Effect of Perioperative Glycemic Control in Progression of Diabetic Retinopathy and Maculopathy

Chikako Suto, MD; Sadao Hori, MD; Satoshi Kato, MD; Kanemitsu Muraoka, MD; Shigehiko Kitano, MD

Objective: To evaluate the contribution of perioperative glycemic control to progression of diabetic retinopathy and maculopathy.

Methods: Postoperative progression of diabetic retinopathy and maculopathy were compared in 87 patients with type 2 diabetes mellitus who underwent monocular phacoemulsification cataract surgery performed by a single surgeon. Twenty-seven patients had had poor glycemic control preoperatively and underwent rapid preoperative glycemic correction; 30 patients had poor control preoperatively that was not corrected postoperatively; and 30 patients had good preoperative glycemic control. The grade of diabetic retinopathy and maculopathy in the operated-on eye and the fellow eye was assessed preoperatively and for 12 months postoperatively.

Results: There were no significant differences in the progression rate of diabetic retinopathy among the 3 groups (P=.27). However, the progression rate of diabetic maculopathy was significantly higher in the group that underwent rapid control than in the other 2 groups (P=.02). Patients with moderate to severe nonproliferative diabetic retinopathy preoperatively in the rapid control group had significantly higher progression rates of diabetic retinopathy and maculopathy (P=.002 and .008, respectively).

Conclusions: Rapid preoperative glycemic control should be avoided in patients with moderate to severe nonproliferative diabetic retinopathy because it may increase the risk of postoperative progression of retinopathy and maculopathy.

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Preventing the progression of retinopathy and maculopathy in patients with diabetes mellitus after cataract surgery is important for improving visual prognosis, but the means to achieve this goal have not been clarified. Postoperative progression of retinopathy is reportedly less common in patients undergoing phacoemulsification than in those undergoing extracapsular cataract extraction, but postoperative progression is still observed in 20% to 30% of patients after phacoemulsification. The causes of progression of retinopathy and maculopathy after cataract surgery include systemic factors (poor glycemic control, use of insulin, and age), the preoperative stage of retinopathy, natural course of the disease, and surgical techniques.

In the present study, we focused on the contribution of perioperative glycemic control to progression of retinopathy because the roles of optimal glycemic control for surgery and the appropriate postoperative management of blood glucose levels remain unclear. We prospectively assessed glycemic control (glycosylated hemoglobin [HbA1c] values) and the progression of retinopathy and maculopathy during the perioperative period, to evaluate the postoperative effects of blood glucose levels on retinopathy and maculopathy. A single experienced surgeon performed all operations with the use of the same procedure and intraocular lens (IOL) implantation, to minimize the variations in surgical invasiveness. The consistency achieved allowed evaluation of the effects of glycemic control on retinopathy and maculopathy.

METHODS

The subjects of the present study were 87 patients with type 2 diabetes mellitus who underwent phacoemulsification and IOL implantation in 1 eye each between March 1, 1999, and February 28, 2003. All procedures were performed by a single experienced surgeon (C.S.) who had performed phacoemulsification cataract surgery in more than 3000 cases. All patients were monitored prospectively from 6 months before surgery to 1 year after surgery.

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The patients were divided into 3 groups. The rapid preoperative glycemic correction (RPGC) group consisted of 27 patients with HbA1c values of 9% or higher at 6 months before surgery in whom HbA1c values were decreased by 3% or more at 3 months before surgery, and in whom good postoperative glycemic control was maintained during hospitalization. The poor control group consisted of 30 patients with postoperative HbA1c values of 8.5% or higher in whom preoperative glycemic control was poor because of refusal to undergo hospitalization and poor compliance. The good control group consisted of 30 patients with preoperative and postoperative HbA1c values of approximately 7.0%.

Cataract surgery was performed with the patient under topical anesthesia. A nonsuture sclerocorneal incision (3.8 mm from the 12-o’clock position) was made, and continuous circular capsulorrhexis was performed. For cataract surgery, phacoemulsification equipment (Legacy; Alcon Laboratories Inc, Fort Worth, Tex) was used, with enriched balanced saline solution (BSS PLUS; Alcon Laboratories Inc) as the perfusion fluid. The ultrasound time [in minutes]: 0.43±0.8, 0.43±0.8, 0.44±1.0, and 0.44±1.0, respectively. (Values are given as mean±SD.)

Table 1. Clinical Profile of Patients

<table>
<thead>
<tr>
<th>Stage of preoperative DR, No.</th>
<th>Rapid Correction (n = 27)</th>
<th>Poor Control (n = 30)</th>
<th>Good Control (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 (NDR)</td>
<td>9</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>20-35 (Mild NPDR)</td>
<td>8</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>43-53 (Moderate-severe NPDR)</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex, No. M/F</th>
<th>15/12</th>
<th>13/17</th>
<th>11/19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>63.0 ± 10.6</td>
<td>63.1 ± 9.2</td>
<td>63.7 ± 6.6</td>
</tr>
<tr>
<td>Duration, mean ± SD, y</td>
<td>7.8 ± 5.9</td>
<td>8.4 ± 4.9</td>
<td>9.1 ± 5.6</td>
</tr>
<tr>
<td>Treatment, No. receiving D/O/I</td>
<td>2/13/12</td>
<td>4/14/12</td>
<td>4/11/15</td>
</tr>
<tr>
<td>Preexisting nephropathy, No.</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Preexisting hypertension, No.</td>
<td>8</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Preexisting maculopathy, No.</td>
<td>8</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>HbA1c, mean ± SD, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo before surgery</td>
<td>10.5 ± 1.2</td>
<td>10.0 ± 1.1</td>
<td>7.6 ± 0.9</td>
</tr>
<tr>
<td>3 mo before surgery</td>
<td>10.3 ± 1.4</td>
<td>9.8 ± 0.9</td>
<td>7.7 ± 0.9</td>
</tr>
<tr>
<td>Immediately before surgery</td>
<td>7.4 ± 1.0</td>
<td>9.5 ± 0.6</td>
<td>7.5 ± 0.9</td>
</tr>
<tr>
<td>3 mo after surgery</td>
<td>7.4 ± 0.9</td>
<td>9.2 ± 0.8</td>
<td>7.4 ± 1.1</td>
</tr>
<tr>
<td>6 mo after surgery</td>
<td>7.4 ± 1.1</td>
<td>9.3 ± 0.8</td>
<td>7.4 ± 1.0</td>
</tr>
<tr>
<td>12 mo after surgery</td>
<td>7.5 ± 0.9</td>
<td>9.3 ± 0.8</td>
<td>7.5 ± 0.9</td>
</tr>
</tbody>
</table>

Abbreviations: D, diet only; DR, diabetic retinopathy; HbA1c, glycosylated hemoglobin; I, insulin therapy; NDR, no diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; O, oral hypoglycemic agent.

Rapid Correction (n = 27)

The characteristics of the subjects are shown in Table 1. There were no intergroup differences in sex, age, disease duration, or treatment method. There were significant differences in HbA1c values among the groups throughout the preoperative and postoperative periods. The HbA1c value at 3 months after surgery was 10.3%±1.4% in the RPGC group, 9.8%±0.9% in the poor control group, and 7.7%±0.9% in the good control group. There was no significant difference between the RPGC and poor control groups (P=.11), but the good control group differed significantly from both the RPGC and the poor control groups (P<.001). The HbA1c value at 3 months before surgery was 10.3%±1.4% in the RPGC group, 9.8%±0.9% in the poor control group, and 7.7%±0.9% in the good control group.

Our primary goal was to investigate whether cataract surgery was responsible for an acceleration in the rate of progression of diabetic retinopathy and diabetic maculopathy. We know that regression of neovascularization should be induced by panretinal photocoagulation before cataract surgery is undertaken. Panretinal photocoagulation was recommended in eyes with severe diabetic retinopathy, including those with severe nonproliferative diabetic retinopathy (NPDR) or non–high-risk proliferative diabetic retinopathy. Furthermore, panretinal photocoagulation was not recommended by the Early Treatment Diabetic Retinopathy Study (ETDRS) research group for eyes with mild or moderate NPDR.20,21 These recommendations may not be possible to follow in practice, however, because the fundus view may be inadequate for safe panretinal photocoagulation, even when using long-wavelength and high-power laser. For the same reason, we did not perform focal or grid laser photocoagulation treatment for diabetic maculopathy as defined by the ETDRS22 before cataract surgery. After surgery, panretinal photocoagulation was performed in all patients who developed proliferative diabetic retinopathy, in accordance with established guidelines. Any patient who developed clinically significant macular edema more than 3 months after surgery was considered to have new or recurrent diabetic maculopathy and therefore was treated with laser photocoagulation according to the ETDRS guidelines as soon as was practically possible.

The characteristics of the subjects are shown in Table 1. There were no intergroup differences in sex, age, disease duration, or treatment method. There were significant differences in HbA1c values among the groups throughout the preoperative and postoperative periods. The HbA1c value at 6 months before surgery was 10.5%±1.2% in the RPGC group, 9.8%±0.9% in the poor control group, and 7.7%±0.9% in the good control group. There was no significant difference between the RPGC and poor control groups (P=.11), but the good control group differed significantly from both the RPGC and the poor control groups (P<.001). The HbA1c value at 3 months before surgery was 10.3%±1.4% in the RPGC group, 9.8%±0.9% in the poor control group, and 7.7%±0.9% in the good control group.
in the poor control group, and 7.7%±0.9% in the good control group; there was no significant difference between the RPGC and poor control groups (P=.13), although the good control group differed significantly from both of the other groups (P<.001). The HbA1c value immediately before surgery decreased to 7.4%±1.0% in the RPGC group because of intensive control, while that in the poor control group was 9.5%±0.6%, and that in the good control group was 7.5%±0.9%. There was a significant difference between the RPGC and poor control groups (P<.001), but not between the RPGC and good control groups (P=.55). Neither were there any significant differences between the RPGC and good control groups with respect to the HbA1c values at 3, 6, and 12 months after surgery (P=.69, .57, and .74, respectively). Generally, the HbA1c level provides information about glycemic conditions present 2 to 3 months before the test is performed.23 The RPGC group had been in good control for at least 2 to 3 months before surgery.

When the preoperative stage of retinopathy could not be determined because of the presence of cataract, it was determined by fundus fluorescein angiography within 1 week after surgery. There were no differences in retinopathy stage among the 3 groups. Fundus examination was performed at 1, 3, 6, and 12 months after surgery. Postoperative progression of retinopathy was defined as advancement of the disease by 1 stage or more, relative to that before surgery, within 1 year after surgery, according to the modified ETDRS retinopathy severity scale.24 Progression of maculopathy was defined as the development and progression of clinically significant macular edema according to the ETDRS criteria.22 Figures 1, 2, 3, 4, and 5 show the ETDRS scale stages 20, 35, 43, 53, and 65, respectively, and Figure 6 shows clinically significant macular edema stages 1 through 3. In addition, progression of diabetic retinopathy and maculopathy was considered to be due to surgical invasion when observed in the operated-on eye alone, or when more severe progression was observed in the operated-on eye than in the fellow eye. The same extent of progression in both eyes was defined as no change. Fundus photography and fluorescein angiography were performed with a fundus camera with a 50° angle (TRC50LX; Topcon Corp, Tokyo, Japan), and ophthalmologists unaware of the objectives of the present study determined the disease stage for each patient.

The SPSS for Windows computer program (SPSS Japan Inc, Tokyo) was used for statistical analysis. Analysis of variance was used for the comparison of preoperative HbA1c values among the 3 groups, and χ² contingency table analysis was used for intergroup comparisons. Univariate and multivariate analyses were performed to investigate the relationships between postoperative progression of retinopathy or maculopathy and 5 preoperative factors (rapid correction of blood glucose levels, preoperative retinopa-
thy of stage 43 or worse, continuous proteinuria, hypertension, and the presence of maculopathy before surgery).

**RESULTS**

**DIABETIC RETINOPATHY**

Progression of retinopathy due to surgical invasion was observed in 8 (30%) of 27 eyes in the RPGC group, 5 (17%) of 30 eyes in the poor control group, and 4 (13%) of 30 eyes in the good control group. There were no significant differences in the rate of retinopathy postoperatively among the 3 groups ($P=0.27$, $\chi^2$ test). The numbers of eyes with progression, including progression likely to be spontaneous and that which was similar in both eyes, were 10 eyes (37%), 10 eyes (33%), and 6 eyes (20%), respectively ($P=0.33$, $\chi^2$ test). Retinopathy was classified into 4 stages in accordance with the ETDRS scale (Table 2). The number of eyes in each group showing progression due to surgical invasion was as follows: 8 eyes in the RPGC group (1 eye with no preoperative diabetic retinopathy and 7 eyes with moderate to severe NPDR), indicating the presence of significant differences according to the preoperative stage of retinopathy ($P=0.002$, $\chi^2$ test); 5 eyes in the poor control group (1 eye with no preoperative diabetic retinopathy, 1 eye with mild NPDR, and 3 eyes with moderate to severe NPDR), ie, no significant differences ($P=0.38$, $\chi^2$ test); and 4 eyes in the good control group (1 eye with no preoperative diabetic retinopathy, 2 eyes with mild NPDR, and 1 eye with moderate to severe NPDR), again showing no significant differences ($P=0.84$, $\chi^2$ test).

Furthermore, 6 eyes (22%) in the RPGC group and 2 (7%) in the poor control group required retinal photocoagulation after cataract surgery. Postoperative progression of retinopathy was observed in all 7 patients who showed postoperative progression of maculopathy with moderate to severe NPDR in the RPGC group.

Univariate analysis showed significant differences in the postoperative progression of retinopathy to be related to the 4 factors shown in Table 3, but not to rapid correction of blood glucose levels. On multivariate analysis, only the presence of maculopathy before surgery was significantly associated with progression (Table 4). The severity of preexisting retinopathy, except for moderate to severe NPDR, was not a risk factor for progression of retinopathy.

**DIABETIC MACULOPATHY**

Postoperative progression of maculopathy was defined as progression in the stage of maculopathy relative to the preoperative stage or new onset of maculopathy after surgery. Progression was found in 9 eyes (33%) in the RPGC group, 4 eyes (13%) in the poor control group, and 1 eye (3%) in the good control group, ie, the number of
eyes with progressive maculopathy was significantly greater in the RPGC group ($P=.02$, $\chi^2$ test). The number of eyes with progression of maculopathy in each group based on the preoperative stage of retinopathy was as follows: 9 eyes in the RPGC group (1 eye with no diabetic retinopathy, 1 eye with mild NPDR, and 7 eyes with moderate to severe NPDR, indicating significant differences related to the preoperative stage of retinopathy [$P=.008$]); 4 eyes in the poor control group (1 eye with mild NPDR and 3 eyes with moderate to severe NPDR [$P=.14$]); and 1 eye in the good control group with mild NPDR ($P=.41$) (Table 5).

Furthermore, 4 eyes (15%) in the RPGC group and 2 (7%) in the poor control group required retinal focal photocoagulation for maculopathy after cataract surgery.

The results of univariate and multivariate analysis of the progression of maculopathy according to the 5 preoperative factors are shown in Table 6 and Table 7.
respectively. Univariate analysis showed a significant influence of 4 factors, with only hypertension having no effect (Table 6). Multivariate analysis showed that rapid correction of blood glucose level and the presence of maculopathy before surgery were significantly associated with progression (Table 7).

A significant advantage of the present study is that a single surgeon performed phacoemulsification cataract surgery in 1 eye of each patient using the same procedure and type of IOL. Furthermore, postoperative progression of retinopathy and maculopathy were compared between the operated-on and non-operated-on eyes of individual patients. Various factors, such as the surgical procedure,11,12,24 IOL type,25 incision width,25 and surgeon,13 may cause differences in surgical invasiveness. We tried to minimize the variations in surgical invasiveness in our patients by standardizing the relevant factors as much as possible. This facilitated evaluation of postoperative progression. We believe that our approach allows spontaneous progression of diabetic retinopathy to be distinguished from that due to surgical invasiveness.

Comparison of recent reports on phacoemulsification cataract surgery shows differences in evaluation methods, such as the observation period (6 months after surgery6,10,13 or 12 months after surgery11,12,24), the method of staging retinopathy (ETDRS scale vs a scale that divides the disease into 4 stages1,2,4,7-9,13 or other scales2,3), and the presence of proliferative retinopathy (ETDRS scale vs a scale that divides the disease into 4 stages1,2,4,7-9,13 or other scales2,3). Each method can be distinguished from that due to surgical invasiveness.

We assessed the changes in retinopathy and maculopathy due to surgical invasion in patients with rapid preoperative glycemic control (RPGC group), patients undergoing surgery despite poor glycemic control (poor control group), and patients undergoing surgery with good glycemic control (good control group).

**POSTOPERATIVE PROGRESSION OF DIABETIC RETINOPATHY**

Postoperative progression of retinopathy was seen in 30% of the RPGC group, 17% of the poor control group, and 13% of the good control group, with no significant differences among the 3 groups. The proportion of eyes with postoperative retinopathy progression in those undergoing phacoemulsification cataract surgery is reportedly 20% to 30%, and it has been suggested that glycemic control has a smaller influence on postoperative progression of retinopathy in patients undergoing phacoemulsification cataract surgery than in those undergoing planned extracapsular cataract extraction because phacoemulsification surgery is less invasive.3,5 It has also been reported that postoperative progression of retinopathy is more common in patients with high HbA1c values immediately before surgery.5,10 Kato et al10 reported that glycemic control does not influence the postoperative progression of retinopathy, with the mean preoperative HbA1c value being the same (7.8%) in the progression and nonprogression groups, and they found postoperative progression due to surgical invasion in 24.2% of their patients at 1 year after surgery. Squirell et al14 reported the progression of retinopathy and maculopathy to be spontaneous and more often observed in patients with higher preoperative HbA1c values and in patients using insulin. On the basis of these findings, the relationship between preoperative glycemic control and postoperative progression of retinopathy is unclear. In the present study, we found the percentage of eyes with postoperative progression of retinopathy to be consistent with existing data. The absence of any significant differences among the 3 groups indicates that postoperative progres-
sion of retinopathy occurs at the same rate regardless of whether preoperative glycemic control is improved. Univariate and multivariate analysis of the relationship between postoperative progression of retinopathy and 5 preoperative factors (RPGC, preoperative retinopathy of stage 43 or worse, continuous proteinuria, hypertension, and the presence of maculopathy before surgery) showed only the presence of maculopathy before surgery to be significantly related to postoperative progression of retinopathy. The use of RPGC did not significantly influence progression, according to the results of univariate and multivariate analyses, and was not detected as a factor causing postoperative progression of retinopathy. The latter indicates that the postoperative rate of retinopathy progression is the same regardless of whether rapid correction is attempted in patients with poor preoperative glycemic control.

The overall rate of progression, including spontaneous progression, was reported to be 36.3% by Kato et al.1 and 22.0% by Squirrell et al.4 The present study showed comparable results with 37% in the RPGC group, 33% in the poor control group, and 20% in the good control group, with no significant differences among the 3 groups. However, the rate of eyes with progression in each of the 3 groups according to the preoperative stage of retinopathy was interesting. Some reports have indicated that the postoperative progression rate is higher in patients without retinopathy before surgery,2,7 so there is no consensus. In our study, unrelated to glycemic control, univariate analysis showed that preoperative retinopathy of stage 43 or worse was associated with postoperative retinopathy progression, whereas multivariate analysis showed that it was not associated. It was difficult to establish a strong correlation between the preoperative retinopathy stage and postoperative progression. However, in the present study, the progression rate in patients with moderate to severe NPDR before surgery was significantly higher in the RPGC group than in the other groups. If the early worsening reported by the Diabetes Control and Complications Trial Research Group26,27 occurs as a result of aggressive correction of glycemic control, the risk of postoperative progression would be greatly affected in patients with moderate to severe NPDR before surgery.

POSTOPERATIVE PROGRESSION OF DIABETIC MACULOPATHY

Only a few studies have separately investigated the postoperative progression of maculopathy and retinopathy. In the present study, we evaluated postoperative progression of maculopathy according to the findings on fundus fluorescein angiographic findings. The postoperative progression rate of maculopathy was significantly higher in the RPGC group (33%) than in the other 2 groups. This result is noteworthy because significant postoperative progression of retinopathy was not observed in the RPGC group. The postoperative progression rate of maculopathy was significantly higher in patients with moderate to severe NPDR as the preoperative stage of retinopathy in the RPGC group. As the result of univariate and multivariate analysis of the relationship between postoperative progression of maculopathy and the 5 preoperative factors (RPGC, preoperative retinopathy of stage 43 or worse, continuous proteinuria, hypertension, and the presence of maculopathy before surgery), the presence of maculopathy before surgery and RPGC were significantly related to postoperative progression. This indicates that early worsening might be due to irreversible invasive damage to the macula resulting from vascular hyperpermeability in patients with rapid correction of glycemic control who have maculopathy before surgery. On the basis of these findings, rapid reduction of
blood glucose levels should not be advocated for patients with moderate to severe NPDR and maculopathy before surgery because it may increase the risk of postoperative progression of both retinopathy and maculopathy.

CONCLUSIONS

The optimal preoperative glycemic control strategy for patients with diabetes mellitus undergoing cataract surgery is yet to be determined. However, the present study indicates that RPGC should be avoided in patients with moderate to severe NPDR because it may increase the risk of postoperative progression of retinopathy and maculopathy. In addition, it appears to be possible to perform surgery in patients whose retinopathy is not in the moderate to severe NPDR stage or worse regardless of whether glycemic control is good or poor. To achieve a good visual outcome, it may be important to perform surgery in cooperation with physicians who are advised to avoid RPGC in patients with moderate to severe NPDR or maculopathy.

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