45.7)

NIPS: Neonatal Infant Pain Scale

Table 2. NIPS and adverse effects distribution.

Category		n (%)
NIPS	Pain (+)	37 (52.9)
	Pain (-)	33 (47.1)
Adverse Effects	No adverse effects	29 (41.4)
	Flushing	16 (22.9)
	Gastric Residuals	7 (10.0)
	Restlessness	1 (1.4)
	Vomiting	6 (8.6)
	Apnea	1 (1.4)
	Flushing + Apnea + Residuals	2 (2.9)
	Flushing + Residuals	2 (2.9)
	Flushing + Apnea	2 (2.9)
	Residuals + Vomiting	2 (2.9)
	Flushing + Restlessness	2 (2.9)

NIPS: Neonatal Infant Pain Scale

Baseline body temperature showed no significant differences between infants undergoing single (36.79±0.43°C) or multiple examinations (36.90±0.59°C, p=0.369). In both groups, body temperature increased significantly at the 1st hour post-examination compared to baseline (single-examination:37.21±0.70°C, p=0.001; multiple-examinations:37.25±0.72°C, p=0.009); however, levels reverted to baseline by the 24th hour (single examination:36.71±0.42; multiple examination:36.81±0.53, p=0.398 and p=0.514). At the 48th hour, a meaningful decline was examined relative to the baseline in both groups (single examination:36.59±0.12; multiple examination:36.56±0.14, p=0.007 and p=0.004). Infants with pain exhibited markedly elevated body temperatures at the 1st (37.50±0.71°C versus 36.93±0.56°C, p=0.001) and 24th hour (39.93±0.58°C versus 36.56±0.15°C, p=0.001) than those without pain. No difference was found at the 48th hour (36.58±0.12 versus 36.57±0.14, p=0.861) (Table 3).

Table 3. Body Temperature variations based on number of examinations and presence of pain.

Time Point	**Single Examination (Mean±SD)**	**Multiple Examinations (Mean±SD)**	**$^{+}$p**
ROP Pre-Examination	36.79±0.43	36.90±0.59	0.369
ROP Post 1st Hour	37.21±0.70	37.25±0.72	0.827
ROP Post 24th Hour	36.71±0.42	36.81±0.53	0.372
ROP Post 48th Hour	36.59±0.12	36.56±0.14	0.351
Comparison	**$^{++}$p (Single Examination)**	**$^{++}$p (Multiple Examinations)**	
Pre vs Post 1st Hour	0.001**	0.009**	
Pre vs Post 24th Hour	0.398	0.514	
Pre vs Post 48th Hour	0.007**	0.004**	
Time Point	**Pain Present (Mean ±SD)**	**Pain Absent (Mean ±SD)**	**$^{+}$p**
ROP Post 1st Hour	37.50±0.71	36.93±0.56	0.001**
ROP Post 24th Hour	39.93±0.58	36.56±0.15	0.001**
ROP Post 48th Hour	36.58±0.12	36.57±0.14	0.861

ROP: Retinopathy of Prematurity; $^{+}$: Student t-test; $^{++}$: Paired sample t-test; **: p<0.01

The analysis of SAP showed no significant baseline variation between the groups based on examination numbers. Similarly, SAP at the first hour post-examination did not differ significantly (86.42±18.06 mmHg vs 85.59±11.72 mmHg, p=0.825). However, at the 24th hour, a significant increase in SAP was noted in the multiple-examinations group (81.06±8.05 mmHg vs. 76.05±10.52 mmHg, p=0.031). There were no constant differences at the 48th hour (76.31±9.59 mmHg vs. 78.25±7.72 mmHg, p=0.362). Within-group comparisons revealed that there was no meaningful alteration at the 1st hour in the single-examination group (p=0.470), but significant decreases were evaluated at the 24th and 48th hours (p=0.002). In the multiple-examinations group, SAP showed a notable rise at the first hour (p=0.018), while no notable changes were determined at the 24th (p=0.696) or 48th hours (p=0.267). Table 4 demonstrates the variations in SAP and HR following ROP examination based on the number of examinations and the presence of the pain. SAP fluctuations appeared dependent on examination frequency and time after the procedure. No significant differences were examined in the mean SAP between infants with pain and the non-pain group at the 1st hour (87.94±18.69 vs.83.91±10.42), 24th hour (77.94±10.89 vs. 78.78±8.41), and 48th hour of post-examination (76.43±9.25 vs.78.06±8.28) (p=0.263, p=0.721, p=0.443, respectively). HR showed a noticeable increase in the multiple examination group compared to the single examination group at baseline (148.50±17.03 bpm vs. 138.92±16.20 bpm, p=0.019) and at the 24th hour post-examination (146.15±11.16 bpm vs. 134.97±9.71 bpm, p=0.001). Similarly, at the 48th hour post-examination, HR remained significantly elevated in the multiple-examination group (137.12±13.66 bpm vs 130.18±11.65 bpm, p=0.025). However, no significant difference was examined at the 1st-hour post-examination (152.02±15.63 bpm vs 159.37±17.01 bpm, p=0.064). Within-group comparisons revealed a meaningful increase in HR at the 1st hour post-examination over baseline in both groups (p=0.001; p=0.002, respectively). HR significantly decreased at the 48th hour relative to baseline in both groups (p=0.002 for both). There were no important changes at the 24th hour post-examination in either group (p=0.121; p=0.420, respectively). These findings indicated that ROP examinations induced transient changes in HR, with more pronounced effects in infants who underwent multiple examinations. Table 4 also summarizes the HR variations with and without pain at different time points of post-examination. HR was substantially higher in infants with pain instead of those without pain at 1st hour post-examination (p=0.001), and no noticeable variations in HR were determined between the groups at 24th- or 48th-hours post-examination (p=0.196; p=0.989, respectively). Within-group comparisons revealed a significant decrease in HR from 1st hour to 24th hours post-examination and from 24th hours to 48th hours post-examination (p=0.001 for both). Thus, pain during the ROP examination was associated with transient elevations in HR, primarily evident within the 1st hour post-examination (Table 4).

Table 5 presents the SpO_2 and respiratory rate changes based on the number of examinations conducted. SpO_2 levels showed no significant differences between infants who underwent single or multiple examinations at any time (p=0.444, p=0.127, p=0.072, p=0.099, respectively). In the single-examination group, SpO_2 significantly increased at both the 24th hour (p=0.002) and the 48th hour (p=0.005) compared to baseline. In contrast, no significant changes were observed in the multiple-examinations group at these time points (p=0.248, p=0.941, p=0.088, respectively). The respiratory rate significantly increased at the 1st hour post-examination (p=0.001) and approached baseline

levels by the 48th hour in the single-examination group (p=0.210). In the multiple-examinations group, there was a substantial increase in respiratory rate at the 1st hour (p=0.043), but no notable changes at the other time points (p=0.630, p=0.539, respectively) (Table 5).

Table 4. Systolic arterial pressure & heart rate variations based on number of examination and presence of pain.

Systolic Arterial Pressure	**Single Examination (Mean±SD)**	**Multiple Examinations (Mean±SD)**	**$^{+}$p**
ROP Pre-Examination	84.13±19.57	80.31±11.88	0.320
ROP Post 1st Hour	86.42±18.06	85.59±11.72	0.825
ROP Post 24th Hour	76.05±10.52	81.06±8.05	0.031*
ROP Post 48th Hour	76.31±9.59	78.25±7.72	0.362
Comparison	**$^{++}$p (Single Examination)**	**$^{++}$p (Multiple Examinations)**	
Pre vs Post 1st Hour	0.470	0.018	
Pre vs Post 24th Hour	0.002**	0.696	
Pre vs Post 48th Hour	0.002**	0.267	
Systolic Arterial Pressure	**Pain Present (Mean ±SD)**	**Pain Absent (Mean ±SD)**	**$^{+}$p**
ROP Post 1st Hour	87.94±18.69	83.91±10.42	0.263
ROP Post 24th Hour	77.94±10.89	78.78±8.41	0.721
ROP Post 48th Hour	76.43±9.25	78.06±8.28	0.443
Heart Rate	**Single Examination (Mean±SD)**	**Multiple Examinations (Mean±SD)**	**$^{+}$p**
ROP Pre-Examination	138.92±16.20	148.50±17.03	0.019*
ROP Post 1st Hour	152.02±15.63	159.37±17.01	0.064
ROP Post 24th Hour	134.97±9.71	146.15±11.16	0.001**
ROP Post 48th Hour	130.18±11.65	137.12±13.66	0.025*
Comparison	**$^{++}$p (Single Examination)**	**$^{++}$p (Multiple Examinations)**	
Pre vs Post 1st Hour	0.001	0.002	
Pre vs Post 24th Hour	0.121	0.420	
Pre vs Post 48th Hour	0.002**	0.002**	
Heart Rate	**Pain Present (Mean±SD)**	**Pain Absent (Mean ±SD)**	**$^{+}$p**
ROP Post 1st Hour	162.13±14.29	147.82±15.82	0.001**
ROP Post 24th Hour	141.81±11.74	138.15±11.64	0.196
ROP Post 48th Hour	133.38±11.76	133.33±14.43	0.989
Comparison	**$^{++}$p**	**$^{++}$p**	
Post 1st Hour vs Post 24th Hour	0.001**	0.001**	
Post 24th Hour vs Post 48th Hour	0.001**	0.001**	

ROP: Retinopathy of Prematurity; $^{+}$: Student t-test; $^{++}$: Paired sample t-test; **: p<0.01

Table 5. Oxygen saturation and respiratory rate changes based on number of examinations.

Oxygen Saturation (SpO_2, %)	**Single Examination (Mean±SD)**	**Multiple Examinations (Mean±SD)**	**$^{+}$p**
ROP Pre-Examination	98.45 ± 1.88	97.94 ± 3.53	0.444
ROP Post 1st Hour	98.47 ± 1.81	97.40 ± 3.51	0.127
ROP Post 24th Hour	99.39 ± 1.32	97.97 ± 4.17	0.072
ROP Post 48th Hour	99.98 ± 0.75	98.43 ± 2.81	0.099
Comparison	**$^{++}$p (Single Examination)**	**$^{++}$p (Multiple Examinations)**	
Pre vs Post 1st Hour	0.941	0.248	
Pre vs Post 24th Hour	0.002**	0.941	
Pre vs Post 48th Hour	0.005**	0.088	
Respiratory Rate (bpm)	**Single Examination (Mean±SD)**	**Multiple Examinations (Mean±SD)**	**$^{+}$p**
ROP Pre-Examination	38.31 ± 6.37	41.75 ± 6.29	0.027
ROP Post 1st Hour	44.31 ± 7.43	43.62 ± 6.65	0.686
ROP Post 24th Hour	40.34 ± 6.15	42.09 ± 5.65	0.222
ROP Post 48th Hour	39.13 ± 6.12	42.09 ± 5.91	0.045
Comparison	**$^{++}$p (Single Examination)**	**$^{++}$p (Multiple Examinations)**	
Pre vs Post 1st Hour	0.001**	0.043*	
Pre vs Post 24th Hour	0.005**	0.630	
Pre vs Post 48th Hour	0.210	0.539	

ROP: Retinopathy of Prematurity; $^{+}$: Student t-test; $^{++}$: Paired sample t-test; **: p<0.01

DISCUSSION AND CONCLUSION

Consistent evaluation and monitoring of preterm infants are crucial for mitigating the advancement of ROP. The adverse effects during ROP examinations may result from both mydriatic drops and procedural stress. Studies suggest that mydriatic drops may contribute to cardiovascular, respiratory, and gastrointestinal side effects due to systemic absorption.[3,6,13] However, distinguishing these pharmacological effects from procedural pain and stress remains a challenge.

In the study, ROP examinations led to temporary changes in body temperature, HR, respiratory rate, SAP, and sPO_2. Although generally mild, these changes resolved within 24 to 48 hours. Notably, 52.9% of infants experienced pain, which was associated with transient HR and temperature increases, particularly within the first hour. This finding aligns with previous research indicating pain-related activation of the sympathetic nervous system.[10] Similarly, Tasdemir et al. have shown that multisensory stimulation effectively reduces procedural pain and improves physiological stability in preterm infants undergoing ROP examinations. This approach has been associated with lower pain scores, reduced heart rate, and improved oxygen saturation levels.[14] However, the absence of meaningful differences in sPO_2 and respiratory rate between infants with and without pain suggested that these parameters were less influenced by pain during ROP examinations. The role of procedural stress, such as the use of speculums and scleral pressure, was highlighted in previous research as contributors to pain.[14],[15] This emphasizes the need for effective pain management and optimization of the fundoscopic examination strategies.

Previous studies revealed no meaningful changes in body temperature during ROP examinations.[16] However, a recent study identified flushing and fever as the most common side effects, occurring in 68% and 46% of cases, respectively.[17] In our study, flushing was predominantly observed with a ratio of 23.5%. On the other hand, a transient increase in body temperature was detected within the first hour post-examination. Among infants experiencing pain, temperature elevations persisted at 24 hours, suggesting a role of stress-induced thermoregulation changes.

The literature presents conflicting results regarding BP changes during ROP examinations.[3] While some studies have reported a decrease in BP, others have observed an increase, potentially due to variations in mydriatic drop regimens. However, other recent studies detected no significant change in blood pressure.[4,6,18] In our study, SAP increased significantly at 24 hours in infants undergoing multiple examinations. Kremer et al. found no significant difference in BP when comparing low-dose and very low-dose regimens.[19] However, a review published in 2020 highlighted the superior safety profile of microdrop administration.[9] These findings suggest that techniques like nasolacrimal pressure application may reduce systemic absorption.

Jiang et al. reported a transient increase in HR during ROP examinations, which peaked during the procedure and approached to near-baseline levels after 60 minutes.[16] Similarly, in the study, an important increase in HR was examined within the first hour post-examination, particularly in infants experiencing pain. By the 48th hour, HRs had normalized. These results reinforce the importance of observing infants for at least 24 to 48 hours post-examination. On the other hand, a recent study revealed that while mydriatic drops may influence HR and regional cerebral oxygenation, they do not appear to significantly impact cerebral blood flow velocities or the metabolic rate of oxygen consumption, indicating their general safety.[18]

Unlike HR and respiratory rates, sPO_2 levels showed minimal fluctuation in the study across groups, contrasting with studies reporting significant oxygen desaturation during ROP screening, presumably due to variances in study design, like the application of supplemental oxygen or variations in procedure duration.[3,6,19] Similarly, Alpay et al. also found a temporary decrease in sPO2 after mydriatic drop administration, but not statistically significant. Since the desaturation coincided with the examination, they blamed procedural stress.[4]

Apnea was observed in five infants, all of whom recovered with tactile stimulation without further intervention. While apnea following ROP screening is commonly reported within 24 to 48 hours, no significant changes were seen at 12 hours in some studies.[6] Publications suggest that apnea may result from procedural pain, stress, stimulation of the oculocardiac reflex, or the anticholinergic effects of mydriatic drops.[3,4,6,10] These findings emphasize the need for immediate post-examination monitoring rather than during the procedure itself.

The results of this study underscore the importance of performing ROP examinations under controlled clinical conditions with appropriate monitoring and pain management strategies. Infants should be closely observed for at least 24 to 48 hours following the examination, particularly in outpatient settings where immediate medical intervention may not be readily available. Additionally, the adoption of micro-drop techniques and other strategies to reduce systemic absorption of mydriatic drops should be prioritized.

This study has a few limitations. Being a single-center study is one of them. Meanwhile, the sample size was constrained, which may limit the extent to which the results can be generalized to larger popu-

lations. Furthermore, pain was assessed using the NIPS, a subjective scale that may introduce variability. The absence of a control group further limits our ability to distinguish the effects of mydriatic drops from procedural stress. Finally, we did not measure biochemical markers or assess long-term outcomes related to the systemic effects of the procedure. Future multicenter studies with larger cohorts and advanced monitoring techniques are needed to validate and expand upon these findings.

In conclusion, ROP examinations transiently affect physiological parameters in preterm infants due to both procedural pain and systemic drug effects. While most side effects are mild and self-limiting, careful monitoring, pain control, and protocol optimization are crucial. Educating caregivers about potential adverse effects may reduce parental anxiety and enhance infant safety.

Ethics Committee Approval: This study was designed in accordance with the Helsinki Principles and received ethical approval from the Ethics Committee of Umraniye Training and Research Hospital. (Date: 16.08.2012, decision no:2012-4). The permissions of the parents of the babies included in the study were obtained via written consent.

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