Predictive Value of a Topical Dexamethasone Provocative Test before Intravitreal Triamcinolone Acetonide Injection

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PURPOSE. To investigate the diagnostic value of a topical dexamethasone (DXM) provocative test before intravitreal triamcinolone acetonide (IVTA) injection for a steroid response.

METHODS. Eligible patients scheduled for first-time IVTA who did not have glaucoma or a history of a steroid response received DXM 0.1% drops 4 times daily over 4 weeks. After that, IVTA was given except in DXM responders with an IOP increase greater than 15 mm Hg. IOP was measured at baseline, 4 weeks after DXM treatment, at weeks 1, 2, and 4, and at months 3 and 6 after IVTA. A steroid response after the DXM test or after IVTA was defined as an IOP increase of 6 mm Hg or greater.

RESULTS. Thirty-six patients (36 eyes) were analyzed. The DXM test had a sensitivity of 25% (95% confidence interval [CI], 0.07–0.52), a specificity of 100% (95% CI, 0.83–1.00), a positive predictive value of 100% (95% CI, 0.40–1.00), and a negative predictive value of 62% (95% CI, 0.44–0.79) for a steroid response after IVTA. In DXM responders, the IOP increase after IVTA was 17.0 ± 7.8 mm Hg versus 5.0 ± 4.4 mm Hg in DXM nonresponders (P = 0.005). The IOP increase after the DXM test correlated with the IOP increase after IVTA (P = 0.001).

CONCLUSIONS. The topical DXM test had a low sensitivity, a high specificity, a high positive predictive value, and a moderate negative predictive value and may be useful to predict a steroid response after IVTA. DXM responders demonstrated high IOP increases after IVTA, and the IOP increase after the DXM test correlated with the IOP increase after IVTA. If the DXM test result is positive, risks and benefits of IVTA should be more carefully weighted.

In recent years, intravitreally administered drugs, including steroids, have been increasingly used. Intravitreal triamcinolone acetonide (IVTA) injection has been widely investigated and has been proven to be useful in age-related macular degeneration, choroidal neovascularization, diabetic retinopathy, diabetic macular edema, cystoid macular edema, uveitis, and central or branch retinal vein occlusion. However, its complications also have been described, of which steroid-induced ocular hypertension is the most important. The therapeutic effect of IVTA is reported to be approximately 2 to 4 months for 4 mg IVTA and up to 9 months for 20 mg IVTA; it also depends on a history of vitrectomy. Such a prolonged period of elevated IOP is likely to be harmful, particularly for patients with advanced glaucoma.

From this perspective, it would be clinically worthwhile to be able to identify patients at risk for steroid response after IVTA injection. Therefore, we evaluated whether a topical steroid test before IVTA by means of a 4-week topical DXM provocative test would be able to predict the occurrence of a steroid response after IVTA. The diagnostic accuracy of this topical DXM test, together with the correlation between the IOP increase induced by the DXM provocative test and the IOP increase after IVTA, were investigated. We hypothesized that the DXM steroid test would have a high predictive value for a steroid response after IVTA and that the IOP increase after the DXM test would be correlated with the IOP increase after IVTA.

METHODS

This study was approved by the institutional review board of the University Hospitals Leuven and followed the tenets of the Declaration of Helsinki. Patients were consecutively recruited at our medical retina division between March 2006 and July 2007. Inclusion criteria were patients without glaucoma, without history of steroid-induced ocular hypertension, scheduled for first-time IVTA, without contraindications to withhold IVTA for 1 month; patients provided signed informed consent before study enrollment and had to have fulfilled all study requirements and visits before being included in the final analysis. A diagnosis of glaucoma was based on the criterion of a glaucomatous appearance of the optic disc or an abnormal visual field test in two consecutive visual fields; elevated IOP was optional. Exclusion criteria were glaucoma, history of steroid-induced ocular hypertension, loss of follow-up, delay in or cancellation of IVTA injection, and insufficient follow-up visits for IOP measurements. Only one eye per patient was considered. If both eyes were eligible, the left eye was included. Patients were given DXM 0.1% eye drops 4 times daily for 4 weeks in the study eye as a provocative DXM steroid test. Subsequently, IVTA was injected. The choice of dosage (4 mg vs. 20 mg) was determined on a consecutive basis in time after current trends in retinology. For ethical and medical reasons, IVTA was not injected in DXM test responders who had IOP increases greater than 15 mm Hg; they were subsequently excluded for final analysis. IOP was measured by appla-

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nation tonometry at different daily time points at baseline, after 4 weeks of DXM eye drops, and at weeks 1, 2, and 4, and months 3 and 6 after IVTA. During this follow-up of 6 months, the maximal IOP was recorded. The IOP increase after the DXM test and the IOP increase after IVTA were both defined as the difference in IOP compared with the baseline IOP measured before the start of the DXM test. Patients were classified, based on IOP increase compared with baseline IOP, into two groups of steroid responders—moderate (6 mm Hg ≤ IOP increase < 15 mm Hg) and high (IOP increase ≥ 15 mm Hg)—in accordance with the classification of Armaly et al.1 The other participants were considered nonresponders.

A statistical software package (SPSS, version 15.0; SPSS for Windows Inc., Chicago, IL) was used. Baseline IOP and absolute differences in IOP after the DXM test and after IVTA injection compared with baseline were considered continuous variables. Data were expressed as mean ± SD unless indicated otherwise. Diagnostic accuracy parameters (sensitivity, specificity, positive and negative predictive value) with 95% confidence intervals (CI) of the DXM test accuracy parameters (sensitivity, specificity, positive and negative predictive value) with 95% confidence intervals (CI) of the DXM test after a steroid response after IVTA were assessed as outlined by the Standards for Reporting Diagnostic Accuracy (STARD) guidelines.2,22 The DXM steroid test and IVTA injections were considered to be positive if the IOP after the DXM test or after IVTA increased 6 mm Hg or more compared with the baseline IOP. The correlation between IOP increase after DXM and IOP increase after DXM testing was first assessed by Spearman analysis. The Mann-Whitney U test was used to compare the IOP increase after IVTA between DXM responders and DXM nonresponders. The effect of the independent variables underlying eye disease, sex, age, baseline IOP, IVTA dosage (4 mg vs. 20 mg), and IOP increase after the DXM test on the dependent variable IOP increase after IVTA was estimated by univariable linear regression analysis. Normality of data was tested by histogram plotting of the residuals. Subsequently, predictors significantly associated with the dependent variable IOP increase after IVTA in the univariable regression analysis were entered into a multivariable linear regression model. P ≤ 0.05 (two-sided) was considered statistically significant.

RESULTS

Forty-three patients were enrolled. Seven patients were post hoc excluded for analysis (two DXM high responders who received no IVTA, one lost to follow-up before IVTA, and four without 4-week DXM test results or with insufficient IOP measurements after IVTA). In total, 36 patients (36 eyes) could be analyzed. Mean age was 65 ± 13 years (range, 36–85); 20 patients were women. The indication for which IVTA was scheduled was diabetic macular edema (n = 17), central or branch retinal vein occlusion (n = 18), or telangiectasias (n = 1). Baseline IOP was 15.0 ± 2.7 mm Hg (range, 9–20). After the topical DXM test, four patients (11%) and two patients (5%) were moderate and high steroid responders, respectively. The two DXM high responders received no IVTA and were subsequently excluded for analysis. Overall (n = 36) IOP after the DXM test was 16.9 ± 4.4 mm Hg (range, 10–28). The IOP difference after the DXM test compared with baseline was 1.8 ± 3.6 mm Hg (range, −4 to 14). Twenty-three patients (64%) received injections of 20 mg IVTA. All patients were followed up for 6 months after IVTA. Twelve patients (33%) and four patients (11%) were moderate and high steroid responders after IVTA, and the remaining 20 patients (56%) were nonresponders. Among the 16 patients with a steroid response after IVTA, 10 patients received 4 mg IVTA and the other six patients received 20 mg IVTA. Maximal IOP after IVTA was 21.3 ± 6.4 mm Hg (range, 11–40). The IOP difference after IVTA compared with baseline was 6.3 ± 6.1 mm Hg (range, −3–23).

Percentages of steroid responders after the topical DXM test and after IVTA injection were 16.6% and 44.4% (with exclusion of the two high DXM responders), respectively. The topical DXM provocative test had a sensitivity of 25% (95% CI, 0.07–0.52), a specificity of 100% (95% CI, 0.83–1.00), a positive predictive value of 100% (95% CI, 0.40–1.00), and a negative predictive value of 62% (95% CI, 0.44–0.79) for a steroid response after IVTA (IOP increase ≥ 6 mm Hg; Table 1). Of the four patients with a steroid response after the DXM test as well after IVTA injection, three received 4 mg IVTA and the other received 20 mg IVTA.

The IOP increase after the DXM test was positively correlated with the IOP increase after IVTA (P = 0.025; Spearman; Fig. 1). The IOP increase after IVTA was 17.0 ± 7.8 mm Hg in DXM responders compared with 5.0 ± 4.4 mm Hg in DXM nonresponders (P = 0.005; Mann-Whitney U test). In univariable regression analysis, underlying eye disease (P = 0.784), baseline IOP (P = 0.398), and IVTA dosage (P = 0.516) were not significantly associated with the IOP increases after IVTA, in contrast to the IOP increases based on DXM test (P = 0.001), sex (P = 0.005), and age (P = 0.031). The latter three variables were entered into a multiple regression model; the IOP increase after the topical DXM test remained the predictor

![Figure 1](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933448/ on 06/22/2017)
most strongly associated with the IOP increase after IVTA ($P = 0.001$). Additionally, sex was correlated with IOP increases after IVTA ($P = 0.029$), with men being more likely to experience IOP increases than women. Finally, age was inversely correlated with the IOP increase after IVTA ($P = 0.041$), with younger patients being at greater risk than older patients for elevated IOP after IVTA.

**DISCUSSION**

Many patients receiving IVTA experience steroid-induced elevations in IOP $^{11-16}$. It would be useful to be able to identify future IVTA steroid responders. To the best of our knowledge, after a computerized search using Medline and PubMed, this is the first study investigating whether a topical provocative steroid test has predictive value with regard to a steroid response after IVTA.

Our results of the diagnostic accuracy of the topical DXM test for a steroid response after IVTA demonstrated low sensitivity (25%), indicating that a negative DXM test result does not rule out a steroid response after IVTA and therefore cannot be used for screening. The high specificity (100%) of the DXM test suggests a very low number of false-positive test results. The positive predictive value of the DXM test was excellent (100%), whereas the negative predictive value was moderate (62%). These predictive values indicate that a DXM test before IVTA may be useful to predict a steroid response after IVTA. Note that predictive values for a test depend critically on the prevalence of the abnormality in the patients undergoing testing.$^{14}$

In this study, the prevalence of a steroid response after IVTA in our nonglaucomatous patients was 44.4%, consistent with other investigations.$^{12}$

If the same study would have been done within a glaucoma population, the prevalence of a steroid response following the DXM test or after IVTA injection would be higher, since it is known that glaucoma patients experience more frequently a steroid-induced IOP elevation after steroid administration.$^{5}$ This would imply that, if this study was done with glaucoma patients, the diagnostic accuracy parameters would be higher and their confidence intervals smaller.

The IOP increase as a result of the topical DXM test was found to be the most strongly associated predictor of the IOP increase after IVTA and could possibly provide a quantitative estimate of it. Indeed, topical DXM responders had clinically and statistically significant higher IOP increases after IVTA than topical DXM nonresponders (17.0 ± 7.8 mm Hg vs. 5.0 ± 4.4 mm Hg).

This prospective study had some shortcomings. First, our sample size was small because of the stringent inclusion criteria, and no a priori sample size calculations were determined. Single diagnostic accuracy values should, therefore, be considered with caution. To deal with this uncertainty, the 95% CI for each diagnostic accuracy parameter was calculated. Note that our sample size was appropriate regarding the correlation between the IOP increase after the DXM test and the IOP increase after IVTA ($P = 0.001$) and for the difference in IOP increase between DXM responders and DXM nonresponders ($P = 0.005$). Second, IOP was assessed by only one measurement at a variable time point. By setting the cutoff for a steroid response at 6 mm Hg or higher, possible effects of diurnal IOP variations may be limited. The fact that the DXM test yielded a high specificity indicates a low number of false-positive values. Third, there was a difference in administrated IVTA dosages (4 mg and 20 mg IVTA). We believe this did not influence our results. Cunningham et al.$^{25}$ reported that data of steroid-induced ocular hypertension in the many studies referenced therein using 4 mg IVTA compared with those using 20 mg IVTA were not markedly different in prevalence and magnitude of IOP elevation after IVTA, suggesting that the IOP increase after IVTA is not dose dependent. However, the duration of IOP elevation caused by IVTA differed. Recently, Tamewar et al.$^{26}$ demonstrated that patients injected with 20 mg IVTA had no significantly greater risk for steroid-induced ocular hypertension than those injected with 4 mg IVTA. In addition, there was no evidence for a significant difference in IOP increase after IVTA between both IVTA dosage groups in this study ($P = 0.516$). Finally, we did not make assumptions regarding glaucoma patients.

In summary, our findings indicate that a topical DXM test before IVTA has a low sensitivity, a high specificity, a high positive predictive value, and a moderate negative predictive value with regard to a steroid response after IVTA injection. IOP elevations after IVTA were significantly higher in topical DXM responders than in DXM nonresponders. Moreover, the IOP increase after the topical DXM test was strongly correlated with the IOP increase after IVTA. We can conclude that the topical DXM test, which is easy to apply in clinical practice, may be useful in predicting IOP elevations after IVTA. If a provocative DXM test result is positive, the provider should more carefully weigh the potential risks and benefits of IVTA injection.

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