Combination of 5% phenylephrine and 0.5% tropicamide eyedrops for pupil dilation in neonates is twice as effective as 0.5% tropicamide eyedrops alone

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ABSTRACT.

Purpose: Comparison of the efficacy of tropicamide eyedrops to the combination of 0.5% tropicamide and 5% phenylephrine eyedrops in order to achieve a proper dilation in premature infants undergoing screening for retinopathy of prematurity.

Methods: A prospective, randomized, double-blind study was conducted to compare the efficacy of two mydriatic regimens: one regimen consisting of three drops of 0.5% tropicamide (TTT regimen), the other regimen consisting of one drop of 5% phenylephrine and two drops of 0.5% tropicamide (PTT regimen). Thirty premature infants were enrolled and received both mydriatic regimens: one regimen in each eye. Outcomes were pupil dilation evaluated by the percentage of pupil diameter over cornea diameter, the percentage of pupil surface over cornea surface and the quality of the eye fundus examination.

Results: The percentage of pupil diameter over cornea diameter was 47.3% (±8.7) with the TTT regimen and 65.9% (±8.8) with the PTT regimen (p < 0.0001). The percentage of pupil surface over cornea surface was 23.1% (±8.3) with the TTT regimen and 43.8% (±7.3) with the PTT regimen (p < 0.0001). Thus, the pupil surface area was 1.9 times greater with the PTT than with the TTT regimen. Visualization of the retinal periphery was possible for 30 of 30 eyes dilated with the PTT regimen and for 16 of 30 eyes dilated with the TTT regimen (p < 0.0001).

Conclusion: The dilated pupil surface area for the combination of 5% phenylephrine and 0.5% tropicamide was almost twice that for 0.5% tropicamide eyedrops alone and provided significantly superior quality of the eye fundus examination.

Key words: mydriatic regimen – phenylephrine – pupil dilation – retinopathy of prematurity – tropicamide

Introduction

Retinopathy of prematurity (ROP) is a vision-threatening disease closely associated with prematurity and low birth-weight (Good et al. 2005). The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (Palmer et al. 2005) and the Early Treatment for Retinopathy of Prematurity Randomized Trial (Early Treatment for Retinopathy of Prematurity Cooperative Group 2003) have demonstrated the efficacy of early treatment for prethreshold and threshold stages in reducing unfavourable structural and visual outcomes. Retinopathy of prematurity (ROP) screening is therefore essential and is based on regular eye fundus examinations (EFE) using a timely schedule recently revisited by the American Academy of Pediatrics, and the American Academy of Ophthalmology and Certified Orthoptists (Fierson et al. 2013). Achieving proper pupil dilation is essential to perform reliable EFEs. Recent studies have shown that there is still no consensus about the drugs, the concentration, the number of drops and the way to use them in order to achieve proper dilation in all cases (Patel et al. 2004).

It has long been suggested that the combination of sympathomimetic and parasympatholytic eyedrops resulted in
greater mydriasis (Carpel & Kalina 1973; Caputo & Schnitzer 1978; Fleck et al. 1994). Phenylephrine, a sympathomimetic drug, stimulates the iris dilator muscle whereas parasympatholytic drugs such as tropicamide, cyclopentolate or atropine inhibit the iris constrictor muscle (Martindale 2009). Therefore, an ideal dilation regimen should probably combine both sympathomimetic and parasympatholytic eyedrops. Among parasympatholytic drugs, cyclopentolate has central nervous system and gastrointestinal side-effects, especially in younger patients (Bauer et al. 1973; Isenberg et al. 1985; Lim et al. 2003) and atropine has potential cardiovascular, neurological and gastrointestinal side-effects (Kounis 1974; Harel et al. 1985; Wright 1992; Baron-Janaillac et al. 2011; Princelle et al. 2013). Tropicamide appears to be the safest parasympatholytic drug available. In France, 5% phenylephrine was at the time of this study the only commercially available sympathomimetic drug that can be used to achieve pupil dilation for ROP screening. Given the side-effects reported under general anaesthesia (Baldwin & Morley 2002; Sbaraglia et al. 2014), however, and with concentrations higher than 5% (Borromeo-McGrail et al. 1973), phenylephrine is sometimes used hesitantly.

We wanted to assess the efficacy of the combination of 5% phenylephrine and 0.5% tropicamide eyedrops. We therefore performed a prospective, double-blind, randomized study that compared the pupil dilation achieved with one drop of 5% phenylephrine and two drops of 0.5% tropicamide to that achieved with three drops of 0.5% tropicamide.

Subjects and Methods

Study design

This prospective, double-blind, randomized study was performed in the neonatology intensive care unit of Caen University Hospital. This study was conducted with the highest respect for the participants, the 1964 Declaration of Helsinki and ethical principles. A written information document was given to the parents about the protocol and their informed consent was obtained. A previous limited study (Lux personal communications) was conducted to determine the necessary number of patients to be included.

Study population

Thirty premature infants weighing 1500 grams or less and/or with a gestational age of 30 weeks or less were enrolled. For each infant, we recorded the sex, colour of iris pigmentation (classified in two groups – dark or light), birthweight, gestational age and postmenstrual age at examination. Their main characteristics are presented in Table 1. Infants with any congenital eye condition were excluded.

Study proceedings

We compared two mydriatic regimens. The TTT regimen (tropicamide-tropicamide-tropicamide) consisted of three drops of 0.5% tropicamide with a 5-min interval between each application. The PTT regimen (phenylephrine-tropicamide-tropicamide) consisted of one drop of 5% phenylephrine followed by two drops of 0.5% tropicamide with a 5-min interval between each application. Each infant received both mydriatic regimens: one regimen in one eye and the other regimen in the other eye. The side in which each regimen was applied was allocated manually for each infant by randomization with a 5-min interval between each application. We compared the pupil dilation achieved with three drops of 0.5% tropicamide to that achieved with two drops of 0.5% phenylephrine.

Table 1. Demographic data.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (57)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (43)</td>
</tr>
<tr>
<td>Iris pigmentation</td>
<td></td>
</tr>
<tr>
<td>Dark</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Light</td>
<td>28 (93)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td></td>
</tr>
<tr>
<td>&lt;26</td>
<td>6 (20)</td>
</tr>
<tr>
<td>26–30</td>
<td>15 (50)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Birthweight (grams)</td>
<td></td>
</tr>
<tr>
<td>&lt;750</td>
<td>6 (20)</td>
</tr>
<tr>
<td>751–1000</td>
<td>10 (33)</td>
</tr>
<tr>
<td>1001–1250</td>
<td>6 (20)</td>
</tr>
<tr>
<td>1251–1500</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Postmenstrual age (weeks + days)</td>
<td></td>
</tr>
<tr>
<td>&lt;34</td>
<td>8 (27)</td>
</tr>
<tr>
<td>34–36</td>
<td>12 (40)</td>
</tr>
<tr>
<td>36 + 1 to 38</td>
<td>6 (20)</td>
</tr>
<tr>
<td>&gt;38</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

between 30 and 90 min prior to the eye fundus examination (EFE). After placing a paediatric lid speculum, the eye fundus was performed with a binocular indirect ophthalmoscope and a 20-dioptre condensing lens by an ophthalmologist specially trained in the evaluation of the retinal periphery of premature infants, who was unaware of the side to which each regimen had been applied. All infants were hospitalized in neonatology intensive care and then monitored for pulse rate, blood pressure, oxygen saturation and respiratory frequency. The result of the EFE was recorded by the operator using the international ROP classification (Section on Ophthalmology American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus 2006). The quality of peripheral retinal visualization during fundus examinations was rated by the same experienced ROP screening operator as follows: good, if retinal visualization including periphery was possible; difficult, if retinal periphery examination required additional time or adjustments; impossible, if retinal periphery examination was impossible. Just after completing the fundus examination, a video (in ‘.mov’ format) was shot on each side with a digital camera (Panasonic HDC-SD800, Kadoma, Osaka, Japan) at a distance of 5 cm from the eye, with the camera’s built-in lamp on. At a distance of 5 cm, the illuminance of this lamp is 2600 lux (measurement with the ‘CHY 630’ luxmeter, IDDM+, Muraux, France). An image (in ‘.pct’ format) was extracted from each video using QuickTime Player 7 version 7.6.6 software (Apple, Cupertino, CA). Using Adobe Photoshop Elements 8 software (Adobe Systems, San José, CA), the cornea was delineated with a 1-mm margin and the zone external to the cornea filled in black. Doing so made it possible to anonymize each image and remove the conjunctival hue. At the end of the study, all photographs were compiled and presented at random to two independent readers. Using the line tool of version 14.4.6 of Microsoft Power Point 2011 software (Redmond, WA, USA), the readers measured the pupil diameter (PD) and the cornea diameter (CD). The final measurement was the mean of the two measurements taken by the two readers.
Statistical analyses

The pupil diameter over cornea diameter (PD/CD) percentage was given with mean ± standard deviation (SD). The difference of the PD/CD percentage between the PTT and the TTT regimens and its variance were calculated. We used a paired $t$-test to assess whether the PD/CD percentage yielded using both regimens differed.

On the assumption that the pupil surface (PS) and cornea surface (CS) could be equated to a circle surface, we calculated the PS over CS percentage (PS/CS). We used a paired $t$-test to assess whether the PS/CS percentage yielded using both regimens differed.

We used an unpaired $t$-test to assess whether the difference of the pupil diameter over cornea diameter differed between the light iris and dark iris groups. The correlation between the PD/CD percentage and the time separating eyedrop application and the examination of the eye fundus was assessed using a linear regression with a 95% confidence interval. The same method was used to assess the correlation between the PD/CD percentage and the postmenstrual age at examination. We used a paired $t$-test to assess whether the difference of the PD/CD percentages between the two regimens as measured by the two readers differed.

We also used a paired $t$-test to assess whether the PD/CD percentages of the good and difficult groups defined according to the quality of the eye fundus differed significantly. Values of $p < 0.0001$ were considered significant.

Prism 5 software (GraphPad 2007, La Jolla, CA) was used for all these statistical analyses.

Results

The PTT regimen was instilled on the right side for 19 of 30 patients.

Pupillary Diameter over Cornea Diameter (PD/CD)

The PD/CD percentage with the TTT regimen was $47.3 \pm 8.7\%$, varying from 27.3 to 63.7%. The PD/CD percentage with the PTT regimen was $65.9 \pm 8.8\%$, varying from 49.4 to 74.5%. This difference was statistically significant ($p < 0.0001$, paired $t$-test, 95% confidence interval: $15.57 \pm 21.78$) (Fig. 1); the combination of 5% phenylephrine and 0.5% tropicamide yielded a PD/CD percentage with a value 1.4 times that of 0.5% tropicamide alone. The PD/CD percentage value was greater for each patient with the PTT regimen than with the TTT regimen. The difference of the PD/CD percentage between the TTT and the PTT regimens ranged between 1.2 and 39.3% with a variance of 8.3%.

Pupillary Surface over Cornea Surface (PS/CS)

On the assumption that the pupil surface (PS) and cornea surface (CS) could be equated to a circle surface, these PD/CD percentages corresponded to PS/CS percentages of 43.8% ($\pm 7.3$) with the PTT regimen and 23.1% ($\pm 8.3$) with the TTT regimen. The difference in PS/CS yielded using the PTT regimen and the TTT regimen was statistically significant ($p < 0.0001$, paired $t$-test, 95% confidence interval: $17.36 \pm 23.89$) and the PS/CS was 1.9 times greater with the PTT regimen than with the TTT regimen (Fig. 2).

Factors influencing the difference between the two regimens

The eye fundus examination was performed on average $55 \pm 17$ min after the instillation of the first eyedrop. We did not find any statistically significant correlation between the PD/CD percentage and the time elapsed between eyedrop application and the examination of the eye fundus ($x$ with a 95% confidence interval comprised between $-0.139$ and 0.268 for the TTT regimen, and between $-0.068$ and 0.199 for the PTT regimen) (Fig. 3A).

The mean postmenstrual age at examination was 35 weeks and 2 days ($\pm 3$ weeks and 5 days). We did not find any statistically significant correlation between the PD/CD percentage and the postmenstrual age at examination ($x$ with a 95% confidence interval comprised between $-0.225$ and 0.02039 for the TTT regimen, and between $-0.115$ and 0.006 for the PTT regimen) (Fig. 3B).

We did not find any statistically significant difference between the two readers for the difference of the PD/CD percentages between both PTT and TTT regimens ($p = 0.066$, paired $t$-test).

Mydriatic regimen applied

Fig. 1. Percentage of pupil diameter over cornea diameter (PD/CD) after instillation of the two mydriatic regimens. The graph indicates the mean and standard deviation (SD) for each regimen and each one of the 30 plots represents the result of the PD/CD percentage for one patient. The PD/CD percentage obtained with the PTT mydriatic regimen (one drop of 5% phenylephrine and two drops of 0.5% tropicamide) (white plots) was $65.9 \pm 8.8\%$ versus $47.3 \pm 8.7\%$ with the TTT regimen (three drops of 0.5% tropicamide) (white squares) ($p < 0.0001$, paired $t$-test).
Quality of the eye fundus examination

For the eye dilated with the PTT regimen, peripheral retinal visualization was classified as good for all infants (30 of 30). For the eye dilated with the TTT regimen, peripheral retinal visualization was classified as good for 16 of 30 infants, difficult in 13 of 30 infants and impossible in 1 of 30 infants.

There was a statistically significant difference between the quality of the eye fundus rated by the examiner and the mean value of the PD/CD percentage of the good and difficult groups defined according to the quality of the eye fundus (p < 0.0001, unpaired t-test, 95% confidence interval: 11.99–23.10 between the good and difficult groups).

Discussion

This study shows that the combination of 5% phenylephrine and 0.5% tropicamide appears to be 1.4 times more effective than 0.5% tropicamide alone. These results had already been suggested in previous reports (Caputo & Schnitzer 1978; Fleck et al. 1994). Caputo and Schnitzer found a mean pupil diameter of 7.4 ± 0.1 mm in the group using a combination: 7.66 mm for 12 patients dilated with three drops of a mixture combining one drop of 2.5% phenylephrine, one drop of 1% cyclopentolate and one drop of 0.5% tropicamide, 7.12 mm for four patients dilated with only one drop of a mixture combining one drop of 2.5% phenylephrine, one drop of 1% cyclopentolate and one drop of 1% tropicamide, and 7 mm for four patients dilated with three drops of this mixture (Caputo & Schnitzer 1978).

Fleck et al. (1994), who studied pupil dilation in 23 neonates, found a mean pupil diameter of 2.7 mm in the group using one drop of 0.5% tropicamide and saline solution compared with 6.0 mm in the group combining one drop of 2.5% phenylephrine and one drop of 0.5% tropicamide. However, these studies compared pupil diameters. On the other hand, the surface of the retina visualized varies with the pupil diameter over cornea diameter percentage and the cornea diameter varies with gestational age (Kirwan et al. 2005). The cornea diameter is 8.0 ± 0.3 mm for premature infants aged 31 weeks’ gestational age and 9.6 ± 0.5 mm for the premature infants aged 40 weeks’ gestational age.

In our study, the infants enrolled had gestational ages between 26 weeks and 6 days and 48 weeks. Extrapolating the results of the aforementioned Kirwan et al. (2005) study by linear regression, the cornea diameter could vary with the postmenstrual age between 7.2 mm and 10.8 mm between 26 weeks and 6 days and 48 weeks. Unfortunately, the studies by Caputo and Schnitzer (1978) and Fleck et al. (1994) did not indicate the mean postmenstrual age of each group and their results should therefore be considered with caution.

The conjunctiva did not appear on the eye photograph, the area beyond the cornea delineation having been filled in with black. This step prevented one potential bias: the conjunctival hue that might have been less reddish in eyes dilated using 5% phenylephrine, the vasoconstrictive properties of which are well known (Houben et al. 2006).

The photographs were anonymized and presented at random to the independent
readers who were asked to communicate only the pupil and cornea diameters without calculating the percentage of these measurements. This step was designed to prevent any influence (rounding-up of figures) on the percentages. The two readers transmitted their results separately and could not communicate. To our knowledge, this study is the first using such a methodology.

We chose to compare the right eye with the left eye. The risk was to minimize the difference between the two regimens, but even with this possibility we demonstrate that there is a great difference between the two mydriatic regimens. The range of the difference of the PD/CD percentage between the TTT and the PTT regimens was large: from 1.2 to 39.3%. This difference resulted in a difficulty for the examiner visualizing the eye fundus for 14 of 30 eyes dilated using the TTT regimen. The visualization of the retinal periphery was even impossible in one case whereas it was possible for all infant eyes dilated with the PTT regimen, combining phenylephrine and tropicamide eye-drops. The quality of peripheral retinal visualization during fundus examination was rated by a single examiner, experienced in ROP screening and blind to the regimen applied.

We chose to use 5% phenylephrine eye-drops because at the time of this study this dosage was the only one commercially available and authorized in France for pupil dilation in premature infants. A previous study conducted in our hospital involving 1033 fundus examinations in premature infants showed the absence of serious side-effects with the use of one drop of 5% phenylephrine and two drops of 0.5% tropicamide (Lux et al. 2015). The use of a commercially available solution appears to be essential for the feasibility, reproducibility and safety of the regimen, as Haddad et al. (1970) demonstrated that a commercially available 10% phenylephrine does not have the same properties as a prepared solution of 10% phenylephrine.

To conclude, the use of a combination of one drop of 5% phenylephrine and two drops of 0.5% tropicamide provides mydriasis, in which the surface area is almost two times greater than that provided by 0.5% tropicamide eye-drops alone. This provides significantly superior eye fundus examination quality.

References


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