Ocular Hypertensive Response to Topical Dexamethasone Ointment in Children

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Purpose: To investigate the rate and the degree of the ocular hypertensive response to dexamethasone ointment in children undergoing eyelid surgery.
Methods: Dexamethasone ointment (Dexcosil®) was applied three times a day for the first week and twice a day for the second to third week postoperatively to children undergoing epiblepharon surgery. Intraocular pressure (IOP) was measured on the day before surgery, postoperative day 1, 7, 14, 21, 28 and 2 weeks thereafter until the IOP reached preoperative levels. Peak IOP, IOP net increase and time to reach a peak IOP were analyzed. Dexamethasone ointment was discontinued if the IOP was 25 mmHg or more.
Results: A total of 96 children (mean age, 6.5±2.7 years) were included. Preoperative mean IOP was 13.6 ±2.9 mmHg (range 7-19). After dexamethasone ointment treatment, the children showed a significant rise in IOP as compared with the preoperative values. The peak IOP was 20.6±4.9 mmHg (range 11-39) and the time to reach peak IOP was 8.5±5.9 days. The low responders (delta IOP $\leq$5 mmHg) of our group comprised 35.4% (34/96) of patients, intermediate responders (delta IOP 6-15 mmHg) comprised 56.3% (54/96) of patients and high responders (delta IOP$\geq$16) comprised 8.3% (8/96) of patients. A net increase in IOP was significantly higher in children 5 years old or less as compared with those older than 5 years (age $\leq$5, 9.4±7.5 mmHg vs age >5, 6.3±4.4 mmHg; p=0.015, unpaired t-test).
Conclusions: Ocular hypertensive response after dexamethasone ointment to the eyelids occurred frequently in children, especially those 5 years old or younger. *Korean Journal of Ophthalmology 20(3):166-170, 2006*

Key Words: Children, Dexamethasone, Epiblepharon, Intraocular pressure

Epiblepharon is a frequently encountered congenital lid anomaly in Asian infants and children. It is a fold of skin, which overlaps the eyelid margin and pushes the lashes against the cornea. Because it causes epiphora and ocular irritation symptoms in some children, it needs to be corrected surgically. To correct epiblepharon, the redundant skin and abundant orbicularis muscle are excised and an adhesion between the subcutaneous tissue of the upper skin flap and the tarsal plate is made.[1]

An absorbable suture is preferred in closing the skin wound because most children can not tolerate suture removal. In most cases, the surgical wound heals without sequale, but sometimes the surgical wound tends to be inflamed and results in a hypertropic scar in relation with suture absorption. Especially in patients with allergic dermatitis, such an inflammatory phase can be severe and the use of steroid ointment may be recommended as a prevention.

Corticosteroids administered as eyedrops, ointment, or used systemically are indispensable in treating inflammatory eye diseases.[2-4] In addition as postoperative management, topical corticosteroids are commonly used. It prevents or suppresses the undesirable consequences of postoperative ocular inflammation including redness, swelling and tenderness. It is well established that prolonged use of topical ophthalmic corticosteroids can produce ocular hypertension and secondary open-angle glaucoma in susceptible individuals.[5-8] However, in children the ocular hypertensive response is not well documented.

We examined ocular hypertensive response to dexamethasone ointment applied to the eyelids in children after epiblepharon surgery.

Materials and Methods

A total of 96 patients (50 boys, 46 girls) who underwent epiblepharon surgery at 2 hospitals between 2003 and 2005 were recruited and prospectively evaluated. The parents of the patients were informed that their children would need

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steroid ointment to reduce inflammation of the surgical wound which may have a possibility of increasing IOP. Only those patients whose parents provided informed consent were included in the study. Patients who had a preoperative IOP of 21 mmHg or more were excluded. Those who had a family history of glaucoma or did not comply with the serial IOP measurement were excluded from the study.

Epiblepharon surgery was performed by 2 surgeons (YJL or KIW) under general anesthesia using the same surgical method.1 Making a skin incision below the lash line, the redundant skin and abundant orbicularis muscle were excised and 3-6 buried rotating sutures between the subcutaneous tissue of the upper skin flap and the tarsal plate were made. The wound was closed continuously with 6-0 fast absorbing gut suture.

After the surgery, the parents of the patients were instructed to apply dexamethasone-neomycin-polymyxin ointment (Dexcosil®, Young Jin Pharm.) only to the surgical wound and not into the eye from the postoperative day 1 to the third week. They used the ointment 3 times a day for the first postoperative week and twice a day up until the third week.

IOP was evaluated on the day before the operation and on postoperative days 1, 7, 14, 21 and 28. It was measured by non-contact tonometry and Goldmann applanation tonometry for a confirmation test in those cases with an IOP higher than 20 mmHg. Non contact tonometry was used because of its acceptability in children and previous reports validating its reliability.[9,10] Therefore, analysis of results in the present study was based on the reading of noncontact tonometry. Three consistent readings were obtained from each eye and the mean value was use for analysis. Dexamethasone ointment was discontinued immediately in any eyes with an IOP higher than 25 mmHg and measurement was continued at 1-week intervals until IOP measurements returned to the preoperative levels. Antiglaucoma medication would be started when the IOP did not decrease during next follow-up visit and sustained increased level. Peak IOP was defined as the highest IOP during follow-up period.

The demographic data of the patients was calculated by descriptive statistics. The unpaired t-test was used to compare the difference in IOP changes between different age groups. A P-value of less than 0.05 was defined as statistically significant.

Results

One hundred and ninety-two eyes of 96 children were included. There was a high correlation between the preoperative IOP in the right eye and left eyes of subjects (p= 0.087). Therefore the results of the right eye were used for analysis. The mean age of the 96 children (50 boys, 46 girls) was 6.5±2.7 years (range, 3-13 years). All the operations were uneventful and there were no postoperative complications.

The mean preoperative IOP of the patients was 13.6±2.9

Table 1. Intraocular pressure (IOP) profile and time to reach peak IOP in children on dexamethasone treatment

Measure	Mean±SD (range)
Preoperative IOP (mmHg)	13.6±2.9 (7-19)
Peak IOP (mmHg)	20.6±4.9 (11-39)
Delta IOP (mmHg)	7.2±5.4 (0-31)
Mean time to reach peak IOP (days)	8.5±5.9 (1-28)

Table 2. Comparison of ocular-hypertensive response to topical dexamethasone 0.1% in different studies

	Armaly[9]	Biender et al.[11]	Lam et al.[14]		Present study
			Group A*	Group B†	
Age (years)					
Mean	Adult	9.7	6.5		6.49±2.7
Range	(16-40)	(4-19)	(3-10)		(3-16)
Frequency of administration (time/day)	3	4	4	4	2-3
Duration of administration (weeks)	4	6	4	2	3
Sample size	80	44	132	142	96
Low responder (⊿IOP <6 mmHg)	53 (66%)	39 (89%)	(21.2%)	(26.8%)	34 (35.4%)
Intermediate responder (⊿IOP 6-15 mmHg)	23 (29%)	4 (9%)	(45.5%)	(54.9%)	54 (56.3%)
High responder (⊿IOP >15 mmHg)	4 (5%)	1 (2%)	(33.3%)	(18.3%)	8 (8.3%)

*: duration of steroid treatment was 4 weeks. †: duration of steroid treatment was 2 weeks.

mmHg (range 7-19 mmHg). The peak IOP after the surgery was 20.6±4.9 mmHg (range 11-39 mmHg). Delta IOP (between the peak IOP and preoperative IOP) was 7.2±5.4 mmHg (range 0-31 mmHg). After dexamethasone treatment there was a significant increase in IOP (paired t-test, P=0.000) (Table 1).

The mean time to peak IOP was 8.5±5.9 days (range from 1 to 28 days). After dexamethasone ointment treatment, the cumulative percentage of eyes having IOP higher than 20 mmHg at days, 1, 7, 14, 21, 28 were 1.0, 29.2, 35.4, 36.5 and 50% respectively. The number of patients with an IOP higher than 20 mmHg in our study was 48 (50%). Any patients with an IOP more than 25 mmHg did not continue steroid treatment and the patients were checked by 1-week interval follow-up until their IOP returned to the preoperative level. After withdrawl of steroid treatment, all the elevated IOP had begun to decrease at the next follow-up. Any patients with an increased IOP did not complain of ocular hypertensive symptom, for example headache, blurring, ocular pain, etc. The one patient with an increased IOP of 39 mmHg was checked by 3-day interval until his IOP was returned to preoperative level. We examined his optic disc, visual acuity which had not changed during increasing IOP, but we could not examine his visual fields because he was too young. His IOP returned to the preoperative level in 6 days and kept the same level until 3 months postoperatively. Any patients with an increased IOP did not need antiglaucoma medication to reduce their increased IOP.

According to Armaly's classification,[11] 35.4% (34/96) of patients in our group were low responders (delta IOP ≤5 mmHg), 56.3% (54/96) were intermediate responders (delta IOP 6-15 mmHg), and 8.3% (8/96) were high responders (delta IOP ≥16). Children 5 years old or less had a higher peak IOP (22.5±6.4 mmHg) compared to that of children older than 5 years (19.7±4.3 mmHg, P=0.020). In addition, the delta IOP was higher in children 5 years old or less (age ≤5 years, 9.4±7.5 mmHg vs. age >5 years, 6.3±4.4 mmHg; P=0.015). The time to peak IOP was not different in the 2 groups (age ≤5 years, 7.9±5.8 days vs age >5 years, 10.0±6.2 days; P=0.120) (Table 3).

Discussion

Steroid-induced ocular hypertension is a well documented entity in adults. The response of IOP to topical corticosteroid treatment had been demonstrated by Armaly[9] after subjecting a segment of the normal population to topical corticosteroid application and monitoring the increase in their IOP. However, in children, there has been limited information.[12] Most clinicians treat pediatric patients based on adult results but there is controversy in reported steroid response in children. Biender et al.[13] has reported an ocular hypertensive response to topical corticosteroid therapy in children with vernal keratoconjunctivitis (n=44, 4-19 years of age). They showed that response to steroids is not significantly different between adults and children.

In contrast, Ohji et al.[14] reported that of 11 children (82%) were high or intermediate steroid responders after administration of topical 0.1% dexamethasone eyedrops for 4 weeks following squint surgery. Kwok et al.[15] reported that ocular hypertensive response to topical dexamethasone in children occurs more frequently, more severely and more rapidly than reported in adults and demonstrated that 56% of the children in the study were high responders. Recently, Lam et al.[16] studied the use of topical dexamethasone 0.1% in 2 different postoperative regimens (4 times vs. twice daily regimen for a 4-week course) after squint surgery and reported that ocular hypertensive response in children was as dose-dependent as age-dependent. Now there is growing evidence that ocular hypertensive response in children is more severe in relation to peak IOP, time to peak IOP and dosage of steroids used. Unitl now, Armaly's classification has been used the most popularly and cited in many different studies.[13-17] Armaly[9] in 1965 reported that only 5% of adult patients in the study were high responders (increase in IOP greater than 15 mmHg) and 35% were intermediate responders (increase in IOP between 6 and 15 mmHg). They also reported that IOP increases more frequently in people aged 40 years or more than in people aged 18-30 years after instillation of 0.1% dexamethasone eyedrops. In our study, low, intermediate and high responders were 35.4% (34/96), 56.3% (54/96), and 8.3% (8/96) respectively.

The proportion of low and intermediate responders in our result were different with Armaly's result, but there was some limitation in comparing our results directly with Armaly's[11] results because there was other variables, for example, operation, frequency of administration, kind of drug. Comparing our results with other different studies on children was summarized in Table 2. Although taking variables into consideration, high responders in children in our study is lower than in Lam et al.[14] and more than Armaly's and Biender et al.[13]

Table 3. Comparison of ocular- hypertensive response to dexamethasone ointment in different age groups

Measure	≤5 years	>5	P value*
Peak IOP (mmHg)	22.5±6.4	19.7±4.3	0.020
Delta IOP (mmHg)	9.4±7.5	6.3±4.4	0.015
Time to reach peak IOP (days)	7.9±5.8	10.0±6.2	0.120

*unpaired t-test.

In comparison to Lam et al.[16], the high responders in our study (8%) were fewer than in Lam et al's (33.3%). It was supposed that they used topical dexamethasone for longer period (4 weeks) and more frequently (4 times) than we did. It is well established that the amount of increase in IOP depends on numerous factors such as drug potency, penetration, dosage and length of administration. Ng et al.[17] demonstrated a dose-dependent ocular hypertensive response to topical dexamethasone in children. They showed the 4 times daily group had a significantly higher peak as well as a higher net increase in IOP than the twice daily group. Moreover steroid eyedrops which were used in many other reports acted directly on the eye. In contrast, we used ointment which had a different penetration in comparison with eyedrops. It was not clear how the steroid ointment could evoke ocular hypertensive response, but it was assumed that it could be related to the systemic absorption of corticosteroid through the skin of the eyelid, especially when there was a surgical wound.[18] Alternatively, a sufficient amount of ointment could have seeped over the eyelid margins to cause the rise in IOP similar to the application of corticosteroid eyedrops. Chua et al.,[19] reported a similar case of accelerated ocular hypertensive response after application of corticosteroid ointment to a 6-year-old boy's eyelid after leveator palpebrae superioris resection. His IOP was elevated to 44 mmHg at 4 days postoperative. This was an alarming case because in children, the ocular hypertensive response may be severe and rapid even with the corticosteroid ointment applied only to the eyelid.

The response to corticosteroids in children has been explained by functional immaturity of the trabecular meshwork, which is unable to respond to this accumulation of glycosaminoglycans resulting in an increased resistance to aqueous outflow.[20-22] This age-dependent response was also demonstrated in rabbits and was supported by the difference in distribution and structure of proteoglycans. Remé and d' Epiney[23] reported that chamber angle structures were immature at birth. Although fully present at birth, it takes approximately 8 years for the whole chamber angle to become as mature as that of an adult. Knepper et al.[24] showed age-dependent steroid-induced glaucoma in a rabbit model. The young rabbits were steroid responders, whereas, none of the older rabbits showed any IOP rise. Lam et al.[16] found that children aged 6 years or younger had a higher peak IOP and a net increase in IOP as compared with children older than 6 years when topical dexamethasone was used 4 times daily. In our study, children less than 5 years old had a higher peak IOP (22.5±6.4 mmHg) as compared to that of children older than 5 years (19.8±4.3 mmHg; $p = 0.020$).

Discontinuation of steroid use is the first line of defense and is often all that is required.[25] Increased IOP returned to preoperative levels in all patients in our study after cessation of ointment. There was no persistent IOP elevation after a week. There are 2 forms of normalization in increased IOP in steroid induced ocular hypertension. In the chronic form, the increased IOP becomes normalized in 1-4 weeks, whereas the acute form typically resolves within days of stopping the steroid. The duration of steroid therapy appears to influence the reversibility of the IOP elevation. Because steroid ointment was used for a short period in this study, all of the patients showed the acute form of ocular hypertension.

In conclusion, our study was performed on patients who underwent epiblepharon surgery, which is commonly performed in Asians and showed that use of steroid ointment to the operated eyelids in children might cause a more severe ocular hypertensive response than in adults. In the future study, it is suggested to design the adults and children group treated with the same operation and the same management and follow-up. Also it needs further investigation why the children with highly elevated IOP did not complain of any symptoms.

Topical dexamethasone ointment should be used carefully in children because exaggerated ocular hypertensive response occurs frequently. It is essential to monitor IOP when corticosteroid ointment is used on the eyelids of young children.

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