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# Adrenal Suppression in Infants Treated with Topical Ocular Glucocorticoids

*Regitze Bangsgaard, MD,*[1] *Katharina M. Main, MD, PhD,*[2] *Gøril Boberg-Ans, MD,*[1] *Morten la Cour, MD, DMSc,*[1] *Julie Lyng Forman, MSc,*[3] *Birgitte Haargaard, MD, PhD,*[1] *Jens Folke Kiilgaard, MD, PhD*[1]

***Purpose:*** To analyze the incidence of adrenal suppression and the glucocorticoid (GC) dose per kilogram body weight given in infants treated with standard protocol for topical ophthalmic GCs after congenital cataract surgery.

***Design:*** Retrospective, consecutive case series.

***Participants:*** All children younger than 2 years of age who underwent operation for congenital cataract between January 2011 and May 2015 in 1 center.

***Methods:*** Patient charts were reviewed to collect data on results and timing of a standard corticotropin (adrenocorticotropic hormone [ACTH]) stimulation test and GC dose per kilogram body weight.

***Main Outcome Measures:*** Incidence of adrenal suppression in children tested on GC treatment. Glucocorticoid dose per kilogram body weight.

***Results:*** Among 26 consecutive infants, 15 (58%) were tested while they were still on GC treatment. Ten of these 15 infants (67%) had adrenal suppression, 2 of whom had obvious clinical signs of Cushing's syndrome and 1 of whom had signs of Addisonian crises during general anesthesia. Eleven of the 26 infants (42%) were tested at a median time of 21 days (range, 6–89) after treatment cessation, and they all had normal test results. Children with suppressed adrenal function had received cumulative GC doses per body weight that were significantly higher the last 5 days before testing compared with children with normal test results. Infants with adrenal suppression were treated with hydrocortisone replacement therapy. Adrenal function recovered after a median of 3.1 months (range, 2.3 months to 2.3 years).

***Conclusions:*** Two thirds of the infants tested during treatment with a standard GC protocol after congenital cataract surgery showed adrenal suppression. There was a significant association between the cumulative daily dose of GCs and the test result. Because adrenal suppression is a serious but treatable condition, we recommend a systematic assessment of adrenal function in infants treated with doses of topical ocular GCs comparable to our regimen and careful evaluations of other treatment regimens. *Ophthalmology 2018;■:1–6 © 2018 by the American Academy of Ophthalmology*

Glucocorticoids (GCs) are widely used to treat inflammatory eye disease and inflammation after eye surgery. To avoid systemic side effects, GCs are often administered locally as eye drops or as subconjunctival or peribulbar injections or administered directly in the anterior or posterior chamber of the eye. In some cases, more than 1 topical administration form is given. This treatment is generally considered well tolerated. However, there have been reports of patients,[1,2] especially children,[3-11] developing adrenal suppression. Even death related to topical GC use has been reported.[12] In some of these cases, the patients also received systemic GCs at some point before developing adrenal insufficiency,[2,4,5] which makes it difficult to know which role the topical ocular GCs played per se. Increasing clinical evidence suggests that any treatment with GCs, irrespective of administration route, may suppress adrenal function and cause Cushing's syndrome.[13,14] Adrenal suppression after topical ocular GCs is not well documented, and the frequency in a common clinical setting is not known. It is likely that the individual predictability of adrenal suppression is poor, but that it is associated with GC potency, dose, length of treatment, and application route, as well as associated to polymorphisms in the GC receptor.[3,15]

In 2011, 2 consecutive infant patients in our department developed clinical symptoms of Cushing's syndrome after surgery for congenital cataract. A standard corticotropin (adrenocorticotropic hormone [ACTH]) provocation test showed complete suppression of the adrenal function. This prompted us to systematically evaluate the adrenal function in all infants younger than 2 years of age operated for congenital cataract from then on.

## Methods

We retrospectively collected data from patients younger than 2 years of age who had undergone congenital cataract surgery between January 2011 and May 2015 in our department. From each patient, we obtained the following information from health records: sex,



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comorbidity diagnosed by a pediatrician, type and number of operations, type and amount of GC injected under the conjunctiva during the operation, age and body weight (kilograms) at the time of the first operation and total number (right plus left eye) of dexamethasone drops per day, number of days from the start of dexamethasone treatment until the ACTH test (if the first ACTH test was performed while the child was still receiving dexamethasone eye drops) or until treatment cessation (if the first ACTH test was performed after cessation of dexamethasone treatment), results of ACTH tests and the time lapse (days) from operation, days between first pathological ACTH test and first normal re-test, and time lapse (days) between the treatment cessation and the first normal re-test.

We evaluated the growth chart of the first index patient for signs of adrenal suppression before the diagnosis of adrenal suppression was made. The parents provided a photograph taken at the time when their child was diagnosed with Cushing's syndrome.

The patients in this retrospective study had all been operated by the same 2 experienced pediatric cataract surgeons (B.H. and G.B.A.) in close collaboration and followed a standard procedure. In infants with equally dense bilateral cataract, the second eye was operated within 2 weeks after the first operation. If there was a less dense cataract in the second eye, the operation of the second eye was postponed accordingly. An intraocular lens was implanted if the child was more than 6 months of age and if the child did not have major ocular malformations such as microphthalmia or persistent fetal vasculature. Additional surgery was performed during the study period in cases of secondary glaucoma, secondary cataract, fibrous membranes, or synechia obstructing the optical axis.

The standard subconjunctival injections during the cataract operation were 0.5 to 1.0 ml methylprednisolone acetate 40 mg/ml (Depo-Medrol, Pfizer, Belgium). In case of an operation for secondary glaucoma, a subconjunctival injection of 0.5 ml dexamethasone 4 mg/ml (Fortecortin, Merck, Germany) was the standard. All glaucoma operations were performed by the same glaucoma specialist.

From the first day after any operation, topical treatment with dexamethasone 1 mg/ml (Maxidex, Alcon, UK) eye drops was administered. The guideline in our department was 6 to 8 drops (first week); 4 to 6 drops (second week); 3 to 4 drops (third week); 2 to 3 drops (fourth week); 1 to 2 drops (fifth week); and 0 to 2 drops (sixth week). But the treatment was administered at the discretion of the surgeon according to the complexity of the operation and clinical symptoms, and increased in case of worsening inflammation or additional surgery. The parents were advised to perform punctal occlusion after each eye drop administration. No systemic GCs were given by the anesthesiology team at operations performed before the first ACTH provocation test.

A standard ACTH provocation test, detailed next, was scheduled approximately 1 month postoperatively, but for logistic reasons, some of the children had the test postponed, and thus, the test was done after stopping treatment. In the cases of the 2 index patients, the first test was done because of clinical symptoms of Cushing's syndrome, and both children were still receiving topical steroids.

We measured plasma ACTH and serum cortisol before intravenously injecting 250 μg ACTH or 36 μg/kg in infants less than 7 kg of body weight (Synacthen, tetracosactide 0.25 mg/ml, New Neopharm BV, Netherland) as a bolus. We measured serum cortisol at 30 and 60 minutes after injection and considered peak cortisol of ≥500 nmol/L at any time point a normal response.

If adrenal insufficiency was diagnosed, the child was treated with hydrocortisone orally 3 times daily in standard replacement doses according to international recommendations,[16] until adrenal recovery was documented by a consecutive ACTH provocation test. Some of the patients were still treated with dexamethasone eye drops after the first pathological test, and re-testing was first conducted after treatment cessation.

All families have given written informed consent to this retrospective study. The Danish Patient Safety Authority 3-3013-1353/1/reference ANHN and The Danish Data Protection Agency journal number 2012-58-0004 approved the study.

We calculated the following values related to the GC given:

Drops GC (mg): The total number (left plus right eye) of dexamethasone drops from the treatment start to the ACTH provocation test (Early group) or the treatment cessation (Late group) was multiplied by drop volume (0.05 ml/drop) and dexamethasone concentration (1 mg/ml).

Injected GC (mg): The sum of injected equipotent doses of Fortecortin (dexamethasone 4 mg/ml) and Depo-Medrol (methylprednisolone acetate 40 mg/ml) in milligrams:

We considered 4 mg methylprednisolone to be equipotent to 0.75 mg of dexamethasone.[17]

Thus,

Injected GC (mg) = X ml of Depomedrol × 40 mg/ml × 0.75/4 + Y ml of Fortecortin × 4 mg/ml.

We calculated the cumulative dexamethasone equivalent dose of GC per kilogram of body weight (Cumulative GC/w (mg/kg)) as follows:

Cumulative GC/w = (Drops GC + Injected GC)/weight (mg/kg)

We calculated the cumulative dexamethasone equivalent dose of GC per kilogram of body weight (Cumulative GC/w [mg/kg]) for the total treatment period, and for each day, the last 30 days before testing.

We summarized categoric data in numbers and percentages and continuous data in medians and ranges. We cumulated the daily GC/w up to 30 days before testing for each child and compared those with normal test results and those with pathological test results using the Mann−Whitney *U* test. We computed exact *P* values from the permutation distribution based on 50 000 random permutations and made adjustment for multiple testing by use of the min-P method, which controls the family-wise error rate to the 5% level. Four of the children with normal test results had stopped treatment more than 30 days before testing, and thus, they had a daily GC/w that was constantly zero. These had to be excluded from analysis for technical reasons, which makes the comparison of the groups conservative. We performed all analyses with R

Table 1. Characteristics of the Infants Who Had an Adrenocorticotropic Hormone Provocation Test

| Clinical Parameters | Early Group N=15 | Late Group N=11 |
|---|---|---|
| Age at first operation - median days (range) | 69 (48−344) | 184 (56−637) |
| Weight at first operation - median kg (range) | 5.5 (3.8−11.5) | 8.1 (4.7−12.0) |
| Patients with systemic disease - No. (%) | 5 (33%) | 4 (36%) |
| Patients with unilateral cataract - No. (%) | 7 (47%) | 7 (64%) |
| Patients with IOL - No. (%) | 3 (20%) | 4 (36%) |
| No. of operations before test - median No. (range) | 2.0 (1−5) | 1.0 (1−3) |
| Time from first operation to test - median days (range) | 41 (13−125) | 55 (29−132) |

IOL = intraocular lens.
Early group was tested while they were still on glucocorticoids treatment. Late group had their first test after treatment cessation.