# Effect of mydriatic administration on cerebral haemodynamics and oxygenation in preterm infants

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Editor,

Retinopathy of prematurity (ROP) is a retinal disorder of preterm neonates and a potential cause of blindness. As early diagnosis and treatment preserve vision, very low birth weight infants must be screened for ROP. Mydriatic eye drops administration is essential to perform funduscopic evaluations. Previous studies showed that mydriatics may cause apnoea, oxygen desaturation, arrhythmias, seizures, increase in blood pressure and heart rate (Bolt et al. 1992; Taketomo et al. 2012). Cerebral blood flow autoregulation depends in part on the adrenergic and cholinergic control of cerebral vasculature (Hamner et al. 2012), but whether mydriatics have an effect on cerebral haemodynamics is unknown.

The aim of the study was to investigate the effect of mydriatics on cerebral haemodynamics and oxygenation during ROP screening in preterm infants, by near-infrared spectroscopy (NIRS). We tested the hypothesis that the currently used protocol would not adversely affect cerebral haemodynamics.

The Institutional Committee for Bioethics approved the study and guidelines of the Helsinki Declaration were followed. Written informed consent was obtained from parents. Based on a preliminary study, a minimum sample size of 23 measurements was needed to obtain a significant variation in cerebral oxygenation (±5%, $p < 0.05$), with 80% statistical power. We performed 25 measurements in 15 newborns (mean gestational age: 29 ± 2 weeks, range: 25–32 weeks; mean birthweight: 1128 ± 236 g, range: 631–1598 g) needing pupillary dilatation for ROP screening.

Three drops of aqueous phenylephrine 2.5% and tropicamide 0.5% were instilled in each eye, with a 10-min interval between drops. No pressure was applied on the lacrimal sac. Cerebral haemodynamics and oxygenation during mydriatic administration were continuously monitored by NIRS (Hamamatsu Photonics, Hamamatsu City, Japan). A single probe with a 3 cm distance between near-infrared light emitter and detector was used. Reflected light was sampled once every second.

Near-infrared spectroscopy (NIRS) estimates changes in the concentration of oxy-haemoglobin ($HbO_2$) and deoxy-haemoglobin (Hbb) in units of micromoles per litre ($\mu$M/l), using the modified Beer-Lambert law. Total haemoglobin (HbTot) is derived as the sum of $HbO_2$ and Hbb. $HbO_2$ and HbTot were considered as estimates of cerebral blood flow and cerebral blood volume, respectively (Meek 2002). Cerebral tissue oxygenation index (CTOI) is also measured, using the spatially resolved spectroscopy method.

Since seven patients were monitored more than one time, variations of $HbO_2$, Hbb, HbTot and CTOI, during mydriatic administration, were analyzed by one-way blocked ANOVA, with random blocks (each participant/one block). Four periods were considered for statistical analysis: one minute before the first instillation, 10 min after the first instillation, 10 min after the second instillation and 10 min after the third instillation.

Statistical analysis showed that $HbO_2$ ($F_{(3,30)} = 1.132$; $p = 0.352$), Hbb ($F_{(3,30)} = 0.661$; $p = 0.582$), HbTot ($F_{(3,30)} = 0.796$; $p = 0.506$) and CTOI ($F_{(3,30)} = 0.084$; $p = 0.968$) did not change during mydriatic eye drops

**Table 1.** One-way blocked ANOVA results

| Measured variable | Baseline† (Mean ± SD) | 1st instillation‡ (Mean ± SD) | 2nd instillation§ (Mean ± SD) | 3rd instillation¶ (Mean ± SD) | Mydriatic administration effect | Interaction between blocks and mydriatic administration |
|---|---|---|---|---|---|---|
| $HbO_2$ ($\mu$M/l) | 0.48 ± 3.46 | 1.57 ± 8.37 | 2.98 ± 10.13 | 4.33 ± 10.24 | $F_{(3,30)} = 1.132$; $p = 0.352$ | $F_{(42,30)} = 1.144$; $p = 0.354$ |
| Hbb ($\mu$M/l) | −0.56 ± 4.56 | −0.10 ± 9.93 | 2.33 ± 11.39 | 1.64 ± 10.66 | $F_{(3,30)} = 0.661$; $p = 0.582$ | $F_{(42,30)} = 1.341$; $p = 0.202$ |
| HbTot ($\mu$M/l) | −0.08 ± 7.61 | 1.47 ± 17.99 | 5.31 ± 21.05 | 5.97 ± 20.43 | $F_{(3,30)} = 0.796$; $p = 0.506$ | $F_{(42,30)} = 1.250$; $p = 0.264$ |
| CTOI (%) | 67 ± 8 | 67 ± 6 | 66 ± 7 | 66 ± 6 | $F_{(3,30)} = 0.084$; $p = 0.968$ | $F_{(42,30)} = 0.737$; $p = 0.821$ |
| HR (bpm) | 147 ± 20 | 154 ± 19 | 147 ± 20 | 148 ± 20 | $F_{(3,30)} = 1.302$; $p = 0.292$ | $F_{(42,30)} = 0.084$; $p = 0.968$ |
| $SatO_2$ (%) | 97 ± 3 | 98 ± 2 | 96 ± 5 | 96 ± 5 | $F_{(3,30)} = 1.116$; $p = 0.358$ | $F_{(42,30)} = 1.419$; $p = 0.159$ |

bpm = beats per minute, CTOI = cerebral tissue oxygenation index, Hbb = deoxy-haemoglobin, $HbO_2$ = oxy-haemoglobin, HbTot = total haemoglobin, HR = heart rate, $SatO_2$ = peripheral oxygen saturation, $\mu$M/l = micromoles per litre.
†One minute before the first instillation.
‡Ten minutes after the first instillation.
§Ten minutes after the second instillation.
¶Ten minutes after the third instillation.

administration (see Table 1). Interaction between blocks and mydriatic administration was not significant. Adequate pupillary dilatation was always achieved. Three infants showed a self-resolving apnoea episode after drops administration.

Mydriatics are routinely used to screen preterm infants for ROP. Several combinations and doses have been used. Although generally safe, mydriatics can occasionally cause systemic side effects in preterm infants (Bolt et al. 1992; Khoo et al. 2000). Although cerebral oxygenation and blood flow are regulated by sympathetic and cholinergic mechanisms, we found no detectable changes associated with administration of phenylephrine 2.5% and tropicamide 0.5%.

Main study limitations were the small sample size and the relatively short monitoring time. We conclude that the current protocol for ROP screening was not associated with measurable side effects on preterm cerebral haemodynamics, as assessed by NIRS.

## References


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# *In vitro* evaluation of the antibacterial activity of Fluorescein® 0.5% eye drops


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Editor,

In patients with a severe corneal abscess (CA), a microbiological sample is usually taken to identify the causative microbe and adapt local antibiotic therapy. The frequency of positive CA cultures ranges from 21% to 81% according to various studies (Ancele et al. 2009; Darugar et al. 2011). Increasing the culture positivity rate is therefore key to improving the management of patients with CA. Several studies have shown the antibacterial activity of local anaesthetics used in ophthalmology, with the risk of a negative culture being produced (Labetoulle et al. 2002; Pelosini et al. 2009). However, there have been no studies looking at the antibacterial activity of Fluorescein®, despite the fact that it is used in clinical practice to diagnose CA.

The objective of our study was to carry out an *in vitro* evaluation of the antibacterial activity of Fluorescein® 0.5% and the main anaesthetic eye drops used in clinical practice.

The main microbes found in cases of CA were tested using clinical isolates: *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Moraxella lacunata*, *Moraxella catarrhalis*, *Serratia marcescens* and *Corynebacterium macginleyi*. The following eye drops were tested: Fluorescein® 0.5%, Oxybuprocaine® 0.4% and Tetracaine® 1% (Fluorescein Faure® single-dose 0.5% from SERB, Oxybuprocaine Hydrochloride® single-dose from THEA and Tetracaine® single-dose 1% from THEA). Minimum inhibitory concentration (MIC) determination was performed in a 96-well plate by microdilution in a liquid growth medium, following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. For increased reliability, the tests were performed three times.

We showed antibacterial activity from Fluorescein® on *Moraxella* Gram-negative cocci (*M. catarrhalis* and *M. lacunata*). The MIC for *M. lacunata* was 625 mg/l (1/8 dilution) and 1250 mg/l (1/4 dilution) for *M. catarrhalis*. No antibacterial activity was shown on the other microbes (MIC > 2500 mg/l). We observed no

**Table 1.** Minimum inhibitory concentration (MIC) results (mg/l) obtained for each of the microbes tested

| | MIC (mg/l) | | | | |
|---|---|---|---|---|---|
| | F 5000 | O 4000 | T 10 000 | F/O 5000/4000 | F/T 5000/10 000 |
| *S. aureus* | >2500 | 2000 | 625 | 1250/1000 | 625/1250 |
| *S. epidermidis* | >2500 | 2000 | 625 | 1250/1000 | 312/625 |
| *S. pneumoniae* | >2500 | 1000 | 625 | 625/500 | 312/625 |
| *C. macginleyi* | >2500 | 500 | 312 | 312/250 | 156/312 |
| *M. lacunata* | 625 | 500 | 625 | 625/500 | 312/625 |
| *M. catarrhalis* | 1250 | 250 | 312 | 312/250 | 156/312 |
| *P. aeruginosa* | >2500 | >2000 | 2500 | >(1250/1000) | >(1250/2500) |
| *S. marcescens* | >2500 | >2000 | 1250 | >(1250/1000) | >(1250/2500) |

F = Fluorescein® 0.5%, F/O = Fluorescein® 0.5% and Oxybuprocaine® 0.4%, F/T = Fluorescein® 0.5% and Tetracaine® 1%, O = Oxybuprocaine® 0.4%, T = Tetracaine® 1%.