A Prospective Study on Ocular Hypertensive and Antiinflammatory Response to Different Dosages of Fluorometholone in Children

Dorothy S. P. Fan, FRCS, 1 Joan S. K. Ng, FRCS, 2 Dennis S. C. Lam, FRCS, FRCOphth 1

Objective: To investigate the ocular hypertensive and antiinflammatory response to different dosages of fluorometholone (FML).

Design: Prospective clinical trial with randomization of fellow eyes to different postoperative treatment.

Participants: Thirty-one consecutive children undergoing bilateral symmetrical strabismus operation.

Intervention: Among 31 children who received bilateral squint operations, one eye was randomized to receive topical FML six times daily (group 1), whereas the other eye received topical FML three times daily (group 2), both for 4 weeks. Intraocular pressure (IOP) and antiinflammatory response were measured serially in the postoperative period for 8 weeks.

Main Outcome Measures: Intraocular pressure was measured on the day before surgery and on postoperative days 1, 3, 6, 13, 20, 27, 41, and 55. The antiinflammatory response was also assessed subjectively and objectively at days 6, 13, 20, and 27 after the operations. Peak IOP, net increase in IOP, and antiinflammatory responses in the two study groups were analyzed.

Results: Thirty-one children, age 3 to 9 years, (mean ± standard deviation [SD], 5.52 ± 1.81) participated in the study. Intraocular pressure increased significantly in both groups compared with the preoperative values (P < 0.001). The peak IOP ranged from 12.00 to 31.00 mmHg and 12.30 to 25.00 mmHg in groups 1 and 2, respectively. The mean peak IOP (19.00 ± 5.06 mmHg vs. 17.13 ± 3.32 mmHg) was significantly higher in group 1 (P < 0.001). The net increase in IOP was similar (mean ± SD, 4.37 ± 4.79 vs. 2.57 ± 3.32 mmHg; P = 0.005). Ranges of the net IOP increase were −1.00 to 16.00 mmHg and −2.50 to 10.30 mmHg in groups 1 and 2, respectively. Children in group 1 reached the peak IOP earlier than those in group 2 (median, 6 vs. 13 days; P = 0.033). However, there was no significant difference in antiinflammatory response between the two groups.

Conclusions: Ocular hypertension occurs in a dose-dependent manner in children treated with FML. Children in group 1 had a quicker onset and more severe ocular hypertensive response than those in group 2. It would be desirable to monitor the IOP regularly when FML is used with a high frequency and for a long duration in children. Ophthalmology 2001;108:1973–1977 © 2001 by the American Academy of Ophthalmology.

Topical corticosteroids are commonly used antiinflammatory agents commonly used in treatment of various ocular diseases and after operations, such as for cataract, glaucoma, and strabismus. The duration of use varies, but sometimes can last for weeks. It has been well known that corticosteroids produce ocular hypertension as one of their major side effects. Clinically, steroid-induced glaucoma is usually symptom free until significant damage has been done to the eye. The ocular hypertensive response in adults to oral, intravenous, topical dermatologic, topical ocular, and periocular corticosteroids is well established. Even inhalation and nasal corticosteroids have been reported to be associated with ocular hypertension in susceptible adults.

The ocular hypertensive response to steroids by adults has been well reported. However, only limited information on children is available from studies that do not concur with each other.10 Ohji et al10 reported that the ocular hypertensive response to topical dexamethasone (DMS) was more marked in children. Conversely, Biedner et al10 had the opposite finding. Our previous studies indicated that the ocular hypertensive response of children to topical DMS
occurred more frequently, severely, and rapidly than that reported in adults. Moreover, this ocular hypertensive response to topical DMS in children occurred in a dose-dependent manner.

Flurometholone (FML; 21-dexoxy-9fluoro-6a methyl prednisolone) is an antiinflammatory steroid with some structural characteristics in common with progesterone. This steroid has been reported to have a reduced risk of increasing intraocular pressure (IOP). Flurometholone had been shown to cause a much less pronounced ocular hypertensive effect than DMS. Akingbehin reported that only 2 of 24 FML-treated eyes showed changes in IOP more than 5 mmHg. In our previous study, in 19 children, one eye was randomized to receive 0.1% DMS six times daily, whereas the fellow eye received 0.1% FML six times daily. We found that 31.6% of the children treated with FML showed a minimum increase in IOP of 6 mmHg. This result was much higher than the one reported by Akingbehin. Flurometholone was used because it could be tolerated more easily by children.

Limited information is available regarding the antiinflammatory effect and the ocular hypertensive response in relation to the frequency of application of FML. We therefore conducted a prospective study to investigate the ocular hypertensive and antiinflammatory responses in children to different dosages of FML. The results may provide us with some guidelines for the usage of topical FML in children.

Materials and Methods

Patients who underwent bilateral symmetrical strabismus operations at Prince of Wales Hospital and Hong Kong Eye Hospital between January 2000 and July 2000 were recruited to participate in this prospective, randomized clinical trial. Children between 3 and 10 years of age with preoperative IOP of 21 mmHg or less and a cup-to-disc ratio of 0.3 or less with absence of other systemic and ocular diseases were recruited. Exclusion criteria included a history of steroid usage in the past year, family history of glaucoma, and failure to comply with treatment, follow-up schedules, and IOP measurement. The study and the measurements followed the guidelines of the Declaration of Helsinki. Written consent was obtained from parents of all study subjects after the nature and possible consequences of the study had been explained. The parents were informed that the children would receive different dosages of treatment in their eyes after the operation. Treatment would be altered further according to the status of the IOPs, and antiglaucomatous treatments would be started in cases where the IOP exceeded 30 mmHg. The study was approved by the ethics committee of the Chinese University of Hong Kong.

Children were examined 1 day before the operation. Intraocular pressure measurements were performed in an assigned room that was quiet and comfortable. Ophthalmic personnel who were experienced in dealing with children performed the measurements. Noncontact tonometry (XPERT NCT Plus, Leica, Buffalo, New York) was used because it could be tolerated more easily by children and its reliability has been reported to be excellent. Three reliable readings were obtained from each eye, and the mean value was used for analysis. Goldmann applanation tonometry (900.4.4, Haag-Streit, Gartenstadtrasse, Switzerland) was performed if the IOP exceeded 21.00 mmHg because noncontact tonometry may give an underestimation when IOP exceeds 21.00 mmHg.

All the operations were performed under general anesthesia by one of the investigators (DSCL, JSKN, or DSPF). One eye was randomized to receive topical 0.1% FML (Flucon; Alcon Laboratories, Ft. Worth, TX) six times daily (group 1), whereas the other eye received topical 0.1% FML three times daily (group 2). Topical 0.25% chloramphenicol (Chloramphenicol; Martinchale Pharmaceuticals Ltd, Ramford, England) was also prescribed for both eyes four times daily. The treatment commenced on the day of the operation and continued for 4 weeks.

Intraocular pressure was measured on postoperative days 1, 3, 6, 13, 20, 27, 41, and 55. The procedure for IOP measurement was administered as described. Flurometholone eye drops were discontinued if any eye had an IOP of more than 30 mmHg, and more frequent follow-up was arranged. Antiglaucomatous therapy was administered until baseline IOP of the patients was reached. The IOP of each patient was measured within 2 hours of the same time at each visit.

The conjunctival inflammatory response was analyzed objectively by comparing the degree of conjunctival injection over the sites of the muscle surgery with a series of color photographs and allocating a ‘conjunctival inflammatory score’ for each eye on postoperative days 6, 13, 20, and 27. A score of 5 denoted a severe inflammatory response and a score of 0 denoted the absence of inflammation. Patient symptoms were also analyzed subjectively by both the patients and the parents regarding ocular discomfort and conjunctival discharge on a scale from 0 to 3. The severity of symptoms was graded on a scale of 0 (asymptomatic) to 3 (severely affected).

Statistics

The demographic data of the patients were calculated by descriptive statistics. The comparison in IOP between the two different treatment groups was made by the paired t test. The chi-square test was used to compare the difference in frequency of patients with elevated IOP. The inflammatory responses in the two groups were compared using the Wilcoxon signed rank test and the Friedman test. The sample size was calculated according to the estimated mean increase in IOP for the groups under study: 5.83 mmHg for group 1 and 2.96 mmHg for group 2. The sample size was estimated to be 28 with a power of 0.8. A P value of < 0.05 was defined as statistically significant.

Results

Ocular Hypertensive Effect

Thirty-one children age 3 to 9 years (mean, 5.52; standard deviation [SD], 1.81 years) participated in the study. Eighteen were boys (58.1%) and 13 were girls (41.9%). They all received bilateral symmetrical strabismus operations. Twenty-three children (74.2%) received bilateral lateral rectus recession, 7 (22.6%) received bilateral medial rectus recession, and 1 child (3.2%) had bilateral medial rectus recession and inferior oblique recession. The mean preoperative IOP was 14.60 mmHg (SD, 2.55 mmHg), with a range of 10.00 to 21.00 mmHg. There was no statistically significant difference in IOP between group 1 (mean, 14.64 mmHg; SD, 2.26 mmHg) and group 2 (mean, 14.55 mmHg; SD, 2.85 mmHg; paired t test, P = 0.77). The mean spherical equivalent refractions of group 1 and group 2 were +0.07 diopters (D) (SD, 1.99 D; range, −4.88 to +3.88 D) and −0.15 D (SD, 2.10 D; range, −5.25 to 4.88 diopters (D).
to +3.55 D), respectively, with no statistically significant difference between them (paired \( t \) test, \( P = 0.08 \)).

Ranges of peak IOP were 12.00 to 31.00 mmHg in group 1 and 12.30 to 25.00 mmHg in group 2. The mean peak IOPs were 19.00 mmHg (SD, 5.06 mmHg) and 17.13 mmHg (SD, 3.32 mmHg) in groups 1 and 2, respectively. Both treatment groups had peak IOPs significantly higher than the preoperative values (paired \( t \) test, both \( P < 0.001 \)). Moreover, the peak IOP in group 1 was significantly higher than that in group 2 (paired \( t \) test, \( P = 0.005 \)). The maximal change in IOP was also higher in children in group 1 (mean, 4.37 mmHg; SD, 4.79 mmHg; range, 1.40 to 16.30 mmHg) than those in group 2 (mean, 2.57 mmHg; SD, 3.22 mmHg; range, −2.50 to 10.30 mmHg; paired \( t \) test, \( P = 0.011 \); Table 1).

In group 1, two eyes (6.45%) had maximum IOP of at least 30 mmHg, with one child having a peak IOP of 30 mmHg and the other having a peak IOP of 31 mmHg. There was not a single case of IOP more than 30 mmHg in group 2. Also, group 1 had a larger number of patients with an IOP of more than 21 mmHg than group 2 (10 versus 4). However, this was not statistically significant (chi-square test, \( P = 0.068 \)).

Table 2 shows the different levels of ocular hypertensive response of the two groups according to the classification system proposed by Armaly\(^4\) and Becker and Hahn.\(^5\) Results were very similar in both classification systems. None of the cases were high responders.

Children in group 1 reached peak IOP earlier than those in group 2 (Wilcoxon signed rank test, \( P = 0.033 \)). The median time to reach peak IOP was 6 days in group 1 versus 13 days in group 2.

There was no correlation between age and peak IOP (group 1, \( r = 0.08, P = 0.677 \); group 2, \( r = 0.13, P = 0.498 \)). Similar findings were also found between refractive error and peak IOP in both groups (group 1, \( r = 0.38, P = 0.200 \); group 2, \( r = 0.51, P = 0.073 \)).

### Table 1. Summary of Intraocular Pressure Changes of Groups 1 and 2

<table>
<thead>
<tr>
<th>Classification</th>
<th>Six-times Group (Fluorometholone Six Times Daily)</th>
<th>Three-times Group (Fluorometholone Three Times Daily)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean preoperative IOP; SD (range)</td>
<td>14.64; 2.26 mmHg (11.3–21.00 mmHg)</td>
<td>14.55; 2.85 mmHg (10.00–20.00 mmHg)</td>
<td>0.77</td>
</tr>
<tr>
<td>Peak IOP; SD (range)</td>
<td>19.00; 5.06 mmHg (12.00–31.00 mmHg)</td>
<td>17.13; 3.32 mmHg (12.30–25.00 mmHg)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Net IOP change; SD (range)</td>
<td>4.37; 4.79 mmHg (−1.00–16.00 mmHg)</td>
<td>2.57; 3.32 mmHg (−2.50–10.30 mmHg)</td>
<td>0.005</td>
</tr>
<tr>
<td>Median time to reach peak IOP (range)</td>
<td>6 days (3–27 days)</td>
<td>13 days (3–27 days)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

### Antiinflammatory Effect

The respective mean conjunctival inflammatory scores at days 6, 13, 20, and 27 in groups 1 and 2 were 2.17 (SD, 0.71) versus 2.24 (SD, 0.64), 1.14 (SD, 0.88) versus 1.00 (SD, 0.85), 0.63 (SD, 0.85) versus 0.53 (SD, 0.82), and 0.29 (SD, 0.53) versus 0.21 (SD, 0.50). The inflammatory scores decreased with time in both groups (Friedman test, both \( P < 0.001 \)). However, there was no statistically significant difference in the inflammatory scores between the two groups (Wilcoxon signed rank test; day 6, \( P = 0.157 \); day 13, \( P = 0.157 \); day 20, \( P = 0.083 \); day 27, \( P = 0.317 \)). The distribution of the scores is shown in Figure 1.

Most of the children had no or very mild discomfort throughout the postoperative period. The respective mean symptom scores at days 6, 13, 20, and 27 in groups 1 and 2 were 0.66 (SD, 1.14) versus 0.69 (SD, 1.20), 0.48 (SD, 0.91) versus 0.41 (SD, 0.78), 0.43 (SD, 0.82) versus 0.40 (SD, 0.77), and 0.18 (SD, 0.48) versus 0.18 (SD, 0.48). There was no statistically significant difference between the two treatment groups (Wilcoxon signed rank test; day 6, day 13, and day 20, \( P = 0.317 \); day 27, \( P = 1.000 \)). The distribution of the scores is shown in Figure 1.

### Discussion

Fluorometholone has been shown to be associated with a lesser degree of IOP rise than DMS in adults in previous studies.\(^{13,17–19}\) However, in steroid responders, ocular hypertensive response to FML has been shown in some studies to be severe\(^1\) and comparable with that of DMS.\(^20\) The ocular hypertensive effect of FML in children has not been well studied.\(^{13,11}\) Akingbehin\(^13\) found that only 8.3% of FML eyes in adults (four times daily for 6 weeks) showed a change in IOP more than 5 mmHg. This was much lower

### Table 2. Ocular Hypertensive Response to Topical Fluorometholone

<table>
<thead>
<tr>
<th>Classification</th>
<th>Low (Net Increase in Intraocular Pressure, &lt;6 mmHg)</th>
<th>Intermediate (Net Increase in Intraocular Pressure, 6–15 mmHg)</th>
<th>High (Net Increase in Intraocular Pressure, &gt;15 mmHg)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armaly(^4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>22</td>
<td>9</td>
<td>0</td>
<td>0.224</td>
</tr>
<tr>
<td>Group 2</td>
<td>26</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

| Low (Peak Intraocular Pressure, <20 mmHg) | Intermediate (Peak Intraocular Pressure, 20–31 mmHg) | High (Peak Intraocular Pressure, >31 mmHg) |
|----------------|-------------------------------------------------|-------------------------------------------------|-------------|
| Becker and Hahn\(^5\) | | | |
| Group 1 | 20 | 11 | 0 | 0.409 |
| Group 2 | 23 | 8 | 0 | |
when compared with the results of our study. Nine children (29.0%) in group 1 and 8 children (25.8%) in group 2 had an increase in IOP of more than 5 mmHg. Moreover, the maximum net IOP increase was up to 16.00 mmHg versus 10.30 mmHg in groups 1 and 2, respectively. The greater ocular hypertensive response in children may be the result of the different degree of maturity of the drainage angle. Remé and d’Epinay\(^2\) found that the angle structures were immature at birth and only became as mature as adult angles at the age of 8 years. Knepper et al\(^2\) reported that ocular hypertensive response was also much more prominent in young than old rabbits. Their study showed that there was a good correlation between the concentration and distribution of the glycosaminoglycans in the anterior segment of the eyes. However, the exact relationship between age and ocular hypertensive effect cannot be differentiated because of the limited sample size.

Ohji et al\(^9\) examined the IOPs of children treated with different types of corticosteroids. None of the children treated with FML three times daily had an IOP more than 20 mmHg. This result was different from our study. Four eyes (12.9%) in group 2 (FML three times daily) had an IOP of more than 21 mmHg. This difference may be in part the result of the duration of the treatment. Fluorometholone was used for only 2 weeks in Ohji et al’s study, in comparison with 4 weeks in our study. Because the median time to reach the peak IOP was 13 days in our study, the longer duration of steroid use may have caused the higher ocular hypertensive response. The age factor probably was not that relevant, because there was only a small difference. The mean ages in Ohji et al’s study and our study were 6.5 and 5.5 years, respectively.

The frequency of steroid application affected the risk of ocular hypertension, as in our study the peak IOP and the maximal change in IOP were significantly higher in group 1. Moreover, there were also more cases that had an IOP more than 21 mmHg in group 1. There were even two cases in group 1 that had peak IOP of at least 30 mmHg. In addition to the amplitude, the rate of IOP surge was also faster in group 1. Because the two eyes of the same patient who received different frequency of FML were compared, confounding factors such as age, race, and the type of operation should not affect our results and interpretation. Moreover, all patients had a negative family history of glaucoma. It therefore is likely that the ocular hypertensive response we noted is due mainly to the effect of topical FML. We cannot exclude the systemic absorption and crossover effect of topical FML. The eyes that received higher frequency of FML may have affected the eyes that received less. This may have caused a stronger response in group 2, in which the eye received a lower frequency regimen. However, the consequence of this factor will dilute and tend to undermine the severity of the dose-dependent response. If the assumption is valid and the systemic absorption is substantial, the dose-dependent phenomenon will be even more obvious when the eyes are treated independently. Further studies in which patients are randomized into different regimens may be warranted to delineate clearly the dose-dependent effect of FML.

Conversely, the antiinflammatory response failed to show a significant difference between the two groups. Therefore, lower dosage of FML after operation should be considered. However, the inflammation after strabismus surgery is mild, but there are conditions in which a stronger antiinflammatory agent is needed.

Although FML was safer than other types of corticosteroids in causing steroid-induced glaucoma, it still caused ocular hypertension in a dose-dependent manner in children. From this and our previous studies,\(^11,12\) the ocular hypertensive effect of steroids in children is much greater than that in adults. However, because of the limited sample size, the relationship between age and the ocular hypertensive effect of steroids cannot be differentiated in this and our previous studies.\(^11,12\) A large-scale, prospective study to investigate this relationship is warranted. Conversely, other antiinflammatory agents such as rimexolone (Vexol, Fort Worth, Texas)\(^23–25\) and nonsteroidal antiinflammatory drugs\(^26–28\) that have been shown to cause no or minimal ocular hypertensive effects should be considered as substitutes for corticosteroids in appropriate cases. When FML is used in children, a lower frequency and shorter duration of usage is recommended because its ocular hypertensive response is dose dependent. When a longer term and higher frequency FML is required, it is desirable to monitor IOP
References

13. Akingbehin AO. Comparative study of the intraocular pressure effects of fluorometholone 0.1% versus dexamethasone 0.1%. Br J Ophthalmol 1983;67:661–3.