Ocular-Hypertensive and Anti-inflammatory Response to Rimexolone Therapy in Children

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Objective: To compare the ocular-hypertensive and anti-inflammatory response to rimexolone (11β-hydroxy-16α-fluoro-6α-methylprednisolone) and fluorometholone (21-deoxy-9α-fluoro-6α-methylprednisolone) therapy in children’s eyes.

Methods: With parental consent, children who underwent surgical procedures for bilateral symmetric strabismus from January 18, 2000, through November 16, 2001, were recruited. One eye was randomized to receive topical 1% rimexolone while the contralateral eye received topical 0.1% fluorometholone, 4 times daily for 4 weeks.

Main Outcome Measures: Intraocular pressures and anti-inflammatory responses were the main outcome measures and were serially measured postoperatively for 8 weeks.

Results: Fifty-four children, aged from 4 to 8 years (mean [SD] age, 5.33 [1.26] years), participated in the study. Intraocular pressure increased significantly in both treatment groups compared with the preoperative values (P<.001). The mean (SD) peak intraocular pressure was significantly higher in the rimexolone-treated group, 19.7 (6.1) vs 17.6 (4.6) mm Hg (P<.001). Similarly, the mean (SD) net increase in intraocular pressure (P<.001), was also higher in the rimexolone-treated eyes, 5.9 (4.4) vs 3.9 (4.1) mm Hg (P<.001). In addition, a greater percentage of the rimexolone-treated patients had no conjunctival erythema on days 13 (11.1% vs 0.0%) and 20 (88.9% vs 55.6%) (P=.03).

Conclusions: Rimexolone seems to be a more effective anti-inflammatory agent than fluorometholone. However, unlike adults, the ocular-hypertensive effect in children treated with rimexolone was higher. It would be desirable to monitor the intraocular pressure regularly when rimexolone therapy is used in children.

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Corticosteroids are commonly used anti-inflammatory agents. They are used in the treatment of various ocular diseases and after cataract, glaucoma, or strabismus surgery. The duration of use depends on the indication, but treatments can last for weeks. The use of corticosteroids carries many significant adverse effects including glaucoma, corneal problems, posterior subcapsular cataracts, and exacerbations of infection. Corticosteroid-induced glaucoma is usually characterized by an elevated intraocular pressure (IOP) after corticosteroid use and can result in irreversible visual field and vision loss. Clinically, corticosteroid-induced glaucoma with an elevated IOP is usually symptom free until significant damage has been done, and then only comes to light when the disease has already reached an advanced stage. The ocular-hypertensive response in adults to oral, topical dermatologic, topical ocular, and periocular corticosteroid agents is well established. Even inhalation and nasal corticosteroids have been reported to be associated with ocular hypertension in susceptible adults.

Armaly studied the ocular-hypertensive response of healthy adults to the application of topical dexamethasone eye-drops as early as 1963. He demonstrated that there was an increase in IOP and a reduction in outflow facility in healthy subjects after 4 weeks of dexamethasone application. Moreover, he classified subjects into the following 3 responder groups according to the degree of their responses to the treatment: a low responder had an increase in IOP of less than 6 mm Hg; an intermediate responder had an increase between 6 and 15 mm Hg; and a high responder had an increase of more than 15 mm Hg. In the general healthy population, 5% were high corticosteroid responders, 35% were intermediate responders, and 60% were low responders.

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remaining 60% of the population had no response. A 1997 study found that the ocular-hypertensive response to topical dexamethasone therapy occurred more frequently, severely, and rapidly in children than in adults. Sixty-two percent (10 of 16 children) were high corticosteroid responders compared with 5% of the adults. Moreover, this ocular-hypertensive response to topical dexamethasone therapy in children was dose dependent. The higher the frequency of dexamethasone application, the more significant was the ocular-hypertensive effect.

Less potent corticosteroids, such as fluorometholone (21-deoxy-9αfluoro-6αmethylprednisolone), have been reported to have a reduced risk of corticosteroid-induced elevation in IOP compared with dexamethasone therapy. However, the anti-inflammatory action is correspondingly reduced by using a less potent corticosteroid. The current strategy for the development of new corticosteroid agents for ocular use is, therefore, to identify drugs that exhibit marked anti-inflammatory activity while decreasing the propensity to raise the IOP.

A new corticosteroid, 1% rimexolone ophthalmic suspension (116-hydroxy-9αfluoro-6αmethylprednisolone), has shown similar anti-inflammatory activity compared with corticosteroids such as 1.0% prednisolone acetate. Rimexolone lacks a hydroxyl substitute at the C-21 position of its chemical structure. Thus, it is proposed to be less likely to elevate IOP. A double-masked, randomized, crossover study of corticosteroid responders compared the effects on IOP of 1% rimexolone with those of 1.0% prednisolone and 0.1% fluorometholone. The results suggested that the IOP-elevating potential was comparable to that of fluorometholone. This medication has been used in the treatment of uveitis and posturgical inflammation in adults. Children’s eyes, however, tend to have a more exaggerated ocular-hypertensive response to dexamethasone therapy than those of adults. To our knowledge, whether children would also have a substantial ocular-hypertensive response to rimexolone therapy is yet unknown.

**METHODS**

**SUBJECTS**

With parental consent, children who underwent bilateral symmetric strabismus surgery at the Prince of Wales Hospital or the Hong Kong Eye Hospital, Hong Kong, from January 28, 2000, through November 16, 2001, were recruited for this study. Eligible candidates were children aged between 3 and 10 years for the original study, but when recruited by us, the children were aged between 4 and 8 years, with a preoperative IOP of 21 mm Hg or less, and a cup-disc ratio of 0.3 or less with no other systemic and ocular diseases. Exclusionary criteria included a history of corticosteroid use in the previous whole year, a family history of glaucoma; and failure to comply with treatment, follow-up schedules, and IOP measurement.

**PROCEDURE**

The study and the measurements followed the guidelines of the Declaration of Helsinki. The study was approved by the ethics committee of The Chinese University of Hong Kong. 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 treatments in their eyes after the operation. 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 IOP measurements. Non-contact tonometry (XPERT NCT Plus Non-Contact Tonometer; Leica, Depew, NY) was used because it could be more easily tolerated by children and its reliability had been reported to be excellent. Three consistent readings were obtained from each eye and the mean value was used for analysis.

All operations were performed by 4 of us (D.S.P.F., C.B.O.Y., C.Y.W., and J.S.K.N.) under general anesthesia. One eye of each child was randomized to receive 0.1% fluorometholone eye drops (Flucon; Alcon Laboratories, Ft Worth, Tex), 4 times per day, and the contralateral eye would receive 1.0% rimexolone eye drops (Voxel, Alcon Laboratories), 4 times per day, after undergoing a bilateral symmetric strabismus operation. Topical 0.25% chloramphenicol, 4 times per day, was also prescribed for both eyes. The treatment commenced from the day of the operation and continued for 4 weeks. Patients, parents, optometrists, and ophthalmologists responsible for assessing the study outcomes were masked by not knowing the eyedrop allocated for each eye.

The IOP and the degree of inflammation were assessed. Intraocular pressure was measured on postoperative days 1, 3, 6, 13, 20, 27, 41, and 55. The procedure for IOP measurement was performed as described earlier. The IOP of each patient was measured within 2 hours of the assessment day. Corticosteroid therapy was discontinued if any eye developed an IOP higher than 30 mm Hg and more frequent follow-up visits were arranged. Antiglaucomatous therapy (a β-adrenergic blocking agent) was initiated until the patient’s baseline IOP was reached. In addition, the optic discs were evaluated with fundi examination.

The conjunctival inflammatory response was analyzed objectively by comparing the degree of conjunctival hyperemia over the sites of the muscle surgery against a series of color photographs and by allocating a conjunctival inflammatory score for each eye on postoperative days 6, 13, 20, and 27. The procedure for IOP measurement was performed as described earlier. The IOP of each patient was measured within 2 hours of the assessment day. Corticosteroid therapy was discontinued if any eye developed an IOP higher than 30 mm Hg and more frequent follow-up visits were arranged. Antiglaucomatous therapy (a β-adrenergic blocking agent) was initiated until the patient’s baseline IOP was reached. In addition, the optic discs were evaluated with fundus examination.

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**STATISTICAL ANALYSIS**

Demographic data of the patients were analyzed by descriptive statistics. The peak IOP and the rise in IOP (calculated as peak IOP minus preoperative IOP) between the 2 eyes were compared using paired t tests. The time taken to reach the peak IOP was assessed between the 2 groups using the χ² test. The inflammation scores between the 2 eyes were compared using the Wilcoxon signed rank test. The inflammation scores were also used as the basis for assessing the percentage of eyes with no inflammation. An eye was defined as having no inflammation if the inflammation score was 0 at that follow-up visit. χ² Test was used to compare the cumulative percentage in each group who presented with no inflammation at the follow-up visits. P<.05 was defined as statistically significant.

The sample size was calculated based on an estimated mean difference in IOP of 2 mm Hg between the 2 groups. With 49 eyes in each group, the study had at least 80% power to detect the clinically important IOP difference. Assuming a dropout
rate of 10%, 55 children were recruited; 54 children participated in the study.

RESULTS

Fifty-five children were recruited; however, only 54 children (24 boys [44.4%] and 30 girls [55.6%]), aged 4 to 8 years (mean [SD] age, 5.33 [1.26] years), participated in the study, because 1 child had been uncooperative during IOP measurement. They all underwent bilateral symmetric strabismus operations. Forty children (74.1%) received bilateral lateral rectus recessions, 11 children (20.4%) had bilateral medial rectus recessions, and 3 children (5.6%) received bilateral inferior oblique recessions. (Owing to rounding, these percentages do not total 100.)

Fifty-four eyes received rimexolone eyedrops (24 right eyes and 30 left eyes), and the fellow 54 eyes (30 right eyes and 24 left eyes) received fluorometholone eyedrops.

The mean (SD) preoperative IOP was 13.7 (3.3) mm Hg. There was no statistically significant difference between the rimexolone-treated group (13.8 [3.5] mm Hg) and fluorometholone-treated group (13.7 [3.3] mm Hg) (paired t test; \( P = .38 \)) (Table 1). The net increase in IOP was calculated by subtracting the preoperative IOP from the peak IOP. The net increase in IOP was also higher in children in the rimexolone-treated group (mean [SD], 5.9 [4.4] mm Hg; range, 1.7-16.0 mm Hg) than those in the fluorometholone-treated group (3.9 [4.1] mm Hg; range, −3.3 to 10.0 mm Hg) (paired t test, \( P < .001 \)), as given in Table 1. A

Table 1. Summary of Intraocular Pressure (IOP) Changes in the 1% Rimexolone- and 0.1% Fluorometholone-Treated Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rimexolone-Treated Group</th>
<th>Fluorometholone-Treated Group</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative IOP, mm Hg</td>
<td>13.8 (3.5) [7.5 to 20.0]</td>
<td>13.7 (3.3) [9.5 to 20.3]</td>
<td>.38</td>
</tr>
<tr>
<td>Peak IOP, mm Hg</td>
<td>19.7 (6.1) [10.3 to 28.0]</td>
<td>17.6 (4.6) [12.3 to 26.0]</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Net IOP change, mm Hg</td>
<td>5.9 (4.3) [1.7 to 16.0]</td>
<td>3.9 (4.1) [−3.3 to 10.0]</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

*Data are given as the mean (SD) [range].

OCULAR-HYPERTENSIVE EFFECT

The ranges of peak IOPs were 10.3 to 28.0 mm Hg in the rimexolone-treated group and 12.3 to 26.0 mm Hg in the fluorometholone-treated group. The mean (SD) peak IOPs were 19.7 (6.1) mm Hg (95% confidence interval [CI], 18.0-21.4 mm Hg) for the rimexolone-treated group and 17.6 (4.6) mm Hg (95% CI, 16.3-18.8 mm Hg) for the fluorometholone-treated group (Figure 1). Both treatment groups had peak IOPs significantly higher than the preoperative values (paired \( t \) test, both \( P < .001 \)). Moreover, the peak IOP in the rimexolone-treated group was also significantly higher than that recorded in the fluorometholone-treated group (95% CI, 1.1-3.1 mm Hg; paired \( t \) test, \( P < .001 \)), as given in Table 1. None of the children had a peak IOP of 30 mm Hg or higher.

Eighteen eyes (33.3%) in the rimexolone-treated group and 15 eyes (27.8%) in the fluorometholone-treated group had IOPs higher than 21 mm Hg (\( \chi^2 \) test, \( P = .53 \)) at some stage of the study. The cumulative percentages of eyes with elevated IOPs of more than 21 mm Hg are shown in Figure 2. After installation of topical corticosteroid eyedrops, the percentage of eyes having IOPs of more than 20 mm Hg at days 6, 13, 20, and 27 were 14.8%, 33.3%, 42.6%, and 46.3% in the rimexolone-treated group, and 9.3%, 11.1%, 22.2%, and 24.1% in the fluorometholone-treated group (paired \( \chi^2 \) test, \( P < .001 \)). The net increase in IOP was calculated by subtracting the preoperative IOP from the peak IOP. The net increase in IOP was also higher in children in the rimexolone-treated group (mean [SD], 5.9 [4.4] mm Hg; range, 1.7-16.0 mm Hg) than those in the fluorometholone-treated group (3.9 [4.1] mm Hg; range, −3.3 to 10.0 mm Hg) (paired \( t \) test, \( P < .001 \)), as given in Table 1. A

Figure 1. The difference between peak intraocular pressure (IOP) measurements of the 1% rimexolone- and 0.1% fluorometholone–treated groups as well as their respective preoperative IOP measurements. The error bars indicate the 95% confidence intervals.

Figure 2. Cumulative percentages of eyes with intraocular pressure measurements greater than 21 mm Hg in the 1% rimexolone– and 0.1% fluorometholone–treated groups.
clinically significant rise in IOP (defined as >10 mm Hg) occurred more frequently in the rimexolone-treated group. Six eyes (11.1%) in the rimexolone-treated group experienced a rise in IOP of higher than 10 mm Hg compared with none in the fluorometholone-treated group.

**Table 2** lists the different levels of ocular-hypertensive response of the 2 groups according to the classification system proposed by Armaly and Becker. Results were similar between the 2 classifications. The proportion of high or intermediate responders was found to be higher in the rimexolone-treated group. There were statistically significant differences in the various levels of ocular-hypertensive response between the rimexolone- and fluorometholone-treated groups according to the classifications of Armaly (χ² test, *P* =.02) and Becker (χ² test, *P* =.003). In all children of whom the fluorometholone-treated eyes had an intermediate ocular-hypertensive response, the fellow rimexolone-treated eyes also had an intermediate to high response.

Eyes that had received rimexolone reached peak IOPs earlier than those that had received fluorometholone eye-drops (Wilcoxon signed rank test, *P* =.02). The median time to reach peak IOP was 6 days for the rimexolone-treated group (range, 1-27 days) vs 13 days for the fluorometholone-treated group (range, 1-27 days).

There was no correlation between age and peak IOP (rimexolone-treated group, *r* =.02, *P* =.88; fluorometholone-treated group, *r* =.13, *P* =.33). Moreover, age was unrelated to the net increase in IOP (rimexolone-treated group, *r* =−.01, *P* =.93; fluorometholone-treated group, *r* =.24, *P* =.08).

**ANTI-INFLAMMATORY EFFECT**

The objective inflammatory scores decreased with time in both groups as shown in **Figure 3**. The conjunctival inflammation in all cases subsided by day 27. A greater cumulative percentage in the rimexolone-treated group than in the fluorometholone-treated group had no conjunctival erythema (objective inflammatory score, 0) on days 13 (rimexolone-treated group, 6 cases [11.1%]; fluorometholone-treated group, 0 cases) and 20 (rimexolone-treated group, 48 cases [88.9%]; fluorometholone-treated group, 30 cases [55.6%]) (χ² test, *P* =.03).

The subjective symptom scores also decreased with time (Figure 3). However, most children had only mild or no discomfort throughout the postoperative period.

The maximal discomfort score was 3 of 5. The number of patients who had no discomfort (symptom score, 0) in the rimexolone- and fluorometholone-treated groups were, respectively, 18 (33.3%) vs 6 (11.1%) at day 13, 45 (83.3%) vs 33 (61.1%) at day 20, and 54 (100.0%) vs 54 (100.0%) at day 27 (χ² test, *P* =.08).

**COMMENT**

Corticosteroids prevent or suppress the undesirable sequelae of postoperative inflammation including redness, swelling, and tenderness. They are widely used in various ocular diseases and after surgical procedures. Although the use of topical corticosteroid therapy carries less risk of systemic complications, it can cause visual loss through its effect on aqueous outflow, an effect that is greater than that seen with systemic treatment. There are different types of corticosteroids with various potencies. Less potent corticosteroids such as fluorometholone have been shown to be associated with a lesser degree of rise in IOP in previous studies. However, this is accompanied by reduced anti-inflammatory activity. Thus, an anti-inflammatory agent that controls inflammation with little effect on IOP would be an ideal agent. One percent rimexolone therapy has demonstrated satisfactory anti-inflammatory effect, comparable with dexamethasone therapy and may be less likely to elevate IOP. Structurally, it contains a methyl group at the C-21 position. Omission of this hydroxyl group and substitution of a methyl group may reduce the propensity for inducing an increased IOP, as demonstrated with fluorometholone.

In adults 1% rimexolone and 0.1% fluorometholone have comparable ocular-hypertensive potential. However, it has been demonstrated in various studies that the ocular-hypertensive responses of children to different types of traditional corticosteroids including dexamethasone and fluorometholone were more frequent, severe, and rapid compared with those of adults. To our knowledge, this is the first study of the anti-inflammatory and ocular-hypertensive effects of rimexolone therapy in children. We found that more than half (55.6%) of the children treated with 1% rimexolone were intermediate responders (peak IOP between 20 and 31 mm Hg) according to Becker’s classification. Moreover, 6 patients (11.1%) had an IOP elevation of more than 10 mm Hg compared with preoperative values. This was more severe than what had been reported in adults. Assil et al...
found that only 2 (1.5%) of 133 rimexolone-treated adults had a similar IOP elevation. The more severe ocular-hypertensive response in children compared with that in adults can be explained by the structural and functional immaturity of the trabecular meshwork.36 Remé and d’Epinay37 reported that although chamber angle components were fully present at birth, the maturation of angle cellular and extracellular components occurred only 1 to 8 years after birth. This age-dependent response was also demonstrated in rabbits.38 Owing to the limited sample size, the exact relationship between age and ocular-hypertensive effect cannot be further differentiated in our study. This warrants a larger-scale, prospective study to investigate this relationship. On the other hand, TIGR protein was proposed to regulate IOP during corticosteroid treatment.39,40 In our previous study, TIGR mutation was contributed to only 1 (1.1%) of the 91 Chinese patients with primary open-angle glaucoma.41 Its role in corticosteroid-induced ocular hypertension might not be significant. However, further study is required to study the effect of the TIGR gene in corticosteroid-induced glaucoma in children.

Previous study results in adults showed that rimexolone therapy had an IOP-elevating potential comparable to that of fluorometholone therapy.5,35 However, when comparing the response of the eyes receiving different types of corticosteroids in this study, the rimexolone-treated eyes had a significantly higher peak IOP (19.7 mm Hg vs 17.6 mm Hg) as well as a net increase in IOP (5.9 mm Hg vs 3.9 mm Hg) than that of the fluorometholone-treated eyes. Moreover, the eyes treated with rimexolone (median, 6 days) also reached a peak IOP earlier than those treated with fluorometholone (median, 13 days). The mean difference in IOP between the 2 groups was only 2 mm Hg. However, we cannot exclude the systemic absorption and crossover effect of the topical corticosteroids. The eyes receiving the more potent corticosteroid may influence the other eye. This may have caused a stronger response in the eyes treated with the less potent regimen. 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, then the dose-dependent phenomenon will be even more obvious when the eyes are treated independently. Further studies in which patients are randomized to different regimens may be warranted to clearly delineate the dose-dependent effect of fluorometholone. Moreover, the corticosteroid eyedrops were continued for 4 weeks postoperatively in our study. There are situations, such as in uveitis, in which the patients require corticosteroid treatment for months.45 The more pronounced dose-dependent ocular-hypertensive effect might be more applicable to those patients.

Our double-masked randomized study evaluated the anti-inflammatory potential of 1% rimexolone and 0.1% fluorometholone, each given 4 times daily for 4 weeks, after bilateral symmetric strabismus operations in children. The outcomes of treatment efficacy included the degree of conjunctival erythema (inflammatory score) and severity of the patient’s discomfort (symptom score). Symptom scores did not demonstrate statistically significant differences favoring rimexolone-treated eyes. The lack of statistical significance (P=.08) for this may be owing to the mild discomfort associated with strabismus operations. On the other hand, the rimexolone-treated group had lower inflammation scores than the fluorometholone-treated group. Also, there were significantly more eyes in the rimexolone-treated group than in the fluorometholone-treated group that had no conjunctival erythema.

In summary, the clinician’s follow-up impression of inflammatory response was significantly in favor of the rimexolone-treated group. Although 1% rimexolone was more effective in controlling inflammation, it was also more likely to cause corticosteroid-induced IOP elevation. Moreover, this ocular-hypertensive response was more pronounced in children compared with adults. In susceptible patients, other types of anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs that...
have been shown to cause minimal or no ocular-hypertensive effects should be considered instead. 46-48

The findings from this study have suggested that 1% rimexolone is a more effective anti-inflammatory drug than 0.1% fluorometholone. However, rimexolone also causes significant ocular hypertension in children. To reduce the chance of provocation of such an IOP rise, corticosteroid use should be minimized with respect to the type of corticosteroid prescribed, the frequency of instillation, and the duration of use. Moreover, it is necessary to monitor IOP in children who receive rimexolone eye-drops especially for those who require treatment for a prolonged period or at an increased frequency.

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