Serum Factors Associated with Neovascular Glaucoma Following Vitrectomy for Proliferative Diabetic Retinopathy

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We performed a retrospective study of serum factors associated with neovascular glaucoma that can occur following vitrectomy for proliferative diabetic retinopathy. The medical records of 183 patients (241 eyes) who received vitrectomy between August 1996 and August 2000 were studied retrospectively and subsequently analyzed by linear logistic regression analysis and multiple logistic regression tests. Neovascular glaucoma developed at an average of 2.7 months in 31 of 241 eyes (14.1%). The overall anatomical success rate of retinal attachment was 82.5% (199 eyes in 241 eyes), although it decreased to 45.1% (14 eyes in 31 eyes) in eyes with neovascular glaucoma. Serum cholesterol (P = 0.041) and fibrinogen levels (P = 0.020) were significantly associated with the development of neovascular glaucoma. However, no significant association could be found concerning hypertension, diabetic retinopathy or hypercholesterolemia (P > 0.05). We suggest that serum creatinine, cholesterol and fibrinogen levels can be used to predict the development of neovascular glaucoma in vitrectomized eyes with diabetic retinopathy and can further provide a more active approach to preventing the development of this condition.

Key words: diabetic retinopathy, neovascular glaucoma, serum factors, vitrectomy

INTRODUCTION

Vitrectomy for complications of proliferative diabetic retinopathy can reduce the incidence of visual loss, although vitrectomy itself can also result in several complications of its own. Studies have been performed on several factors that influence these complications. Neovascularization of the iris and neovascular glaucoma are some of the most severe and intractable complications that can develop following vitrectomy.

Most vitreoretinal surgeons encounter neovascularization of the iris after vitrectomy and many have reported on the various factors associated with its occurrence. The development of diabetic complications and their prognostic factors have been studied systematically by the DCCT (Diabetes Control and Complication Trial) since the 1980's. The results have shown us that studies associated with the development of neovascular glaucoma can also be

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conducted in terms of serum factors and changes in hemodynamics. This can be used to predict the relative risk of neovascular glaucoma.

In this study we evaluated the serum factors and systemic diseases that are thought to be associated with the development of neovascular glaucoma.

**MATERIALS AND METHODS**

Medical records of 183 patients (241 eyes) who received vitrectomy for complications of proliferative diabetic retinopathy between August 1996 and August 2000 were analyzed retrospectively. Indications for vitrectomy included vitreous hemorrhage that persisted for more than three months, tractional retinal detachments that involved the macula and combined tractional and rhegmatogenous retinal detachments.

Sclerotomies were performed three millimeters from the limbus, and pars plana vitrectomy was performed. Lensectomies were performed if the cataract was severe. Intraocular panretinal photocoagulation was performed in all eyes. Balanced salt solution, air, intraocular gas (SF₆ or C₃F₈), or silicone oil was used depending on the intraocular state.

Anatomical success was defined as the complete removal of the vitreous opacity and attached retina. Best-corrected visual acuity at the most recent follow-up examination was used as final visual acuity.

Sex, age, duration of diabetes, coexistence of other systemic diseases as well as blood sugar, hemoglobin A1c, BUN, creatinine, serum cholesterol, high-density lipoprotein, low-density lipoprotein, neutral fatty acid and fibrinogen levels were used as variables in the study.

Blood sugar was measured four times daily, and the average value was used. Coexisting systemic diseases such as hypertension, renal disease and hyperlipidemia were diagnosed preoperatively.

During admission, if the systolic pressure was 210 mmHg or greater, or the diastolic pressure was 120 mmHg or higher in a single measurement, or if the systolic pressure was 140 mmHg or higher and diastolic pressure was 90 mmHg or greater for more than three measurements, the patient was categorized as demonstrating hypertension.

Preoperative serum creatinine levels of 1.4 mg/dL or higher and proteinuria ++ or higher were defined as renal disease.

Hyperlipidemia was recorded if the serum cholesterol level was 240 mg/ml or higher or if it was diagnosed at the internal medicine department.

Neovascular glaucoma was defined as a neovascularization of the iris by gonioscope and an intraocular pressure of 22 mmHg or higher.

Statistical analysis was done with univariate and multivariate logistic regression analysis tests using the SPSS for Windows 10.0.

**RESULTS**

The mean age of the patients was about 53 years (range of 23 to 83 years). The mean duration of diabetes was 13.4 years, and the mean postoperative follow-up examination period was 24 months.

Functional success was defined as a postoperative final visual acuity of 0.025 or higher. One hundred forty-five eyes (60%) of the total 241 eyes achieved functional success. Anatomical success was defined as the successful reattachment of the retina and complete removal of the vitreous opacity. 199 eyes (82.5%) achieved anatomical success and neovascular glaucoma developed in 14 eyes (7.0%). In comparison, 17 eyes (40.5%) developed glaucoma in which the retina failed to attach.

Six eyes had preoperative neovascularization of the iris, and among these, 4 eyes developed neovascular glaucoma postoperatively. Regression of the aberrant iris vessels was observed in two eyes. Neovascular glaucoma developed postoperatively in 27 eyes which were free of neovascularization preoperatively, although there was no case with bilateral development.

Endolaser photocoagulation was performed on all eyes. Lensectomy was done in 25 eyes (80.6%) of the postoperative neovascular glaucoma patients. Two patients had previous cataract extraction, however, the posterior capsule was intact. In comparison, lensectomy was performed in 118 eyes (56.2%) that did not develop postoperative glaucoma. The lens capsule was preserved in all cases. 11 eyes had previous cataract extraction, and among these the lens capsule was absent in 3 eyes.

The preoperative visual acuity of the patients who developed neovascularization postoperatively varied
Table 1. Comparison of final visual acuity according to the presence of neovascular glaucoma (eyes %)

<table>
<thead>
<tr>
<th>Final visual acuity</th>
<th>Neovascular glaucoma</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>≥ 0.5</td>
<td>0 (0)</td>
<td>32 (15.2)</td>
<td></td>
</tr>
<tr>
<td>0.1–0.4</td>
<td>1 (3.2)</td>
<td>85 (40.5)</td>
<td></td>
</tr>
<tr>
<td>0.025–0.08</td>
<td>8 (25.8)</td>
<td>24 (11.4)</td>
<td></td>
</tr>
<tr>
<td>FC</td>
<td>4 (12.9)</td>
<td>39 (18.6)</td>
<td></td>
</tr>
<tr>
<td>HM</td>
<td>10 (32.2)</td>
<td>21 (10.0)</td>
<td></td>
</tr>
<tr>
<td>LP(+)</td>
<td>1 (3.2)</td>
<td>9 (4.3)</td>
<td></td>
</tr>
<tr>
<td>LP(-)</td>
<td>7 (22.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>31 (100)</td>
<td>210 (100)</td>
<td></td>
</tr>
</tbody>
</table>

FC: finger count, HM: hand movement, LP: light perception

The results of Table 1 indicate a complete loss of light perception (Table 1).

Linear logistic regression analysis showed serum creatinine (P = 0.029, Odds ratio = 5.210), total cholesterol (P = 0.041, Odds ratio = 6.541) and fibrinogen (P = 0.029, Odds ratio = 3.413) to have a significant influence (Table 2). Multiple logistic regression analysis revealed that among these factors total cholesterol (P = 0.041, Odds ratio = 21.712) and fibrinogen (P = 0.020, Odds ratio = 39.104) were significantly related to neovascular glaucoma (Table 3). Serum creatinine showed a significant correlation with total cholesterol (R = 0.385, P < 0.01) (Fig. 1).

DISCUSSION

Removal of the lens, intraocular lens implantation, retinal detachment and photocoagulation are known to be risk factors for the development of neovascular glaucoma following vitrectomy for the treatment of proliferative diabetic retinopathy.4,5,9-11 Wand et al11 have reported that among these factors,

Table 2. Univariate analysis of systemic factors associated with neovascular glaucoma following vitrectomy for proliferative diabetic retinopathy using linear logistic regression test

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>6.541</td>
<td>1.543-27.093</td>
<td>0.041</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3.413</td>
<td>1.280-11.323</td>
<td>0.010</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.281</td>
<td>0.961-20.026</td>
<td>0.206</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.065</td>
<td>0.754-1.385</td>
<td>0.292</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.931</td>
<td>0.672-1.291</td>
<td>0.657</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>2.412</td>
<td>1.394-2.985</td>
<td>0.076</td>
</tr>
<tr>
<td>Glucose</td>
<td>14.132</td>
<td>8.43-131.192</td>
<td>0.053</td>
</tr>
<tr>
<td>BUN</td>
<td>3.504</td>
<td>0.366-30.471</td>
<td>0.427</td>
</tr>
<tr>
<td>Creatinine</td>
<td>5.210</td>
<td>3.122-10.997</td>
<td>0.029</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.713</td>
<td>1.285-4.132</td>
<td>0.300</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>1.210</td>
<td>0.992-1.240</td>
<td>0.062</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.937</td>
<td>0.318-2.802</td>
<td>0.868</td>
</tr>
</tbody>
</table>

Table 3. Individual effects and significance levels in multivariate analysis of selected factors found to be associated significantly with neovascular glaucoma following vitrectomy for proliferative diabetic retinopathy in the univariate analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>6.212</td>
<td>2.741-17.663</td>
<td>0.051</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>21.712</td>
<td>2.186-116.175</td>
<td>0.041</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>39.104</td>
<td>3.233-191.124</td>
<td>0.020</td>
</tr>
</tbody>
</table>
persistent retinal detachment has the highest risk of developing postoperative neovascular glaucoma.

Neovascular glaucoma is known to develop when vasoactive factors released by the ischemic retina reach the iris and induce neovascularization of the iris. The forward movement of these factors from the vitreous toward the anterior chamber is proven by iris neovascularization cases in which the crystal lens is absent or when Nd:YAG posterior capsulotomy is performed. The recent trend in preserving the anterior capsule when performing lenectomy has diminished the lenticular factor on neovascularization of the iris. Lenectomy was performed in 143 eyes (68.1%) of 241 total eyes examined, however, preservation of the anterior capsule may have decreased the incidence of neovascular glaucoma to 25 cases (17.5%). Endolaser photocoagulation was performed in all eyes.

Operative techniques are not the only factors that affect the final result. The general state of the patient is also very important in the final outcome, which can be expressed in terms of visual acuity. Neovascular glaucoma has a profound effect on final visual acuity, thus evaluating the preoperative systemic factors associated with it permits us to predict the relative risk and enable us to maximize our effort on preventing it.

In our study, disregarding interference, serum total cholesterol (≥ 240 mg/dL, P = 0.041), serum creatinine (≥ 2.5 mg/dL, P = 0.029) and serum fibrinogen (≥ 500mg/dL, P = 0.010) had the most significant correlations. Significant independent factors that could affect neovascularization were total cholesterol (P = 0.041, Odds ratio = 21.712) and serum fibrinogen (P = 0.020, Odds ratio = 39.104).

Diabetic nephropathy had no significant association whereas serum creatinine was significant in our study. This discrepancy may result from the fact that we used a reference creatinine value of 2.5 mg/dL, whereas diabetic nephropathy has been defined at 1.4 mg/dL. If a higher value had been used for the definition of nephropathy, it could have resulted in a significant association. A significant correlation was observed between cholesterol and creatinine (R = 0.385, P < 0.01) (Fig. 1), and this may also have influenced the result.

An increase in total cholesterol is known to be associated with intravascular hypercoagulability and the progression of diabetic retinopathy. Abnormalities in lipid metabolism cause atherosclerosis, and this kind of change could aggravate retinal ischemia.

Changes in hemorheological factors occur in the diabetic patient, and among these an increase in fibrinogen is among the most significant. In vivo ischemia-reperfusion models have revealed that excessive deposition of fibrinogen occurs in the arterioles and venules when they are reperfused. This kind of excessive fibrinogen deposition occurs because of increased expression of ICAM-I.
ischemia-reperfusion state activates this process. At present we are unable to explain whether this increase in fibrinogen does indeed influence neovascularization or whether it is only associated with the severity of the retinopathy.

Operative techniques vary from one surgeon to another, and are also influenced by the severity of diabetic complications. Vitreous substitutes such as intraocular gas or silicone oil can be used, and these may affect the development of neovascular glaucoma as well. These differences and postoperative intraocular complications such as retinal detachments should also be considered, however, Kim et al5 have previously reported on these kinds of operative risks associated with neovascular glaucoma, so in our present study we could concentrate on the general picture of systemic factors. A combined evaluation of operative risks and serum factors would provide more detail on risk factors associated with neovascular glaucoma and also decrease bias. In our study, a single surgeon performed all operations and a large number of 241 cases were studied so as to minimize bias.

In conclusion, if the preoperative cholesterol level is 500 mg/dL or higher or if the serum fibrinogen level is high, there exists a high risk of neovascular glaucoma. Prudent preoperative examination of the iris before dilatation and intraocular pressure measurement is recommended. Further study is required to evaluate whether fibrinogen has a direct causative role in the development of neovascularization or whether it is only an indirect index of the risk.

REFERENCES


