1968

Topical corticosteroids and their relationship to intraocular pressure

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TOPICAL CORTICOSTEROIDS AND THEIR RELATIONSHIP TO INTRAOCULAR PRESSURE

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A THESIS

Presented to the Faculty of

The College of Medicine in the University of Nebraska

In Partial Fulfillment of Requirements

For the Degree of Doctor of Medicine

Omaha, Nebraska

February 1, 1968

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INTRODUCTION

The purpose of this thesis is to review the increasing number of reports concerning the use of topical corticosteroids on the eye, and their relationship to intraocular pressure. In order to better understand the evolution of present day concepts this paper will be presented as follows:

1) A brief review of the early reports concerning both systemically and topically administered corticosteroids inducing changes in the eye compatible with glaucoma

2) A review of controlled studies designed to observe changes in intraocular pressure secondary to topical corticosteroids

3) The hereditary implications of these studies

4) A summary of the postulated mechanisms of the changes in intraocular pressure secondary to topical corticosteroids

5) The present and future clinical significance of these findings

Early Reports

Francois in 1954 showed that topical administration of corticosteroids could yield increased intraocular pressure, cupping of optic discs and visual field changes [15]. Laval reported in 1955 that patients treated with topical steroids for uveitis developed increased intraocular pressure [18]. Case histories also were presented by Linner in 1959 and Goldmann in 1962 along the same lines [20] [16]. As the increasing number of reports had trickled in, [13] [12] [28] interest continued to grow. Investigators wondered what caused the increases in intraocular pressures, if the increases could result in visual changes, and if so, what relationships could this have to glaucoma or the study of glaucoma. These and many other questions needed answering. The following studies were attempts to answer these questions.

Changes in Intraocular Pressure Secondary to Topical Corticosteroids and the Variation in Response

In 1963, Becker et. al. published the first such study. Using 0.1 percent bethamethasone four times a day, his group definitely established that the use of topical corticosteroids could and did result in increased intraocular pressure [6]. Becker et. al. further

stated in 1964 that topical corticosteroids did result in significant increased intraocular pressure and decreased outflow facility in proven primary open-angle glaucoma (11). This was also true in glaucoma suspects with no other evidence of glaucoma than a positive water-drinking provocative test (5) (25). Becker's criteria for a positive response to topical corticosteroids was 1.) an increase in intraocular pressure of greater than six millimeters of mercury (which had to be equal to the difference of intraocular pressure between the control eye and the provoked eye) or 2.) a decrease in outflow facility of 33 percent or greater. In both studies, Becker used 0.1 percent bethamethasone four times a day to one eye only (11).

Studying the effects of topical corticosteroids on the intra-ocular pressure of patients known to have secondary glaucoma, Becker et. al. (using the same previous criteria for a positive response) found a positive response in 32 to 36 percent of these patients. These results did not nearly reach the prevalence of similar reactions in primary open-angle glaucoma patients, where the percent of positive responses was nearly three times this. Thus he concluded the positive responses were not as consistantly found in eyes with already damaged outflow channels due to secondary glaucoma (9). In 1964 Becker, Kolker, and Mills reported the effect of topical

steroids on intraocular pressure and visual fields in (a)'normal,' and (b) proven open-angle glaucoma patients. By raising the intraocular pressure with topical steroids, Becker was also able to study the susceptibility of each group to field loss secondary to increased intraocular pressure.

The results in summary are as follows:

1) Many patients with glaucomatous field loss demonstrated an increase in scotomata when intraocular pressure was increased. This was reversible when the intraocular pressure was decreased to normal levels.

2) Some patients with no field loss and borderline values for intraocular pressure demonstrated characteristic glaucomatous field changes with moderate elevation of intraocular pressure. The field loss was reversible when intraocular pressure was returned to normal levels.

3) Some patients as glaucoma suspects failed to show any visual field changes when intraocular pressure was increased to high levels for periods of days to weeks. This occurred in individuals with no evidence of visual field loss but also in eyes with established glaucoma and proven field loss. The apparent resistance to optic nerve damage was related to systemic blood pressure. One patient with a blood pressure of 225/105

millimeters of mercury and intraocular pressure of 36 to 38 millimeters of mercury showed no field loss but showed early field loss with intraocular pressure of 24 millimeters of mercury and blood pressure of 140/80 millimeters of mercury. In most patients though, the field loss correlated best with intraocular pressure.

4) Some of the patients tested having proven glaucoma and visual field loss showed improvement in visual fields when the intraocular pressure was decreased [8].

In 1965 Spiers et. al. reported on ninety-three out-patients. Spiers divided the group into

I. Normals -- intraocular pressure less than 20 millimeters of mercury and normal visual fields

II. Patients with intraocular pressure 20 to 23 millimeters of mercury and no other changes

III. Patients with intraocular pressure greater than 23 millimeters of mercury and no other changes

The results showed that the greatest increase in intraocular pressure took place among the patients with the highest initial intraocular pressures as they were given dexamethasone 0.1 percent topically to the one eye. The other eye was used as a control. In these ninety-three out-patients, the patients with a positive family history for glaucoma gave a significantly greater response in increased intraocular pressure than did those

with no positive family history (25) (26). Fully sure that topical corticosteroids did increase intraocular pressure, investigators were simultaneously trying to decide what could be considered a clinically significant elevation of intraocular pressure; and if there were possible groupings according to the response. Armaly studying the effects of topical dexamethasone on the 'normal eye' divided the patients into two groups.

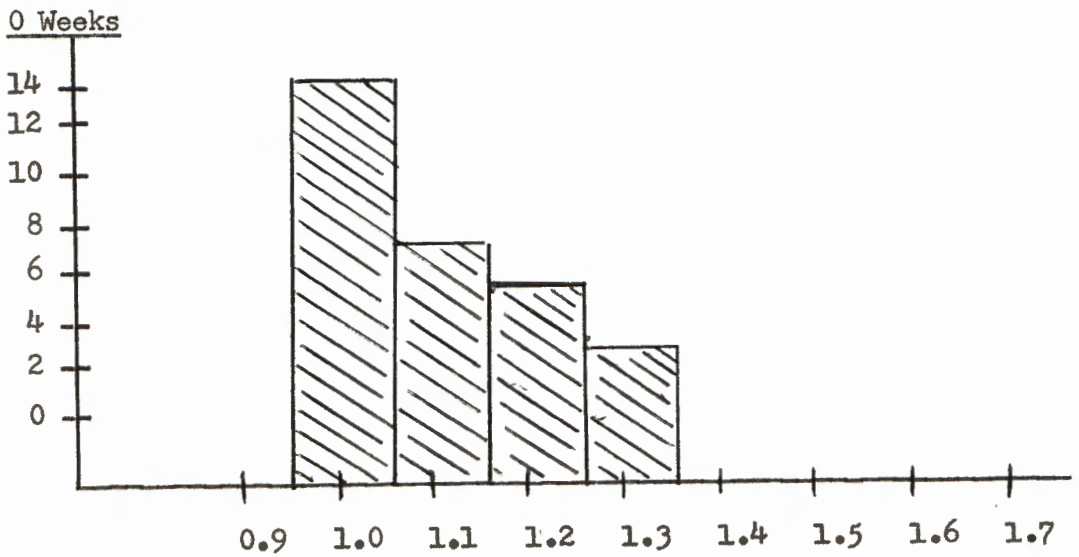
Group I -- Normal intraocular pressure, no positive family history, thirty patients, ages 18 through 32

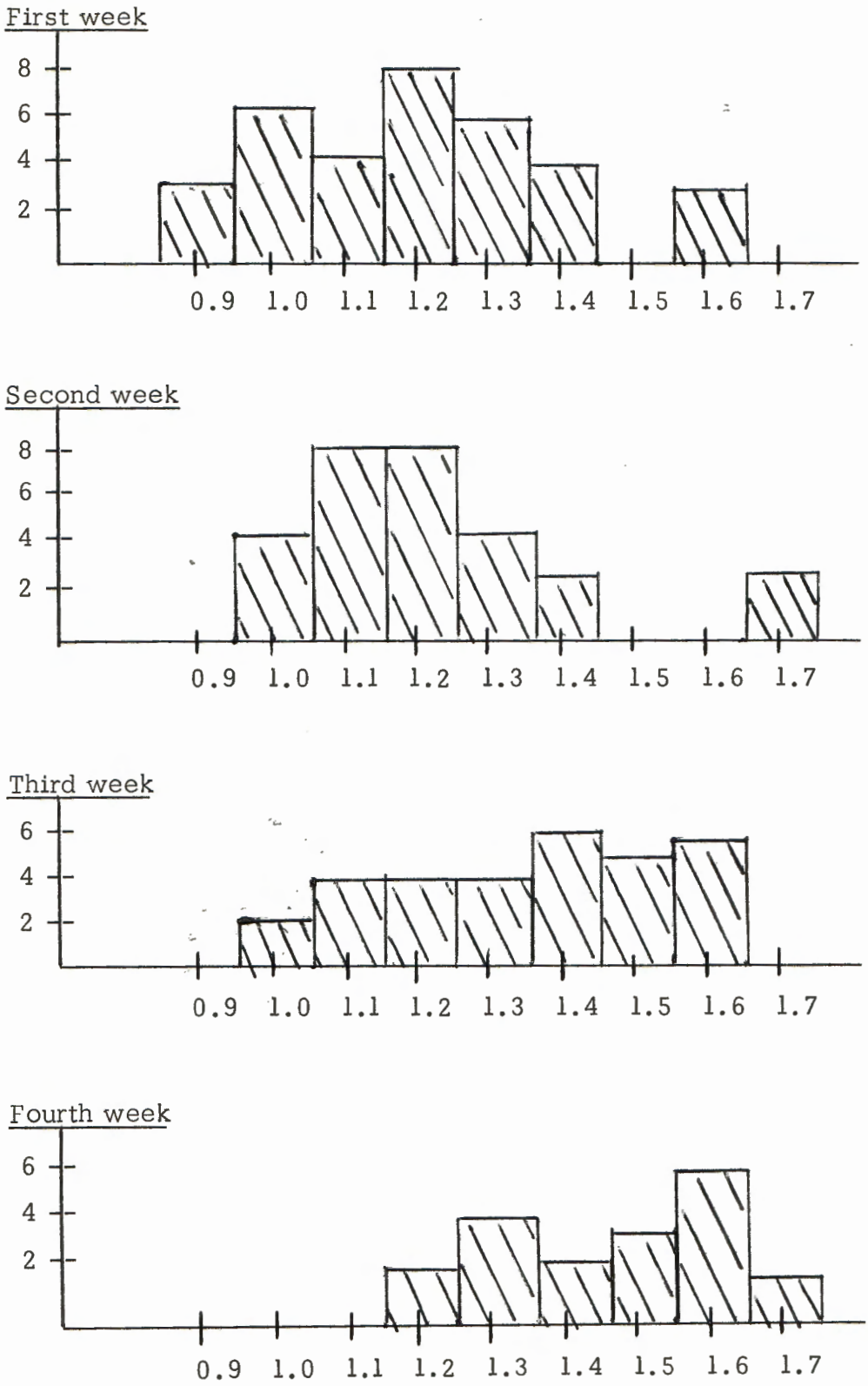
Group II -- Normal tension, no positive family history, twenty-three patients, ages 40 through 62 (fifteen were ages 45 through 50)

To isolate 'background differences' the difference in intraocular pressure of treated and untreated eyes was taken.

Results:

Figure 1 -- The frequency distribution of the ratio Pr, applanation pressure in right eye, to Pl, applanation pressure in left eye, before and at weekly intervals during dexamethasone application





* Armaly, M.: Effect of Corticosteroids on Intraocular Pressure and Fluid Dynamics, I. The Effect of dexamethasone in the normal eye, Arch Ophthal 70:482, 1963, page 485

1) Hypertensive intraocular effects evident even at one week.

2) If treated greater than four weeks, this increased the hypertensive effects.

3) The intraocular pressure increases were greater in the older age group and were statistically significant at the 1 percent level. Thus, they concluded increased vulnerability or sensitivity of the 'normal eye' to hypertensive intraocular effects of dexamethasone with increasing age. (2)

Armaly then turned his attention to the effects of topical dexamethasone in the glaucomatous eye. The patients were divided into the following groups:

Group I -- Medically controlled hypertensive open-angle glaucoma patients, ages 42 through 62, nineteen patients

Selection criteria:

1) Untreated intraocular pressure of at least 25 millimeters of mercury

2) Presence of constant arcuate scotoma 45^{o} or more

3) Open-angle and visible trabecular meshwork by gonioscopy and a normal anterior segment by slit lamp examination

Group II -- Patients with low tension open-angle glaucoma

Selection criteria:

1) Applanation pressures never had exceeded 22 millimeters of mercury

2) Diurnal variation did not exceed 5 millimeters of mercury

3) Constant arcuate scotoma 45° or more by tangent screen and Goldmann perimeter (Bilateral in nine cases)

4) Normal skull x-rays

5) Normal ophthalmoscopic examination except varying degrees of excavation and atrophy of the optic nerve head

6) Open-angle and visible trabecular meshwork by slit lamp examination

7) No history suggestive of retrobulbar neuritis Ages of this group 45 through 64

Results:

Group I -- All had a rise of 11 millimeters of mercury or greater at the end of three weeks in the provoked eye.

Group II -- The relative magnitude of the dexamethasone effect was identical to the effect in the hypertensive glaucoma group. Both groups showed marked increase over that considered the normal group [3].

Further study by Armaly using 0.1 percent dexamethasone stimulation on eighty 'normal' subjects demonstrated three distinct and statistically different levels of response. Armaly classified patients as low, intermediate, and high responders [1], (see table following page).

The results indicated topical dexamethasone challenge as a sensitive criterion, and there was a definite segregation of genotypes [1].

TABLE 1 -- Explanation of Genotype Classification for First Persons Tested (Page 32)

Phenotype of Pressure Rise	Low	Intermediate	High
Limits of pressure rise in millimeters of mercury	5 or less	6-15	16 or more
Mean pressure rise in millimeters of mercury	1.96	10.0	19.5
Standard deviation in millimeters of mercury	$\pm$ 2.00	$\pm$ 2.5	*
Genotype	Pl Pl	Pl Ph	Ph Ph
Number of individuals	53	23	4
Percent of individuals	66%	29%	5%

* Range in sample 18 to 22 millimeters of mercury

TABLE 2 -- Results of Testing Parents with Offspring of Genotype Ph Ph and Pl Pl (Page 33)

Group	Number Subjects	Pl Pl $\Delta P <$ 6 mm Hg	Pl Ph ΔP 6-15 mm Hg	Ph Ph $\Delta P >$ 16 mm Hg
Random Sample	80	66%	29%	5%
Parents of Pl Pl Offspring	30	87%	13%	0
Parents of Ph Ph Offspring	8	0	87%	13%

Armaly, H.: Heritable Nature of Dexamethasone Induced Ocular Hypertension, Arch Ophthal 75:32, 1966.

Becker, pursuing the same lines, had reported earlier in 1965 that

1) 0.1 percent bethamethasone stimulation in patient with proven open-angle glaucoma resulted in marked increases of intraocular pressure in the provoked eye and that

2) 20 percent of the offspring of open-angle glaucoma parents responded in a similar manner.

Testing eighty-four offspring of proven open-angle glaucoma patients, Becker showed 81 percent of the population exhibited an intermediate response (greater than 6 millimeters of mercury) after topical steroid provocation; also, that 19 percent showed dramatic increase of intraocular pressure (greater than 31 millimeters of mercury) (7).

A previous study by Becker in 1964 of seventy-five offspring of patients with proven open-angle glaucoma showed the following results.

WATER DRINKING and TOPICAL BETHAMETHASONE PROVOCATIVE TESTING

Diag.	No. Patients	Water Provocative	Topical Bethamethasone (3 to 6 weeks)			
		Po/C≥100	Po/C≥100	C<o.18	A>21	C/Co≤2/3	A>6
A. Comparison of responses of glaucoma, glaucoma suspects, volunteers and glaucoma offspring (all ages)							
Glaucoma*	50	100%	100%	98%	96%	90%	92%
Suspects†	50	100%	100%	96%	96%	88%	80%
Volunteers	50	0	30%	32%	28%	38%	32%
Offspring	75	47%	97%	96%	87%	84%	73%
B. Comparison of volunteers and glaucoma offspring 40 years of age or younger							
Volunteers	20	0	25%	25%	20%	35%	25%
Offspring	20	35%	100%	95%	95%	90%	80%

EXPLANATION OF TABLE (Preceding Page)

* Primary open-angle glaucome controlled medically at Po < 21 mm Hg

+ Positive water tonogram

A = applanation pressure
L = outflow facility

C/Co = ratio of outflow facility after (c) topical steroids to that before (co) steroids

Po = Schotz pressure

Δ A = change in applanation pressure induced by topical steroids

Armaly and Becker both now had good evidence pointing to the fact that open-angle glaucoma was a homozygous state. And secondly, the transmission of this type of glaucoma was recessive. In addition, the heterozygous or carrier state of the disease (greater than 6 millimeters of mercury increased intraocular pressure) may be differentiated from the normal state (less than 6 millimeters of mercury increased intra-ocular pressure) by response to topical corticosteroids. If this is not true, then Becker believes the positive response to topical corticosteroids is a monogenic dominant trait (1) (7) (11). Armaly states that it remains important to establish the relationship between the genotype description with respect to the alleles Pl Ph and the development of clinical open-angle glaucoma. The question is whether it is one of identity or if it is

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*Preceding page table
Becker & Hahn: Topical Corticosteroids and Hereditary in Primary Open-Angle Glaucoma, Amer. Journal Ophthal, 57:543 - 50, 1964.

one in which the genotype Pl and Ph are only one of the factors involved in spontaneous development of open-angle glaucoma. To him, this question had not been fully answered and required further study (4)..

Postulated Mechanisms

Various theories have been put forth to explain the effects of topical corticosteroids on intraocular pressure. Armaly et. al. in 1963 postulated the use of topical steroids resulted in increased mucopolysaccharides secondary to mass cell degeneration; and that at the same time, there was a decreased ability to remove the mucopolysaccharides because of earlier injury or changes in the trabecular meshwork. He did note that there was a marked suppression of aqueous formation (3). J. P. Nicholas in his studies felt there was a striking lack of relationship between outflow facility coefficients and intraocular pressure (22). This work did not agree with Becker's where he found that with 1.) intraocular pressure greater than 31 millimeters of mercury correlated with outflow facility less than 0.08, 2.) intraocular pressure greater than 24 millimeters of mercury correlated with outflow facility less than 0.14, and 3.) minimal responders averaged only 1.5 millimeters of mercury increase, and this third group was considered normal. Thus, Becker definitely showed in his study there was a correlation between outflow and intraocular pressure (9).

Miller in search for possible mechanisms stated that the increased intraocular pressure due to corticosteroids was not related to mydriasis nor lid ptosis. He felt the most intriguing possibility was the thickening of the cornea associated with changes of the corneoscleral trabecular meshwork changes. But this possibility in his study did not prove to be consistant (21).

Paterson felt the explanation was due to a decreased outflow and increased aqueous formation, but the study he admitted was not well controlled and he felt the sample too small to be statistically significant (23).

Armaly, using eighty patients, concluded that the decrease in outflow facility (or increased resistance to outflow) as well as the magnitude of change closely paralleled the changes in intraocular pressure, and suggested this to be the major mechanism. Studying aqueous formation, he found no statistically significant change from control values. He also stated that the response of intraocular pressure was dependent upon the concentration of the dexamethasone. Armaly advocated dilution of 0.1 percent dexamethasone to 0.5 percent or even .01 percent, thus still anti-inflow action, but reducing the increase in intraocular pressue (1). Most of the theories do not fully explain the effects of topical corticosteroids, but it is felt that mucopolysaccharides either from local production or deposition may yield thickening of the

the trabeculum and cause decreased outflow facility. Corticosteroids could precipitate this by 1.) increased local production, 2.) increased aqueous viscosity, or 3.) by increasing water binding capacity of the trabecular mucopolysaccharides resulting in swelling and blocking the outflow. In the 'normal' eye the mucopolysaccharides are continually removed and the final amount present is the resultant of deposition and removal. It would be expected that degenerative changes in the trabeculum due either to aging or glaucoma might predispose the eyes to a greater effect by the steroids which has been shown.

Present and Future Clinical Significance of These Findings

Thus, an unwanted side-effect of topical corticosteroids has provided a research tool enabling investigators to better study open-angle glaucoma and its pathogenesis (24). The patient with borderline tensions may now be tested with a provocative topical corticosteroid challenge; and from the results one may be able to decide whether the patient is 1.) merely a carrier, 2.) whether he is a latent glaucoma victim, and 3.) if he should be treated. Also before treating a patient with topical steroids one may more closely question the patient concerning his family history and thus be able to avoid a tragedy. Now one may more intelligently follow a patient under treatment with topical steroids, and be alert to the possibility of the drug side effects. Now one may be able to discover low

tension open-angle glaucoma patients early, and thus allow early treatment. Thus, by early treatment visual losses may be prevented [14] [17]. Further study and long-term family studies may enable these and many new ideas to be achieved.

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