Ocular Hypertensive Response to Topical Dexamethasone in Children

A Dose-dependent Phenomenon

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Objective: To investigate the ocular-hypertensive response to different dosages of topical dexamethasone eye drops in Chinese children.

Design: Prospective, randomized clinical trial.

Participants: Thirty-one consecutive children undergoing bilateral strabismus surgery.

Intervention: Topical dexamethasone (0.1%) was administered to children undergoing bilateral strabismus surgery. They were all less than 10 years of age. One eye was randomized to receive a regimen of four times daily, and another received a twice daily regimen. Intraocular pressure (IOP) was serially measured in the postoperative period for 4 weeks or more. Topical steroids were discontinued if IOP was 30 mmHg or more.

Main Outcome Measures: Intraocular pressure was measured on the day before the surgery, on postoperative days 1, 3, 5, 8, 12, 15, 22, 29, and 2 weeks thereafter until the IOP reached preoperative levels. Peak IOP, IOP net increase, and time to reach an IOP more than 20 mmHg in the two study groups were analyzed.

Results: A total of 31 patients (20 male, 11 female) were examined. The mean age was 5.8 ± 2.0 years (range, 2–10 years). Preoperative IOP in groups treated twice daily and four times daily were similar. After topical dexamethasone treatment, both groups showed a significant rise in peak IOP compared with preoperative values (twice daily, 25.2 ± 6.8 mmHg vs. 14.3 ± 2.4 mmHg, P < 0.001; four times daily, 28.7 ± 6.9 mmHg vs. 14.3 ± 2.9 mmHg, P < 0.001). The peak IOP was significantly higher in the four times daily group (P < 0.001), as was the net increase in IOP (twice daily, 10.9 ± 5.8 mmHg vs. four times daily, 14.5 ± 6.4 mmHg; P < 0.001). There was no difference in time for both groups to achieve the peak IOP, but the time to exceed its upper normal value (20 mmHg) was shorter in the four times daily group (twice daily, 12.3 ± 9.1 days vs. four times daily, 10.0 ± 7.4 days; P < 0.05).

Conclusions: In children treated with topical dexamethasone, ocular hypertension occurs in a dose-dependent manner. Children in the four times daily group had a quicker onset and more severe ocular hypertensive response than the twice daily group. Nevertheless, even the twice daily regimen produced significant IOP rise, suggesting that dexamethasone use in children should be avoided if possible, and it would be desirable to monitor the IOP twice weekly when it is administered to children.

Dexamethasone is a commonly used antiinflammatory drug. In various conditions such as uveitis, ¹ vernal keratoconjunctivitis, ² and most of the postoperative cases, ³ topical steroids are the mainstay of treatment. Some of the patients may need a high dose or prolonged course of treatment. One of the common side effects of steroid therapy is glaucoma. For safe and effective use of topical steroids, it is important to identify those high-risk groups and have a good understanding of their ocular pressure response.

Previous studies have described the type, ⁴–⁷ strength, ⁵,⁸ dosage frequency, ⁹ duration of treatment, ¹⁰ and the route of administration of steroid that may contribute to steroid-induced glaucoma. Most of these studies were performed on adults. One of our previous studies indicated that the ocular hypertensive response to topical dexamethasone of children occurred more frequently, more severely, and more rapidly than that reported in adults. ¹⁴ In this follow-up study, we investigated the ocular hypertensive response of children to different dosages of topical dexamethasone. The results will be of value in formulating guidelines for intraocular pressure (IOP) monitoring in children receiving topical dexamethasone.
Intervention and Method

This was a prospective, randomized clinical trial. A total of 31 children undergoing bilateral strabismus surgery at the Alice Ho Miu Ling Nethersole Hospital were recruited. All patients were ethnically Chinese and less than 10 years of age. Before surgery, their IOP levels were normal, and cup-to-disc ratios were 0.3 or less. Patients with a family history of glaucoma, a history of steroid use within 1 year before the time of study, or those who did not comply with serial IOP measurements were excluded from the study. Approval from the institutional review board and informed consent from parents of the patients were obtained.

Bilateral muscle recession was performed on all patients by the same surgeon (JSKN). Apart from the assigned regimen of topical dexamethasone, no other steroids were used before or after surgery. After surgery, one eye was randomized to receive topical 0.1% dexamethasone (Maxidex, Alcon Laboratories, Belgium) four times daily, whereas another group was treated twice daily. Both eyes received topical 0.25% chloramphenicol eye drops four times daily. The treatment commenced on the day of operation and was continued for 4 weeks.

Intraocular pressure measurements were taken on the day before operation and on postoperative days 1, 3, 5, 8, 12, 15, 22, and 29. Measurement was continued at 2-week intervals until IOP measurements returned to preoperative levels. Intraocular pressure was measured by noncontact tonometry (XPERT NCT Plus, Leica, Buffalo, New York). A mean of three reliable readings was taken. Goldmann applanation tonometry (900.4.4, Haag-Streit, Koeniz, Switzerland) was performed as a confirmation test if the IOP measured by the noncontact tonometry exceeded 20 mmHg. According to the conclusion of Myers et al.'s study on IOP measurements of 620 eyes, noncontact tonometry is a highly accurate and reliable test. It agreed very closely with Goldmann applanation tonometry in which the population IOP means agreed within 0.3 mmHg and the slope of regression coefficient was 1.025. Therefore, analysis of results in the present study was based on the readings of noncontact tonometry. Dexamethasone eyedrops were discontinued in any eyes with IOP levels more than 30 mmHg. Close monitoring of IOP and antiglaucomatous therapy were started until baseline IOP of the patients was noted. The IOP of each patient was measured within 2 hours of the same time of each day's visit.

Statistics

The demographic data of the patients was calculated by descriptive statistics. The comparison between the four times daily and the twice daily topical dexamethasone regimen was made by the paired t test. The chi-square test was used to compare the difference in frequency of patients with elevated IOP. Based on the estimated minimal mean difference of 15% between the two groups and the standard deviation of the data as well as the power of 0.8, the sample size was estimated to be 26. A P value less than 0.05 was defined as statistically significant.

Results

The mean age of our 31 patients (20 male, 11 female) was 5.8 ± 2.0 years (range, 2–10 years). All patients underwent bilateral recession surgery for strabismus (lateral rectus recession, n = 19; medial rectus recession, n = 6; lateral rectus plus inferior oblique recession, n = 6). Thirty-one eyes were randomized to receive the four times daily regimen, whereas fellow eyes received the twice daily regimen. Mean preoperative IOP was 14.3 ± 2.6 mmHg. There was no significant difference in preoperative IOP between the twice daily and four times daily groups (twice daily, 14.3 ± 2.4 mmHg vs. four times daily, 14.3 ± 2.9 mmHg).

The cumulative percentage of eyes with elevated IOP of more than 20 mmHg and more than 30 mmHg are shown in Figure 1. After topical dexamethasone treatment, the percentage of eyes having IOP levels more than 20 mmHg at days 3, 8, 15, and 29 were 9.7, 48.4, 61.3, and 90.3 in the twice daily group and 9.7, 58.1, 74.2, and 90.3 in the four times daily group, respectively. The percentages of eyes having an IOP more than 30 mmHg at days 3, 8, 15, and 29 were 3.2, 9.6, 19.2, and 22.4 in the twice daily group and 3.2, 19.3, 38.6, and 48.3 in the four times daily group, respectively. It was found that the four times daily group had a significantly larger number of patients with an IOP more than 30 mmHg than the twice daily group at day 29 of treatment (four times daily, 15 eyes [48.4%] vs. twice daily, seven eyes [22.6%]; chi-square = 4.5, P = 0.03).

Both treatment groups had a peak IOP significantly greater than the preoperative value (twice daily, 25.2 ± 6.8 mmHg vs. 14.3 ± 2.4 mmHg, P < 0.001; four times daily, 28.7 ± 6.9 mmHg vs. 14.3 ± 2.9 mmHg, P < 0.001). The peak IOP was significantly higher in the four times daily group than in the twice daily group (P < 0.001; Fig 2). In addition, the net increase in IOP was significantly larger in the four times daily group (twice daily, 10.9 ± 5.8 mmHg vs. four times daily, 14.5 ± 6.4 mmHg; P < 0.001).
0.001). A difference in frequency distribution of net increase in IOP in both groups is shown (Fig 3).

There was no difference in the duration of reaching peak IOP (twice daily, 15.5 ± 7.3 days vs. four times daily, 14.1 ± 7.2 days) and an IOP of more than 30 mmHg (twice daily, 10.3 ± 4.7 days vs. four times daily, 11.6 ± 5.9 days) between groups. However, the four times daily group took a shorter time (twice daily, 12.3 ± 9.1 days vs. four times daily, 10.0 ± 7.4 days; P < 0.05) to exceed the upper normal value of IOP (20 mmHg; Fig. 4). The time when the IOP returned to the preoperative level after termination of dexamethasone treatment was 9.4 ± 6.5 days in the twice daily group and 10.4 ± 6.6 days in the four times daily group.

There was no correlation between age and peak IOP in either group (twice daily, r = 0.22, P = 0.24; four times daily, r = 0.12, P = 0.53). Also, no correlation was noted between age and duration to reaching an abnormal IOP in either group (twice daily, r = −0.03, P = 0.88; four times daily, r = 0.02, P = 0.92).

Discussion

The use of corticosteroids could be a painless cause of visual loss resulting from increased IOP. Although topical therapy carries less risk of systemic complications, its effect on aqueous outflow facility is greater than systemic therapy.13 In adult eyes, topical steroids induce a rise in IOP that correlates with the duration and frequency of drug administration. Most clinicians treat pediatric patients based on these results, although data on children are limited. Kass et al18 reported that in two infants who received long-term topical corticosteroid therapy, a clinical picture similar to congenital glaucoma had developed. In Ohji et al’s19 study, a marked elevation in IOP after 0.1% dexamethasone instillation was noted frequently in children less than 10 years of age. In this study, 67.8% and 28.9% of eyes had IOP levels more than 20 mmHg and more than 30 mmHg at day 15 after topical dexamethasone treatment. When we categorized the results of similar studies in patients of different age groups (Table 1), it appeared that a higher proportion of those who were considered high responders to topical steroid therapy were younger patients.14,20,21 This age-dependent response was also demonstrated in rabbits and was supported by the difference in distribution and structure of proteoglycans.22

The difference in ocular hypertensive response between children and adults can be explained by the structural and functional immaturity of trabecular meshwork.19 Remé and d’Epinay23 reported that although chamber angle components were fully present at birth, the maturation of angle cellular and extracellular components occurred 1 to 8 years after birth. In our investigation, the age of study participants ranged from 2 to 10 years. There was no correlation between age and peak IOP or duration to reach an abnormal IOP. It therefore appears that there is no age-related steroid response within this age group. However, the correlation may be masked by the small sample size.

When comparing the response of the eyes receiving different dosages of topical dexamethasone in this study, the four times daily group had a significantly higher peak as well as net increase in IOP than did the twice daily group. The frequency distribution of net increase in IOP in Figure 3 also showed a skew distribution toward higher IOP rise in the four times daily group. In addition to the amplitude, the rate of pressure surge was also higher in the four times daily group. Therefore, the results of this study demonstrate a dose-dependent ocular hypertensive response to topical dexamethasone in children. It is desirable to monitor the IOP closely after commencement of topical steroid therapy. As shown in Figure 1, approximately 10% and 50% of patients already had an IOP more than 20 mmHg, whereas 3% and 15% of patients had an IOP more than 30 mmHg at 3 days and 1 week after treatment, respectively. To detect the abnormal rise in IOP, especially those with exaggerated steroid responsiveness, we advocate measurement of IOP twice weekly if topical dexamethasone is used in children.

Because the fellow eye of each patient was used as the control, 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 and past history of glaucoma. It is therefore likely that the ocular hypertensive response we noted is mainly contributed by the topical dexamethasone. We cannot exclude the effect of systemic absorption of topical dexamethasone. This may have caused
a stronger response in the eye receiving the twice daily regimen. However, the consequence of this factor will dilute and tend to underestimate the severity of a 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.

Additional information can be obtained when comparing the results of our previous study with those of this study. The methodology and outcome measures are the same in both studies. The peak IOP and the net increase in IOP for the four times daily regimen were 28.7 ± 6.8 mmHg and 10.9 ± 6.6 mmHg, respectively. In this study, the peak IOP and the net increase in IOP for the four times daily regimen were 28.7 ± 6.9 mmHg and 14.5 ± 6.4 mmHg, respectively, whereas for the twice daily regimen, they were 25.2 ± 6.8 mmHg and 10.9 ± 5.8 mmHg, respectively. Although the statistical significance cannot be calculated directly because of different confounding factors in the two studies, a rising trend of ocular hypertensive response to increasing dosage frequency of topical dexamethasone is observed.

In conclusion, topical dexamethasone should be used carefully in children because exaggerated ocular hypertensive response occurs frequently, even on the twice daily regimen. It is recommended that IOP be monitored closely, with earlier and more frequent IOP measurements when higher dosages of topical dexamethasone are used.

References

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