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Cost-Effectiveness of Cycloplegic Agents: Results of a Randomized Controlled Trial in Nigerian Children

Anne Ebri, Hannah Kuper, and Susanne Wedner

PURPOSE. To compare the cost and effectiveness of three cycloplegic agents among Nigerian children.

METHODS. Two hundred thirty-three children aged 4 to 15 years attending outpatient eye clinics in Nigeria were randomized to (1) 1% cyclopentolate, (2) 1% cyclopentolate and 0.5% tropicamide, or (3) 1% atropine drops in each eye (instilled at home over 3 days). Ten children were lost to follow-up, nine from the atropine group. An optometrist measured the residual accommodation (primary outcome), dilated pupil size, pupil response to light, and self-reported side effects (secondary outcomes). Caregivers were interviewed about costs incurred due to cycloplegia (primary outcome). The incremental cost effectiveness ratios (ICERs) were calculated as the difference in cost divided by the difference in effectiveness comparing two agents. The 95% confidence intervals (CI) for ICERs were estimated through bootstrapping.

RESULTS. The atropine group had significantly lower mean residual accommodation (0.04 ± 0.01 D [SE]), than the combined regimen (0.36 ± 0.05 D) and cyclopentolate (0.63 ± 0.06 D) groups (P < 0.001). Atropine and the combined regimen produced better results for negative response to light and dilated pupil size than cyclopentolate. Atropine was more expensive, but also more effective, than the other agents. The ICER comparing atropine to the combined regimen was 1.81 (95% CI = −6.51–15.55) and compared to cyclopentolate was 0.59 (95% CI = −3.47–5.47). The combined regimen was both more effective and less expensive than cyclopentolate alone.

CONCLUSIONS. A combination of cyclopentolate and tropicamide should become the recommended agent for routine cycloplegic refraction in African children. The combined regimen was more effective than cyclopentolate, but not more expensive, and was preferable to atropine, since it incurred fewer losses to follow-up. (Invest Ophthalmol Vis Sci. 2007;48:1025–1031) DOI:10.1167/iovs.06-0604

In the Refractive Error Study in Children (RESC), standardized methods were used to measure the prevalence and causes of visual impairment in children in different international settings. Estimates of visual impairment (presenting visual acuity [VA] ≤6/12 in the better eye) ranged from 1.2% in South African children aged 5 to 15 years to up to 10.1% in Malaysian children aged 7 to 15 years. Uncorrected significant refractive error was the main cause of visual impairment in all RESC settings, and provision of correct spectacles would have reduced considerably the prevalence of visual impairment, for instance, to only 0.3% in South African and 1.4% in Malaysian children. These data show that uncorrected significant refractive error in children is a substantial, yet avoidable, problem that could have adverse effects on academic performance and professional development in later life. The provision of spectacles to children with uncorrected refractive error has therefore been made a priority of VISION 2020: The Right to Sight, the global initiative of the World Health Organization (WHO) and the International Agency for Prevention of Blindness, for the elimination of avoidable blindness by the year 2020.

Cycloplegic refraction is needed to measure refractive error accurately in children, as it inhibits accommodation during refraction and thereby prevents overestimation of myopia and the underestimation of hyperopia. Atropine, cyclopentolate, and tropicamide are the most commonly used cycloplegic agents. Atropine produces the greatest amount of cycloplegia, making it the gold standard, but it has logistic drawbacks, as it can produce severe side effects, requires prolonged recovery, and necessitates the examination of the child a few days after administration. In contrast, cyclopentolate and tropicamide have a relatively short duration of action and are used widely in clinical practice, and cycloplegic refraction with cyclopentolate eye drops was used in all RESC studies.

There is concern, however, that cyclopentolate and tropicamide on their own are less effective cycloplegic agents in children with dark irides than in those with light irides and could lead to underestimation of the prevalence and severity of hyperopia in African and Asian populations. As an example, the RESC in South African children reported that approximately half of the children whose eyes were dilated with cyclopentolate had inadequate cycloplegia, and inadequate cycloplegia was also reported in the RESC in Malaysia and in India. Tropicamide 1% on its own is not a suitable alternative cycloplegic agent in an African setting as it is less effective than cyclopentolate in inhibiting accommodation, and its effectiveness seems to vary with ethnicity. Another drawback of tropicamide is that its maximum cycloplegic effect lasts less than 1 hour, making it impractical for use in a busy African outpatient clinic. Tropicamide in combination with cyclopentolate may increase cycloplegia in children with dark irides, while remaining fast acting, and this may provide the best alternative to atropine.

The purpose of this study was to compare the cost and effectiveness of three cycloplegic drug regimens (atropine, cyclopentolate, and a combination of cyclopentolate and tropicamide) in a randomized controlled trial in Nigerian children aged 4 to 15 years.

METHODS

Participants

The trial was conducted in Akwa Ibom and Cross River States in South Eastern Nigeria. Children aged 4 to 15 years who presented with an eye complaint at the Abak eye center or the Ministry of Health eye center

From the University of Calabar Teaching Hospital, Calabar, Nigeria; and the International Centre for Eye Health, London School of Hygiene and Tropical Medicine, London, United Kingdom.

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between May 5 and July 5 2005 were eligible for participation. Children were excluded if they had anterior segment disorders severe enough to interfere with retinoscopy (e.g., corneal scar or lens opacity), a history of corneal or cataract surgery, glaucoma, or known allergies to any of the cycloplegic drops used. Children with irides that were not brown (i.e., green or albino) were also excluded, as the purpose of the study was to compare the cost-effectiveness of cycloplegic agents for dark irides.

**Ethical Considerations**

Ethics approval was granted by the ethics committees of the University of Calabar Teaching Hospital, Nigeria, and of the London School of Hygiene and Tropical Medicine. The study was explained to the children and their parents. Written consent was obtained from all parents and verbal assent from all children who agreed to participate. All data were kept confidential throughout the study. The research adhered to the tenets of the Declaration of Helsinki.

**Interventions**

There were three treatment arms in the trial:

1. Atropine 1% eye drops: 1 drop instilled three times daily for 3 days, administered by the child’s parents after verbal and written instructions had been provided.
2. Cyclopentolate 1% eye drops: 2 single drops administered by a nurse 5 minutes apart.
3. Cyclopentolate 1% and tropicamide 0.5% eye drops: 1 drop of each followed by a second drop of each after 5 minutes, administered by a nurse.

**Objectives**

The objectives of this study were:

1. To compare the cycloplegic effect of the three regimens in Nigerian children with dark irides.
2. To compare the effect on pupillary dilation and response to light and self-reported side effects of agent.
3. To compare the costs of the three regimens.

**Outcomes**

**Costs.** The parents or guardians of eligible children who had agreed to participate were interviewed by trained hospital personnel. They were asked about their out-of-pocket expenses, both direct and productivity costs, incurred as a result of the cycloplegic refraction. Direct costs are those that arose directly from delivering the intervention, including travel costs and any other costs such as accommodation and food directly attributable to the cycloplegic refraction. Productivity costs refer to changes in productivity on account of the intervention, including (as applicable) the carer’s wages lost because the carer had to accompany the child to the clinic, the children’s school fees lost because the child was at the clinic for the cycloplegic refraction. The parents/guardians were also questioned about their sociodemographic status and their child’s ocular and general medical history.

**Ophthalmic Examination before Cycloplegia.** VA of the children was tested by an ophthalmic assistant using a logMAR E-chart at 4 m illuminated with two fluorescent strip bulbs. VA results were converted and reported in 6·m equivalents. The anterior segment was examined by an optometrist and an ophthalmologist using a pen torch and a slit lamp (Haag Streit, Wedel, Germany), and oculomotor activity was measured by assessing the corneal reflex and neutralization with prisms.

The children were refracted in a dark room by an optometrist (AE) using a streak retinoscope (Keeler, Windsor, UK) at a measuring distance of 66 cm, equivalent to 1·5 D. Fixating an object at 6 m. This was followed by subjective refraction and direct ophthalmoscopy of the posterior pole (Keeler). Refractive errors were described by using spherical equivalents for the right eye, since there was a high correlation between VA for the right and left eyes. A child was classified as myopic if the spherical equivalent was $-0.5$ D or worse and as hyperopic if the spherical equivalent was $+1.0$ D or worse. Children with a spherical equivalent between $-0.5$ D and $+1.0$ D were classified as emmetropic.

**Ophthalmic Examination with Cycloplegia.** After cycloplegia, children had their pupil dilatation and response to light measured by two independent optometrists who were not aware of their colleague’s measurement. Pupil dilatation was assessed by measuring the pupillary diameter with a ruler to the nearest millimetre and pupillary reaction to light was graded as “response to light” or “no response to light.” For five children there was a 1-mm difference in pupillary diameter between the optometrists and/or disagreement on pupillary reaction to light, and so an ophthalmologist repeated the examination. In all five cases, the ophthalmologist agreed with one of the optometrists’ assessments, and so the consensus measurement was recorded.

Cycloplegic objective refraction was performed by distance retinoscopy by the same technique as was used for noncycloplegic refraction. Dynamic near retinoscopy was performed while children moved fixation from a distance object at 6 m to a near object at 40 cm. All retinoscopies were performed by the same optometrist (AE). The study ophthalmologist examined the anterior and posterior segment with a slit lamp and by direct ophthalmoscopy. After the examination, the children (or parents of young children) were asked by a trained optometrist or auxiliary nurse whether they had experienced any side effects from the agent. The children were classified as having side effects if they complained about pain, stinging, profuse tearing, or discomfort or if tearing was observed.

**Primary and Secondary Outcomes.** The primary outcome measures were the mean residual accommodation and the mean total cost for each regimen. Residual accommodation was determined by subtracting the cycloplegic near retinoscopy results from the cycloplegic distance retinoscopy results.

Secondary outcome measures were (1) the proportion of children whose pupils were dilated to 6 mm (2) the proportion of children whose pupils did not contract when exposed to the light of a pen torch, and (3) the proportion of children who reported side effects from the agent.

**Sample Size**

A sample size of 78 children in each of the three intervention arms was necessary to detect a difference of at least 0·25 D in residual accommodation between the interventions, with 80% power and a 5% confidence level and allowing for 10% loss to follow-up.

**Randomization and Masking**

Children were randomly assigned to one of the three intervention arms. The intervention group was concealed in numbered, opaque envelopes which were contained in a box. Each child selected one envelope and gave it to the nurse, who opened the envelope. If the child was assigned to the cyclopentolate or combined-regimen group, then the nurse administered the appropriate cycloplegic agent at that time. If the child was assigned to the atropine group, then the nurse gave verbal instructions in the native dialect to the parents on how to administer the atropine drops at home and gave the parents an instruction leaflet and application chart. The parents of the children in the atropine group were instructed to bring the child back to the dilation room on the third day with the used bottle of atropine. The nurse recorded the child’s name, identification number and type of drug on a form that was not available to the study optometrist. Children who had been given short-acting cycloplegic drugs were examined after 30 minutes and children given atropine were examined after 3 days. The masking of the optometrist was incomplete, because children in different treatment groups were examined at different time intervals.

**Statistical Methods**

All data were checked for consistency and completeness at the end of each day. Data were entered onto computers (EpiData; EpiData Asso-
Statistical analysis was performed in only the right eye, because the results in the left and right eyes were similar. Continuous data were described using means and standard errors for normally distributed data, whereas medians, quartiles, and ranges were used for data that were not normally distributed. Categorical data were described using frequencies and percentages. Normally distributed continuous data were tested for significance using the Student’s *t*-test or the analysis of variance (ANOVA). The Wilcoxon rank sum test was used for continuous data that did not follow a normal distribution, and the Pearson’s *χ*² test was used for categorical data.

Mean and median costs incurred as a result of the intervention were calculated for the three regimens. For children who had extremely high costs (i.e., in the 99th percentile), the costs of children’s school fees lost were truncated at £1 per day (three children) and transport costs were truncated at £4 (two children). The incremental costs and effectiveness of the three treatments were compared in a cost-effectiveness analysis. The mean difference in effectiveness (i.e., residual accommodation) and costs were calculated comparing two cycloplegic agents in turn. The incremental cost-effectiveness ratio (ICER) was calculated as the difference in cost between the two agents divided by the difference in effectiveness. This gives the additional cost per 1-D decrease in residual accommodation for one agent compared to another. It is assumed that the mean additional cost for a 1-D reduction in residual accommodation is twice the mean additional cost of a 0.5-D reduction. A sampling distribution of the incremental costs and effectiveness was estimated through nonparametric bootstrapping with 1000 replications, a simulation method for statistical inference. Each bootstrap sample was obtained by repeated random sampling with replacement from the original data points. A bootstrap ICER was calculated for each of the 1000 bootstrap replicates. The ICERs comparing two cycloplegic agents were calculated from the 2.5 and 97.5 percentile of the ICERs. The bootstrapped ICERs were graphically represented on a cost-effectiveness plane, which shows the relative costs and effectiveness of the two agents. All costs and benefits were measured at the present time and were not discounted (i.e., when we reduce the value given to future costs and future benefits in relation to how far in the future they are measured).

**RESULTS**

**Participant Flow**

Two hundred forty-seven children aged 4 to 15 years were assessed for eligibility, 183 identified from the Abak eye center and 64 from the Ministry of Health eye center in Calabar (Fig. 1). Of these, 14 children were excluded because of pupil anomalies (*n* = 4), uniocular lens opacity (*n* = 2), ocular albinism (*n* = 2), suspected glaucoma (*n* = 2), pseudophakia (*n* = 2), uniocular aphakia (*n* = 1), or green iris (*n* = 1). The remaining 233 children were randomly allocated to the cyclopentolate (*n* = 76), combined regimen (*n* = 78) or atropine (*n* = 79) groups. Ten children were lost to follow-up: nine from the atropine group who did not return after 3 days and one child from the combined-regimen group who refused to continue after the first drops. All 10 were boys. Those lost to follow-up were younger (mean, 9.3 ± 0.6 years [SE]) than those included (mean, 10.4 ± 0.2 years) and had a slightly higher refractive error (mean, 0.5 ± 0.1 D vs. +0.4 ± 0.1 D). The results were analyzed for the remaining 223 children.

**Baseline Data**

Sociodemographic and ophthalmic characteristics were similar in the three groups (Table 1). The mean age was 10.1 ± 0.23 years in the cyclopentolate group, 10.6 ± 0.32 years in the combined-regimen group, and 10.4 ± 0.29 years in the atropine group. There were slightly more girls in the combined-
regimen group (67%) than in the others (55% in cyclopentolate and 47% in atropine), though the difference did not reach statistical significance. The educational status of the three groups was similar. In each of the three groups, most of the children were emmetropic or hyperopic, and few were myopic.

Effectiveness of Cycloplegic Agents

The primary outcome for effectiveness in this study was mean residual accommodation. Significantly lower mean residual accommodation was achieved in the atropine group (mean, 0.04 ± 0.01 D [SE]), than in the combined-regimen (0.36 ± 0.05 D) or cyclopentolate (0.63D ± 0.06 D; P < 0.0001) group. None of the children in the atropine group had a residual accommodation ≥0.5 D, compared with 22 in the combined-regimen group (29%), and 35 children in the cyclopentolate group (46%; Table 2). All the children in the atropine group had a dilated pupil size of at least 6 mm, which was achieved by all except five (94%) children in the combined-regimen group, but only 40 (53%) of the 76 children in the cyclopentolate group. Response to light was negative in 97% of the children in the atropine group (68/70), 66% of the combined-regimen group (51/77), and only 23% of the cyclopentolate-treated children (19/76). Self-reported (or, for younger children, parent reported) side effects were mild and associated with instillation of drops (stinging sensation, 52% of side effects; peppery sensation, 30%; discomfort, 15%; haloes around colors, 2%). Only 5 (7%) of 70 subjects in the atropine group had side effects from the agent, compared with 22 (29%) of 76 subjects in the cyclopentolate group and 22 (29%) of 77 subjects in the combined-regimen group. However, all the children in the atropine group reported prolonged blurry near vision when they were refracted 3 days after the initial examination. No systemic side effects were reported.

Table 1. Baseline Characteristics of Participants in the Three Intervention Arms

<table>
<thead>
<tr>
<th></th>
<th>Cyclopentolate (n = 76)</th>
<th>Combined Regimen (n = 77)</th>
<th>Atropine (n = 70)</th>
<th>P Pearson χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–6</td>
<td>6 (8)</td>
<td>9 (12)</td>
<td>6 (9)</td>
<td>0.43</td>
</tr>
<tr>
<td>7–9</td>
<td>26 (34)</td>
<td>16 (21)</td>
<td>18 (26)</td>
<td></td>
</tr>
<tr>
<td>10–12</td>
<td>30 (39)</td>
<td>28 (36)</td>
<td>28 (40)</td>
<td></td>
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<tr>
<td>13–15</td>
<td>14 (18)</td>
<td>24 (31)</td>
<td>18 (26)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (45)</td>
<td>28 (36)</td>
<td>37 (53)</td>
<td>0.13</td>
</tr>
<tr>
<td>Female</td>
<td>42 (55)</td>
<td>49 (67)</td>
<td>35 (47)</td>
<td></td>
</tr>
<tr>
<td>Education*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preschool</td>
<td>3 (4)</td>
<td>4 (5)</td>
<td>1 (1)</td>
<td>0.79</td>
</tr>
<tr>
<td>Primary</td>
<td>47 (62)</td>
<td>44 (59)</td>
<td>43 (61)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>26 (34)</td>
<td>27 (36)</td>
<td>26 (37)</td>
<td></td>
</tr>
<tr>
<td>Glasses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (17)</td>
<td>16 (21)</td>
<td>13 (19)</td>
<td>0.84</td>
</tr>
<tr>
<td>No</td>
<td>63 (83)</td>
<td>61 (79)</td>
<td>57 (81)</td>
<td></td>
</tr>
<tr>
<td>Refractive status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myopia</td>
<td>4 (5)</td>
<td>6 (8)</td>
<td>4 (6)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hyperopia</td>
<td>23 (30)</td>
<td>17 (22)</td>
<td>19 (27)</td>
<td></td>
</tr>
<tr>
<td>Emmetropia</td>
<td>49 (64)</td>
<td>54 (70)</td>
<td>47 (67)</td>
<td></td>
</tr>
<tr>
<td>Mean refractive error (SE)†</td>
<td>0.47 (0.11)</td>
<td>0.41 (0.17)</td>
<td>0.46 (0.20)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Data are the number of subjects with the percentage of the total group in parentheses, except for mean refractive error, which is the mean ± SE

* There were two missing values.
† P derived through ANOVA.

Table 2. Effectiveness of the Cycloplegic Agents: Residual Accommodation, Pupillary Dilatation, Pupillary Response and Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Cyclopentolate (n = 76)</th>
<th>Combined Regimen (n = 77)</th>
<th>Atropine (n = 70)</th>
<th>P Pearson χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual accommodaton</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0–0.5 D</td>
<td>41 (54)</td>
<td>55 (71)</td>
<td>70 (100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;0.5–1.0 D</td>
<td>24 (32)</td>
<td>19 (25)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>&gt;1.0–1.5 D</td>
<td>8 (11)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>&gt;1.5 D</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Dilated pupil size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mm</td>
<td>36 (47)</td>
<td>5 (6)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥6 mm</td>
<td>40 (53)</td>
<td>72 (94)</td>
<td>70 (100)</td>
<td></td>
</tr>
<tr>
<td>Response to light</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>19 (25)</td>
<td>51 (66)</td>
<td>68 (97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Positive</td>
<td>57 (75)</td>
<td>26 (34)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Side effects of agent*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>54 (71)</td>
<td>55 (71)</td>
<td>65 (93)</td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>22 (29)</td>
<td>22 (29)</td>
<td>5 (7)</td>
<td></td>
</tr>
</tbody>
</table>

Data are the number of subjects with the percentage of the total group in parentheses.

* All side effects were mild. Prolonged blurry near vision was not included, as only children in the atropine group were reviewed 3 days after the initial examination.
**Cost**

The cost of the agent for each treated child was £0.07 for 1% atropine, £0.05 for 1% cyclopentolate and £0.12 for the combined regimen (Table 3). Travel costs and carer’s wages lost were similar in the three groups. The children’s school fees lost were significantly higher in the atropine group than the other groups. Overall, the median total costs were significantly higher in the atropine group (£2.27) than in the cyclopentolate (£2.08, \( P < 0.01 \)) or the combined-regimen (£1.72, \( P < 0.01 \)) group. Costs were significantly higher in the cyclopentolate in than the combined-regimen group (\( P < 0.01 \)).

**Cost Effectiveness**

The effectiveness unit was a 1-D decrease in residual accommodation. The cost unit was a 1% increase in cost. The ICER was the additional cost per 1-D decrease in residual accommodation for one agent compared to another. Atropine was more expensive than the combined regimen, but also more effective, with an ICER of 1.81 (95% CI = −0.61–4.28; Table 4). This indicated that atropine costs an additional £1.81 per 1-D decrease in residual accommodation achieved. Atropine was also more expensive and more effective than cyclopentolate, giving an ICER of 0.59 (95% CI = −0.81–1.98), or £0.59 per 1-D decrease in residual accommodation achieved. The combined regimen was cheaper than cyclopentolate and achieved lower levels of residual accommodation, and therefore it was the superior treatment with an ICER of −0.85 (95% CI = −5.26–2.16). All confidence intervals included the null value, indicating that no agent was significantly more cost-effective than the other. The estimates of the ICER calculated from the bootstrap method were close to the true population ICER (data not shown), and so the bias-corrected percentile method was not used. Figure 2 shows the bootstrap results of the comparison of costs and effectiveness of cycloplegic agents, with 95% CIs, plotted on the cost-effectiveness plane. It illustrates that atropine was more effective than either the combined regimen or cyclopentolate and that the combined regimen was more effective than cyclopentolate. There was greater variation, however, in the relative costs of the treatments.

**DISCUSSION**

Cycloplegic refraction is necessary for measuring refractive error accurately in children; however, the cycloplegic agent of choice for children with dark irides has not yet been established. This randomized controlled trial in Nigerian children showed that atropine was a more effective cycloplegic agent than either a combined regimen of tropicamide and cyclopentolate or cyclopentolate alone. The children in the atropine group had superior results in terms of lower mean residual accommodation, with a higher proportion having a negative response to light and adequate dilated pupil size. The combined regimen was better on all these scales compared to cyclopentolate alone. The combined regimen and cyclopentolate groups reported more side effects on instillation than the atropine group, although side effects were assessed immediately after administration of drops for the combined and cyclopentolate groups, but after a 3-day interval in the atropine group. All the children in the atropine group complained of prolonged blurry near vision when they presented at the eye clinic 3-days after the initial examination, whereas the other children were not re-examined 3-days later. Costs in the atropine group were marginally higher than in the other groups, because two trips were required by the carer and child rather than the single trip for the other agents. The costs per child were significantly lower for the combined regimen than for cyclopentolate, which is surprising because both regimens required only one trip for the carer and child. This significant difference is probably due to random variation in the data, as there is no obvious alternative explanation. Overall, combined cyclopentolate and tropicamide was more effective than cyclopentolate alone, but not more expensive. Atropine was both more expensive and more effective than cyclopentolate or the combined regimen, but had far higher losses to follow-up.

Our results support those in other studies that show the superior effectiveness of atropine in suppressing accommodation in children with dark irides. In a study of 50 Japanese children, the average refractive error obtained by autorefractor was 0.7 D higher in children after instillation of atropine drops (0.5% or 1% twice daily over 7 days) compared with cyclopen-
tolate 1% (instilled three times every 5 minutes).\(^1^9\) In 25 Chinese children with pigmented irides, atropine 1% (applied twice daily over 3 days) detected a higher degree of hyperopia (\(+5.7\) D) compared with a combined regimen of cyclopentolate 1% and tropicamide 1% (\(+5.3\) D).\(^1^5\) The main disadvantage of atropine; however, is that it requires examination of children a few days after administration, and this may have contributed to the high loss to follow-up experienced in the atropine group in our study. Atropine can also produce severe side-effects (mainly due to its anticholinergic action), although longer term side effects (e.g., ultraviolet light damage to the lens and the retina as a result of chronic pupillary dilatation from long-term use of atropine) are unlikely to occur if atropine is used only for diagnostic purposes.\(^2^0\) The inadequate

<table>
<thead>
<tr>
<th>Incremental Cost Effectiveness Ratio (ICER)</th>
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<tbody>
<tr>
<td>Benchmark: Atropine 2.72 0.58 0.04 0.32 1.81</td>
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<tr>
<td>Alternative: Combined regimen 2.14 0.36</td>
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<tr>
<td>Benchmark: Atropine 2.72 0.35 0.04 0.59 0.59</td>
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**Figure 2.** Representation of the uncertainty in differential mean costs and effectiveness showing 1000 bootstrap replications, with 95% CI. Horizontal axis: difference in mean residual accommodation; vertical axis: difference in mean cost. (a) Atropine was significantly more effective than the combined regimen, but not more expensive. (b) Atropine was significantly more effective than cyclopentolate, but not more expensive. (c) The combined regimen was significantly more effective than cyclopentolate, but not more expensive.
cycloplegia attained by cyclopentolate shown by other studies,2,8,9 is consistent with our findings, in which 15% of children had a residual accommodation of >1 D. Tropicamide may boost mydriasis in cyclopentolate in children with dark irides, and this may be the best alternative to atropine,14 as shown by the present study. No previous cost-effectiveness study has been conducted on these agents in a low-income setting to allow comparison of results.

Study Limitations
This study was too small to find statistically significant differences in ICERs or to assess differences in the effectiveness of the cycloplegic agents between age groups. The hospital costs were not recorded (except for the direct costs of the drugs), since the time spent with the child by the ophthalmologist and optometrist was assumed to be the same for all three intervention arms. Masking of the optometrist was incomplete, because the cyclopentolate and combined-regimen groups were examined 30 minutes after instillation of drops, whereas the atropine group was examined after 3 days. Side effects for cyclopentolate and the combined regimen were assessed on the same day as the instillation of drops, whereas the atropine group was questioned about side effects after 3 days, which may have contributed to the difference in reported side effects. The duration of side effects was also not assessed, although side effects tended to be mild and apparent mainly on instillation of drops.

Study Strengths
We used a randomized controlled trial to assess the effectiveness of the cycloplegic agents, a question that has not been answered previously for an African population. We used the trial as a framework for economic evaluation and this allowed us to collect and analyze patient-specific resource use data. The same optometrist performed all the refractions. This was an effectiveness study rather than an efficacy study, as we did not use expensive equipment so that our study results would reflect the real-world circumstances of the African hospital. The CONSORT (Consolidated Standards of Reporting Trials) guidelines were adhered to for the trial.21

Public Health Implications
Inadequate cycloplegia may result in overdiagnosis of myopia and underdiagnosis of hyperopia, and a distortion of the magnitude of refractive errors among African children. Accurate cycloplegia is therefore important, but until now no randomized controlled trials have been undertaken in African children to identify the most cost-effective cycloplegic agent. This study confirms that atropine is more effective than cyclopentolate or the combined regimen, although it is not ideal for use in routine clinical practice because of the high loss to follow-up, and the prolonged impaired near vision produced by atropine may also reduce participation in trials, cohort studies, and surveys. Cyclopentolate was less effective but not cheaper than the combined regimen of cyclopentolate and tropicamide and may yield unreliable data on examinations in children. This implies that the combination of cyclopentolate and tropicamide should become the recommended cycloplegic agent of choice for routine cycloplegic refraction and large-scale studies of refractive error in African children. Atropine may remain the agent of choice, however, when a very accurate refraction is needed, such as for children with esotropia. Relative costs and effectiveness of the three regimens may vary between populations, and therefore more studies are needed before assessing whether the results are generalizable to other populations, although this may be less of an issue on the African continent.

Summary
Atropine was the most effective cycloplegic agent, but had practical limitations due to its requirement for examination after 3 days of treatment and consequent high loss to follow-up. A combination of cyclopentolate and tropicamide was more effective than cyclopentolate alone, but not more expensive, and should become the recommended cycloplegic agent of choice for routine cycloplegic refraction in African children.

References