J Pediatr Res 2025;12(3):134-142
DOI: 10.4274/jpr.galenos.2025.03708

Original Article

Cerebral and Mesenteric Perfusion Changes Due to Mydriatic Use for Retinopathy of Prematurity by Near-Infrared Spectroscopy

Burçe Emine Dörtkardeşler[1], Fırat Ergin[2], Serhad Nalçacı[3], Özge Altun[2], Demet Terek[2], Mehmet Yalaz[2], Mete Akısü[2], Nilgün Kültürsay[2]

[1]Ege University Faculty of Medicine, Department of Pediatric, Division of General Pediatrics, İzmir, Türkiye
[2]Ege University Faculty of Medicine, Department of Pediatric, Division of Neonatology, İzmir, Türkiye
[3]Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye

ABSTRACT

Aim: Retinopathy of prematurity (ROP) screening requires pharmacologic pupil dilation, which may be associated with systemic side effects in preterm infants. This study aimed to evaluate the impact of low-dose mydriatic eye drops on cerebral and mesenteric tissue oxygenation using near-infrared spectroscopy (NIRS).

Materials and Methods: In this single-center prospective observational study, 30 preterm infants gestational age ≤32 weeks and/or birth weight ≤1,500 g) underwent 61 ROP examinations. A low-dose mydriatic protocol (0.625% phenylephrine and 0.25% tropicamide) was administered in two cycles. Regional oxygen saturation (rSO_2) was measured at multiple time points (from 15 minutes before to 48 hours after administration) at three sites: (rSO_2- cerebral right), (rSO_2-cerebral left), and mesenteric (rSO_2-M). Splanchnic-cerebral oxygenation ratios (SCOR-R and SCOR-L) were calculated. Clinical complications were recorded.

Results: Complications occurred in 13% of examinations, including apnea (6.5%) and feeding intolerance (9.8%), predominantly in infants with lower gestational age and primarily after the first examination. Overall temporal changes in NIRS parameters were minimal. However, in infants who developed complications, rSO_2-M and SCOR-R values were significantly lower during the first examination compared to the second (p=0.043 and p=0.044, respectively). rSO_2-M values below 70% and SCOR below 0.75 were noted within the first 6 hours post-medication, followed by recovery within 36-48 hours.

Conclusion: Low-dose mydriatic regimens appear to be safe in preterm infants, with minimal disturbances in cerebral and mesenteric oxygenation. Transient reductions in mesenteric perfusion parameters may help identify those infants at risk of gastrointestinal intolerance, supporting delayed refeeding after ROP screening. These findings support the use of NIRS for monitoring post-mydriatic effects and may contribute to safer ROP screening protocols in premature infants.

Keywords: Retinopathy of prematurity, mydriatics, near-infrared spectroscopy, premature infant, oxygen saturation

Corresponding Author
Burçe Emine Dörtkardeşler, MD, Ege University Faculty of Medicine, Department of Pediatric, Division of General Pediatrics, İzmir, Türkiye
E-mail: burceyasar@gmail.com **ORCID:** orcid.org/0000-0002-6212-9286
Received: 19.06.2025 **Accepted:** 05.09.2025 **Publication Date:** 03.10.2025

Cite this article as: Dörtkardeşler BE, Ergin E, Nalçacı S, et al. Cerebral and mesenteric perfusion changes due to mydriatic use for retinopathy of prematurity by near-infrared spectroscopy. J Pediatr Res. 2025;12(3):134-142

Introduction

Retinopathy of prematurity (ROP) remains one of the leading causes of preventable visual impairment in children (1,2). Initial screening, specifically a retinopathy of prematurity eye examination (ROPEE), must be conducted before discharge from a neonatal intensive care unit (NICU) with pre-examination local analgesia under close monitoring (3). The recommended medications for pupil dilation include 0.5-1% tropicamide or 0.5% cyclopentolate, followed by 2.5% phenylephrine, administered two or three times at five-minute intervals (4-6). Optimal pupil dilation is typically achieved 45-60 minutes after medication.

Mydriatic drops are associated with various systemic side effects including gastrointestinal and neurological disturbances (7-9). Additionally, necrotizing enterocolitis (NEC) may develop due to the systemic effects of mydriatic drops, potentially caused by disrupted intestinal perfusion and tissue hypoxia (10). The risk of systemic adverse effects is heightened with repeated administration due to increased dosage volume (11). A systematic review recently recommended the lowest effective regimen: Phenylephrine 1% combined with cyclopentolate 0.2% (12). However, we further reduced the dosage to 0.625% phenylephrine and 0.25% tropicamide following a previous incident of NEC in one of our patients who was treated at the recommended dosage (13).

Near-infrared spectroscopy (NIRS) is a non-invasive technique which measures regional oxygen saturation (rSO_2) to assess tissue blood flow. Studies suggest that NIRS can detect early-stage intestinal perfusion disorders, which are challenging to identify in the initial stages of NEC (14-18). This study aimed to investigate cerebral and mesenteric perfusion changes in premature infants receiving mydriatic drops for ROP screening using NIRS.

Materials and Methods

This single-center prospective observational study included 30 premature infants followed up in an NICU. Eligible participants had a gestational age (GA) ≤32 weeks and/or a birth weight (BW) ≤1,500 grams. NIRS measurements were performed during routine ROPEE. Demographic data were recorded for all cases. Ethical approval was obtained from the Ege University Faculty of Medicine, Clinical Research Ethics Committee (approval number: 15-11/15, date: 18.12.2015), and written informed consent was provided by the parents or legal guardians.

To minimize the risk of vomiting and aspiration, patients fasted for three hours prior to medication and received intravenous fluid replacement. Mydriatic drops (0.625% phenylephrine and 0.25% tropicamide) were administered to both eyes at one drop per cycle, five minutes apart. The first cycle was termed "Medication-one", and the second cycle, administered 15 minutes later, was termed "Medication-two". The eye examination, using 0.5% proparacaine for local anesthesia, was conducted 45 minutes after "Medication-two".

NIRS measurements were obtained using the Equanox 7600 device (Nonin Medical Inc., MN, USA). Probes were placed on the right and left frontal regions to record cerebral oxygenation [rSO_2-cerebral right (rSO_2-CR) and rSO2- cerebral left (rSO_2-CL)] and on the periumbilical region to measure mesenteric oxygenation [rSO_2-mesentery (rSO_2-M)]. Stabilization was ensured with five minutes of monitoring before data collection. Measurements were taken at predefined intervals: "Premed" (15 minutes before medication), "Med" (between "Medication-one" and "Medication-two"), "Postmed" (15 minutes after "Medication-two"), "Postexam" (15 minutes after the examination), and at the 3rd, 6th, 12th, 24th, 36th, and 48th hours after medication. The timeline of measurements and examinations is shown in Figure 1.

The splanchnic-cerebral oxygenation ratio (SCOR) was calculated as the ratio of mesenteric rSO_2 to cerebral rSO_2 (SCOR-R=rSO_2-M / rSO_2-CR; SCOR-L=rSO_2-M / rSO_2-CL). During NIRS measurements, heart rate (HR), blood pressure, oxygen saturation, and perfusion index were also recorded.

Statistical Analysis

Data analysis was performed using IBM SPSS 22.0 (IBM Corp., Armonk, NY, USA). NIRS measurements, SCOR values, and vital signs were evaluated for temporal changes at each interval. Repeated-measures ANOVA was used to analyze normally distributed variables, including rSO_2-M, SCOR-R, SCOR-L, HR, and blood pressure. Non-parametric variables, such as rSO_2-CR, rSO_2-CL, perfusion index, and oxygen saturation, were analyzed using the Brunner-Langer model (F1-LD-F1 design, R3.1.3, nparLD package). Post-hoc tests included the t-test for parametric data and the Mann-Whitney U test for non-parametric data, with Bonferroni correction applied to p-values from two-way comparisons. The Brunner-Langer model (F1-LD-F1 design) was selected because it accommodates repeated-measures data with non-normal distributions and allows robust analysis even when normality is inconsistent across time points.

Analyses were conducted separately for "ROPEEs with and without complications" and for "first versus repeated

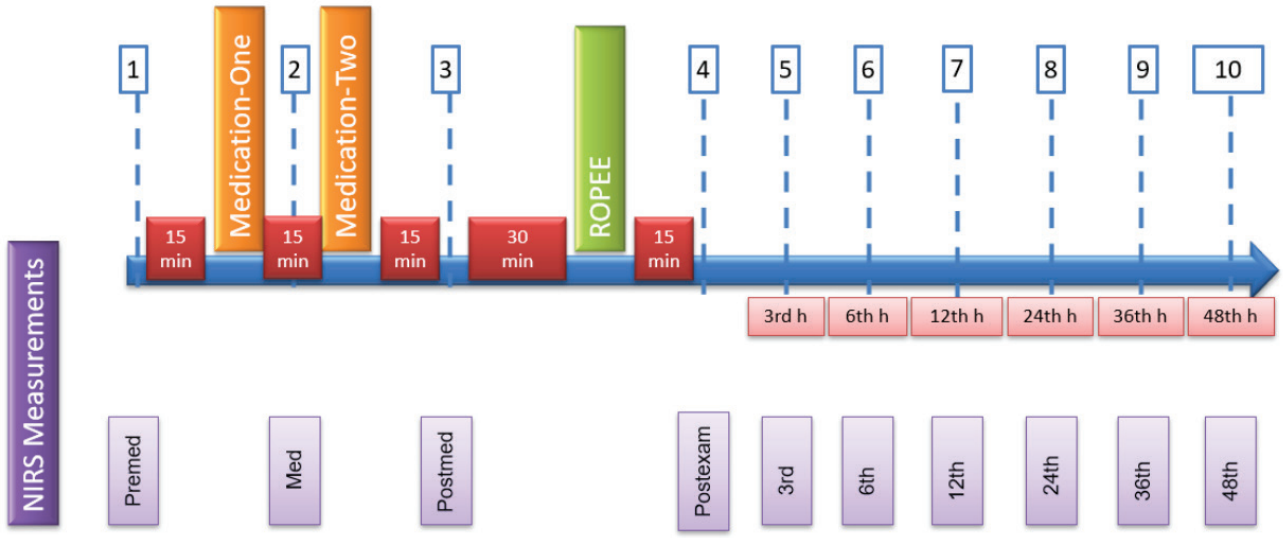

Figure 1. The timeline of NIRS (near-infrared spectroscopy) measurements and examination
ROPEE: Retinopathy of prematurity eye examination

ROPEEs". The Brunner-Langer model was used to assess temporal changes, as normality was not consistent across time points. Interactions between groups and temporal changes were also examined. Similar temporal patterns across groups were indicated by the absence of interaction effects. Finally, BW and GA differences between groups with and without complications were analyzed using Student's t-test. Statistical significance was defined as $p<0.05$.

Results

A total of 610 measurements were analyzed from 61 ROPEEs conducted on 30 premature infants. The median number of ROPEEs per patient was two (range: 1-6). The mean BW of the patients was 1,346.23±496.00 grams, and the mean GA was 29.40±2.52 weeks.

Complications occurred in six patients (20%, 6/30) following eight ROPEEs (13%, 8/61), all within the first 24 hours. Two patients experienced complications in two separate ROPEEs, and one patient had complications only during the second ROPEE. Apnea was observed in 6.5% (4/61) of ROPEEs, while feeding intolerance occurred in 9.8% (6/61). Complications began as early as the 6th hour post-ROPEE. In four of the eight cases, complications resolved within 24 hours, while in the remaining 4 cases, they persisted up to 48 hours. No complications extended beyond 48 hours.

Those infants with complications had a significantly lower GA (27.50±2.16 weeks) and lower BW (1,180.00±366.76 grams) compared to those without complications (GA 29.87±2.41 weeks, BW 1,387.79±521.48 grams). The difference in GA was statistically significant ($p=0.037$), but the difference in BW was not ($p=0.368$). Complications were more frequent during the first ROPEE (18.5%) than during repeated ROPEEs (8.8%), but this difference was not significant ($p=0.447$).

Vital signs, including HR, mean arterial pressure, perfusion index, and oxygen saturation, showed no significant temporal changes across all measurements ($p=0.471$, $p=0.413$, $p=0.095$, and $p=0.135$, respectively).

When assessing temporal changes in NIRS measurements (rSO_2-CR, rSO_2-CL, rSO_2-M, SCOR-R, and SCOR-L), a significant difference was identified only for rSO_2-CL ($p=0.007$) as shown in Figure 2 and Table I. Post-hoc analysis revealed significant differences between "Postmed" and "3rd hour" and between "Postmed" and "6th hour" measurements ($p=0.014$ and $p=0.002$, respectively) (Figure 2b). Median values and temporal change curves indicated an insignificant decline in rSO_2-CL between "Med" and "Postmed" ($p=0.112$).

Comparing patients with and without complications, HR values were significantly higher in the group with complications across all time points ($p=0.013$). However, no

temporal changes in HR were observed (p=0.644), as shown in Figure 3a. Temporal changes in rSO_2-CL were significant overall (p=0.012), with similar patterns in both groups, indicating no interaction (p=0.119). In the complications group, an insignificant decline in rSO_2-CL was observed between "Premed" and "Med" (median values: 76.00 vs. 74.50; p=0.081). Significant improvements in rSO_2-CL were identified when comparing "Med" vs. "12th hour", "Postmed"

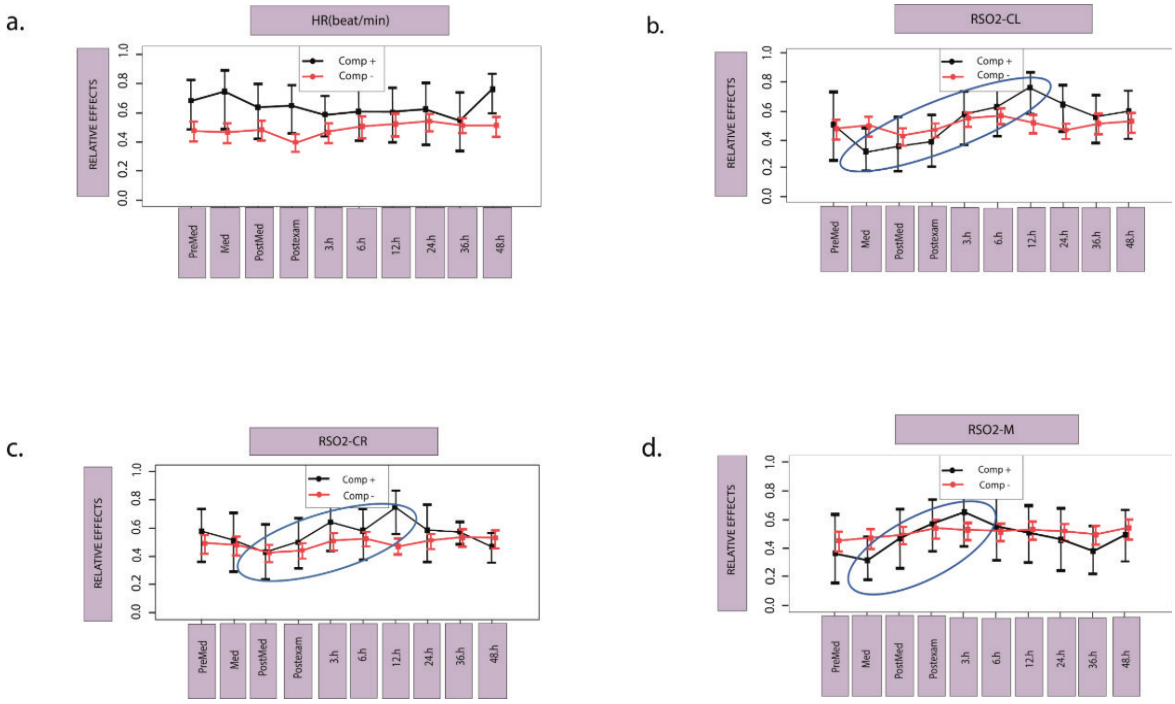

Figure 2. Temporal changes in rSO_2 (regional tissue saturation) values during the 48-hour follow-up: (a) rSO_2-CR (cerebral right), (b) rSO_2-CL (cerebral left), (c) rSO_2-M (mesenteric), (d) SCOR-R (splanchnic-cerebral oxygenation ratio using rSO2-CR), (e) SCOR-L (using rSO_2-CL)

Table I. Median, minimum, and maximum values of rSO_2-CR, rSO_2-CL, and mean value rSO_2-M, SCOR-R, and SCOR-L measurements

	rSO_2-CR	**rSO_2-CL**	**rSO_2-M**	**SCOR-R**	**SCOR-L**
Measurement time	**Median (Min-Max)**	**Median (Min-Max)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Premed	78.00 (24-91)	77.00 (63-93)	63.59 (±2.95)	0.84 (±0.21)	0.83 (±0.17)
Med	76.00 (30-100)	77.00 (52-90)	64.93 (±11.08)	0.85 (±0.18)	0.85 (±0.15)
Postmed	76.00 (28-93)	76.00 (54-90)	65.86 (±10.03)	0.88 (±0.17)	0.88 (±0.14)
Postexam	77.00 (57-86)	77.00 (54-88)	67.83 (±10.56)	0.89 (±0.14)	0.90 (±0.14)
3rd hour	78.00 (55-100)	78.00 (52-100)	67.85 (±11.03)	0.87 (±0.16)	0.87 (±0.15)
6th hour	78.00 (60-92)	79.00 (67-93)	67.33 (±9.89)	0.86 (±0.14)	0.86 (±0.13)
12th hour	78.00 (60-90)	77.00 (66-100)	66.96 (±9.62)	0.86 (±0.13)	0.85 (±0.13)
24th hour	78.00 (59-89)	77.00 (60-89)	66.36 (±9.97)	0.85 (±0.14)	0.87 (±0.14)
36th hour	79.00 (60-97)	77.00 (61-100)	65.70 (±8.93)	0.84 (±0.11)	0.84 (±0.12)
48th hour	78.00 (48-92)	78.00 (62-92)	67.22 (±10.17)	0.87 (±0.16)	0.87 (±0.14)
p-value	0.071	**0.007***	0.197	0.465	0.219

rSO_2-CR: Regional tissue saturation-cerebral right, rSO_2-CL: Regional tissue saturation-cerebral left, rSO_2-M: Regional tissue saturation-mesenteric, SCOR-R: Splanchnic-cerebral oxygenation rate-right, SCOR-L: Splanchnic-cerebral oxygenation rate-left, SD: Standard deviation
*p<0.05

vs. "6th hour", "Postmed" vs. "12th hour", and "Postexam" vs. "12th hour" (p=0.007, p=0.028, p=0.036, and p=0.021, respectively). Temporal change patterns for rSO_2-CR and rSO_2-M followed a similar trend, showing an initial decline followed by improvement, though these changes were not statistically significant (p=0.105 and p=0.240, respectively) (Figures 3c-d).

When comparing the first and second ROPEEs in patients with complications, five of the six patients with complications experienced them during the first ROPEE, while three patients experienced complications during the second ROPEE. Although the difference between first (18.5%) and repeated ROPEEs (8.8%) was not statistically significant, this higher frequency in the initial exams likely reflects lower GA at the time of screening. rSO_2-M, SCOR-R, and SCOR-L showed notable drops after the 6th hour during the first ROPEE, with recovery observed between the 24th and 36th hours as shown in Figure 4. These temporal changes were not statistically significant (p=0.338, p=0.397, and p=0.278, respectively). However, when comparing the first and second ROPEEs in infants with complications, significant between-group differences were observed for rSO_2-M and SCOR-R values (p=0.043 and p=0.044, respectively), as shown in Figure 4. No significant differences or temporal changes were found in rSO_2-CR and rSO_2-CL values between the first and second ROPEEs (p=0.314 and p=0.964 for group differences; p=0.628 and p=0.225 for temporal changes, respectively).

Discussion

This study was the first to evaluate the effects of mydriatic drops on mesenteric and cerebral oxygenation during ROPEE and 48 hours after ROPEE using NIRS and their associations with cerebral and gastrointestinal complications. Our findings suggest that monitoring cerebral and mesenteric oxygenation with NIRS in the early period after mydriatic drop administration may be beneficial in promptly detecting potential complications. Furthermore, the use of low-dose mydriatics, compared to the recommended doses, appears to result in a lower incidence of systemic side effects. These findings highlight the need to explore lower-dose protocols to enhance safety, particularly in preterm infants, and suggest that routine monitoring with NIRS after ROPEE could be incorporated into clinical practice.

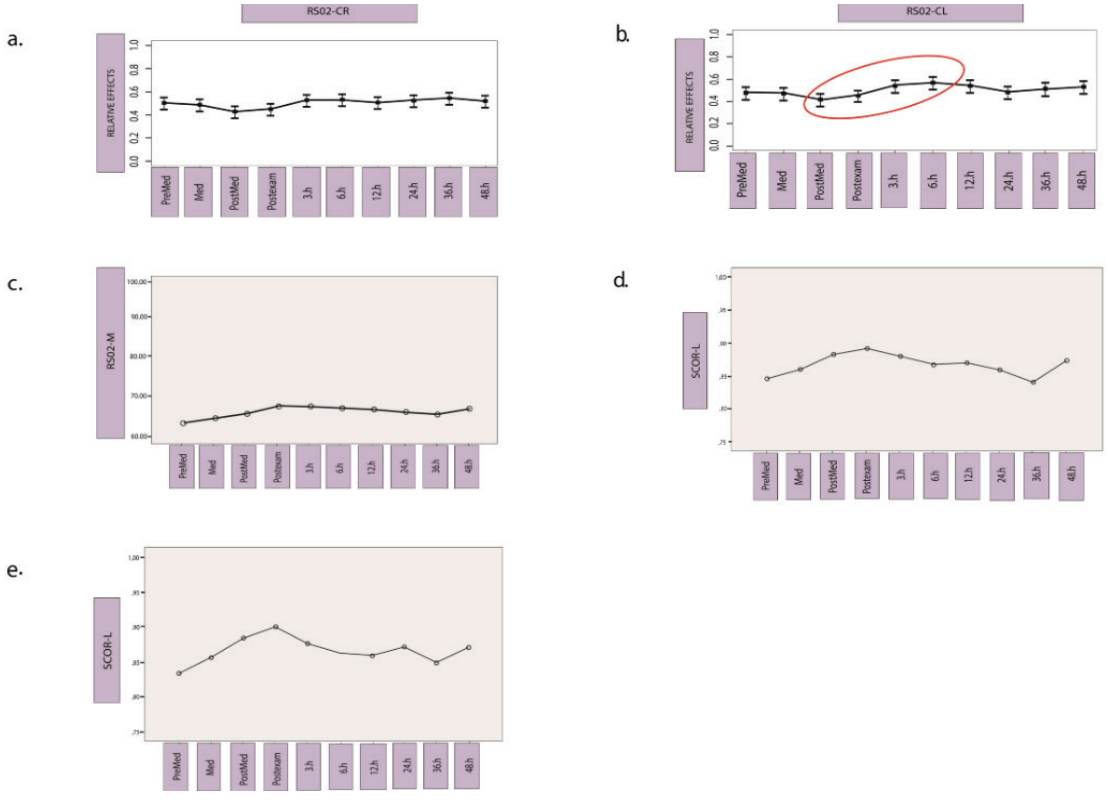

Figure 3. Comparison of patients with and without complications: (a) heart rate (HR), (b) rSO_2-CL, (c) rSO_2-CR, (d) rSO_2-M over time

Previous studies have identified apnea as a common adverse effect following ROPEE (19-21). Among non-mechanically ventilated patients, the incidence of apnea was reported as being 11.7% within the first 24 hours and 23.5% between 24 to 48 hours after ROPEE (22). In contrast, the rates observed in this study were notably lower, at 6.5% (4/61) and 4.9% (3/61), respectively. This reduction in apnea incidence may be attributed to the use of mydriatic drops at lower concentrations in the present study.

Another set of complications identified following ROPEE involves the gastrointestinal system, including temporary paralytic ileus and feeding intolerance (23-25). Hermansen and Sullivan (26) reported abdominal distention in 12% of cases and increased gastric residual volume in 16% after using 2.5% phenylephrine and 0.5% cyclopentolate. In our observations, feeding intolerance was the most frequently noted gastrointestinal adverse effect, occurring in 9.8% of cases. Notably, feeding intolerance is considered a precursor to NEC, one of the most severe complications associated with ROPEE (13,27). However, none of our patients developed NEC.

Siu et al. (28) reported on cases of NEC in two out of three 27-week triplets who had received 2.5% phenylephrine and 0.5% cyclopentolate for pupil dilation. While both initially improved with supportive care, one was seen to have developed severe bradycardia and apnea at a follow-up examination and subsequently died due to NEC. This case raised concerns regarding systemic risks associated due to repeated mydriatic use. In contrast, our study observed more complications during the first ROPEEs, likely due to the lower gestational ages at the time of screening.

A previous report suggested that adverse effects following ROPEE may be mediated via the oculocardiac reflex (29). However, in our study, we considered the complications unlikely to be attributable to the ROPEE itself, as the earliest events occurred six hours after mydriatic administration (i.e., five hours post-examination).

Increases in cerebral blood flow are typically associated with elevated cerebral oxygenation values, whereas disruptions in cerebral perfusion, such as those caused by hypotension or apnea, are reflected by decreases in cerebral rSO_2 values (30-32). In our analysis of 61 ROPEEs, significant temporal changes were observed only in rSO_2-CL values. Specifically, the median rSO_2-CL values showed a non-significant decline between the "Med" and "Postmed" time points, potentially indicating a transient reduction in cerebral perfusion due to medication. This was followed by a significant increase between "Postmed" and both the 3rd and 6th hour measurements. This trend may suggest a compensatory cerebrovascular autoregulatory response. While these changes did not reach pathological thresholds, they likely reflect intact cerebrovascular autoregulation. These compensatory increases highlight the resilience of cerebral perfusion following pharmacologic pupil dilation, and reinforce the importance of interpreting statistically significant changes in the context of their clinical impact.

The association between NEC and mesenteric NIRS measurements indicative of intestinal ischemia has been previously reported on (14,33). A 2014 study demonstrated that mesenteric rSO_2 values in infants with NEC (70.7% ±19.1) were significantly lower than in those without NEC, and that rSO_2 values below 56% were associated with a 14-fold increased risk of developing NEC (34). In contrast, in our study, rSO_2-M values remained stable in both patients with and without complications, which may be attributable to the use of a lower-dose mydriatic regimen.

During hypoxic-ischemic events, blood is redistributed from the mesenteric circulation to the brain. Accordingly, the SCOR, calculated by dividing mesenteric NIRS values by cerebral NIRS values, serves as a useful indicator of mesenteric ischemia (35). Stapleton et al. (33) observed a decrease in both mesenteric NIRS and SCOR values during NEC with recovery-associated increases in a term infant with congenital heart disease. Similarly, Fortune et al. (15) reported a significantly lower median SCOR value of 0.66 in those infants with acute abdominal pathology compared to 0.96 in healthy controls. A SCOR value below 0.75 was considered indicative of intestinal ischemia, while values above 0.96 were regarded as safe. That study also reported a 90% sensitivity for SCOR in detecting intestinal ischemia.

In the temporal changes analysis of NIRS data from the first and second ROPEEs in the six patients who experienced complications, statistically significant differences were observed in rSO_2-M and SCOR-R values. Although SCOR-L followed a similar trend, the difference was not statistically significant. These findings indicate that rSO_2-M, SCOR-R, and SCOR-L values were lower during the first ROPEE. Notably, during the first ROPEE, the decline in rSO_2-M and SCOR values began after the "Postexam" time point and became more pronounced at the 6th hour measurement, with values falling below 70% and 0.75, respectively (Table II and Figure 4). Recovery in these parameters was observed after the 36th hour measurement. Although overall temporal changes in rSO_2-M and SCOR values were minimal across the entire cohort, the transient reductions below 70% and 0.75 within the first 6 hours in those infants who

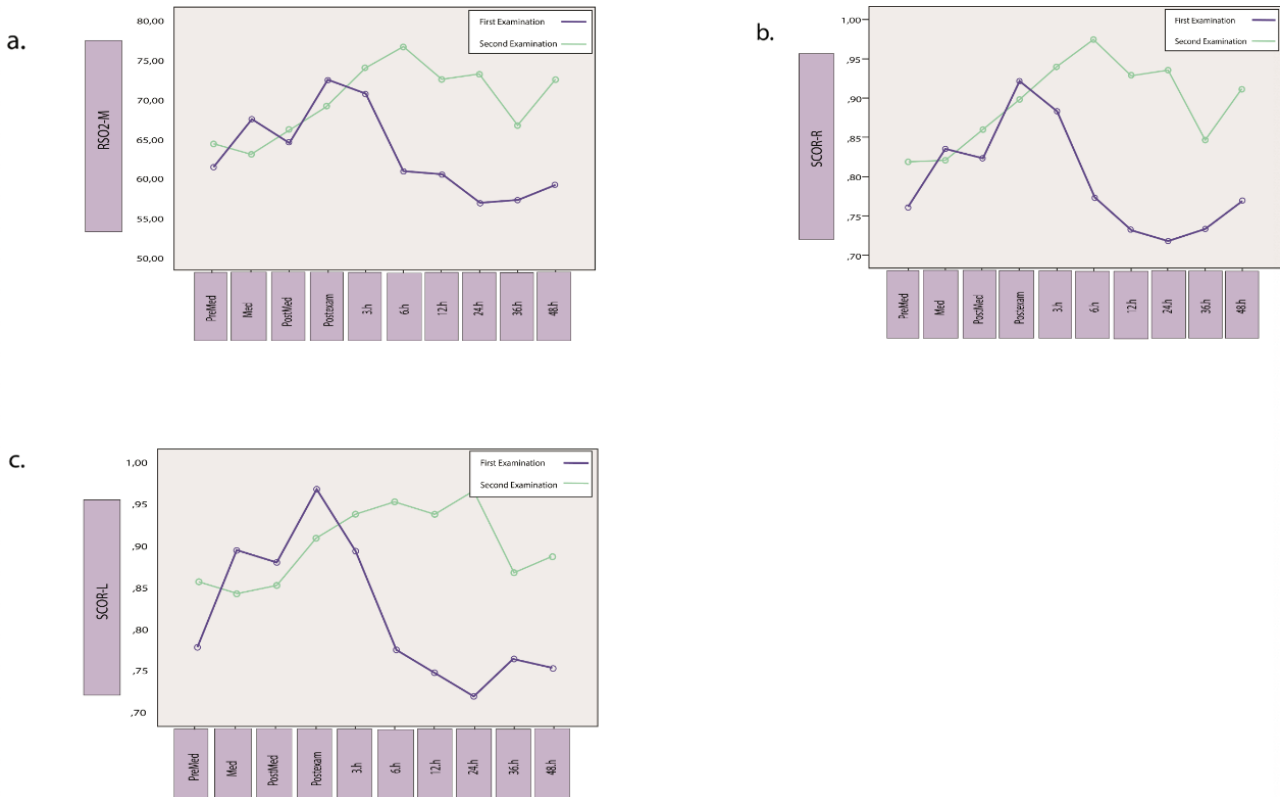

Figure 4. Temporal changes in mesenteric perfusion parameters in the six patients with complications, comparing first and second ROPEEs: (a) rSO_2-M, (b) SCOR-R, (c) SCOR-L
ROPEE: Retinopathy of prematurity eye examination, rSO_2-M: Regional tissue saturation-mesenteric, SCOR-R: Splanchnic-cerebral oxygenation rate-right, SCOR-L: Splanchnic-cerebral oxygenation rate-left

Table II. Mean (SD) values of rSO_2-M, SCOR-R, and SCOR-L from first and second ROPEEs for the six patients with complications

	rSO_2-M Mean (SD)		**SCOR-R Mean (SD)**		**SCOR-L Mean (SD)**	
Measurement time	**First examination**	**Second examination**	**First examination**	**Second examination**	**First examination**	**Second examination**
Premed	61.33 (±10.72)	64.33 (±5.52)	0.76 (±0.12)	0.81 (±0.07)	0.77 (±0.13)	0.85 (±0.07)
Med	67.50 (±5.89)	63.00 (±3.86)	0.83 (±0.05)	0.82 (±0.05)	0.89 (±0.07)	0.84 (±0.04)
Postmed	64.50 (±7.56)	66.16 (±2.40)	0.82 (±0.09)	0.86 (±0.02)	0.88 (±0.09)	0.85 (±0.02)
Postexam	72.50 (±5.09)	69.16 (±3.24)	0.92 (±0.07)	0.89 (±0.04)	0.96 (±0.07)	0.90 (±0.03)
3rd hour	70.66 (±5.17)	74.00 (±3.33)	0.88 (±0.08)	0.94 (±0.05)	0.89 (±0.08)	0.93 (±0.02)
6th hour	60.83 (±2.58)	76.66 (±4.57)	0.77 (±0.05)	0.97 (±0.05)	0.77 (±0.05)	0.95 (±0.05)
12th hour	60.50 (±2.69)	72.50 (±3.41)	0.73 (±0.02)	0.92 (±0.04)	0.74 (±0.03)	0.93 (±0.06)
24th hour	56.83 (±3.42)	73.16 (±3.40)	0.71 (±0.03)	0.93 (±0.05)	0.71 (±0.03)	0.96 (±0.07)
36th hour	57.16 (±3.98)	66.66 (±4.02)	0.73 (±0.04)	0.84 (±0.05)	0.76 (±0.05)	0.86 (±0.06)
48th hour	59.16 (±4.65)	72.50 (±2.14)	0.77 (±0.05)	0.91 (±0.03)	0.75 (±0.05)	0.88 (±0.02)
p-value	**0.043***		**0.044***		0.114	

rSO_2-M: Regional tissue saturation-mesenteric, SCOR-R: Splanchnic-cerebral oxygenation rate-right, SCOR-L: Splanchnic-cerebral oxygenation rate-left, SD: Standard deviation
*p<0.05

developed complications may represent clinically relevant early warning indicators of gastrointestinal compromise. These results support the notion that SCOR values below 0.75 and rSO_2-M values below 70% may guide clinicians to delay enteral feeding after ROP screening, in line with the prior findings by Fortune et al. (15) and Patel et al. (34).

Few studies have investigated the effects of mydriatic eye drops used during ROP screening on neonatal tissue oxygenation using NIRS. In one study involving 26 infants, two measurements were taken before and after mydriatic administration in order to assess early hemodynamic effects, with no significant changes reported in vital signs or NIRS parameters (36). Another study, which included 62 infants, performed four cerebral NIRS measurements at baseline, 15-30 minutes, 30-60 minutes, and beyond, revealing a significant decline in oxygenation during the latter two-time intervals (37). In contrast, our study is the first to extend NIRS monitoring up to 48 hours post-administration, enabling the evaluation of both the immediate and delayed effects of mydriatic drops on cerebral and mesenteric perfusion.

This study's strengths include all NIRS measurements being performed by the same investigator and the consistent execution of all ROPEEs by the same experienced ophthalmologist, which enhanced measurement reliability. Additionally, this study had extended post-examination monitoring for up to 48 hours following mydriatic administration, offering valuable insight into the short-term temporal course of perfusion changes. The single-center nature and the relatively small sample size of this study limit the statistical power and external validity of our findings. A small cohort increased the risk of type II error, meaning that clinically relevant effects may not have reached statistical significance. Furthermore, rare adverse events such as NEC might not have been detected due to the limited sample size. While the observed trends were clinically relevant, multicenter studies with larger cohorts are warranted in order to validate and generalize these results.

Another limitation was the absence of a control group (e.g., infants receiving standard or higher-dose mydriatic regimens). Our observational design precluded definitive causal inference regarding the safety and efficacy of the low-dose protocol compared to standard practice.

Conclusion

Our findings suggest that low-dose mydriatic protocols cause minimal disruption to cerebral and mesenteric oxygenation in preterm infants. However, transient reductions in rSO_2-M and SCOR observed within the first 6 hours post-administration may serve as early indicators of gastrointestinal intolerance. These results support the implementation of extended NIRS monitoring and cautious refeeding strategies after ROP screening, particularly in those infants with lower gestational ages.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ege University Faculty of Medicine, Clinical Research Ethics Committee (approval number: 15-11/15, date: 18.12.2015).

Informed Consent: Written informed consent was provided by the parents or legal guardians of the participants.

Acknowledgement: We want to thank the "Statistics Department of Ege University", especially Prof. Dr. Mehmet Orman and Semiha Özgül, for contributing to the statistical analysis of this study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.E.D., F.E., S.N., N.K., Concept: B.E.D., S.N., Ö.A., D.T., M.Y., M.A., N.K., Design: B.E.D., Ö.A., D.T., M.Y., M.A., N.K., Data Collection or Processing: B.E.D., F.E., Ö.A., D.T., Analysis or Interpretation: B.E.D., F.E., Ö.A., D.T., N.K., Literature Search: B.E.D., F.E., S.N., Ö.A., D.T., M.Y., M.A., N.K., Writing: B.E.D., F.E., S.N., Ö.A., D.T., M.Y., M.A., N.K.

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

Financial Disclosure: The authors received no financial support for the research, authorship, and/or publication of this article.

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