23-gauge microincision total vitrectomy without anti-vascular endothelial growth factor treats proliferative diabetic retinopathy Short title: 23-gauge microincision total vitrectomy without anti-VEGF treats PDR

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Abstract: Objective: To explore how to treat proliferative diabetic retinopathy (PDR) with 23-gauge microincision total vitrectomy (23G MTV) and how to prevent intraocular bleeding with methods beyond anti-vascular endothelial growth factor (anti-VEGF) drugs. Methods: This was a Retrospective case cohort series study of patients who received 23G MTV for the treatment of PDR. All operations were carried out by one vitreoretinal surgeon. The anti-bleeding management were used except anti-VEGF injection. The follow-up period was 10.25 ± 2.29 months. Pre-/past-operative IOP and best corrected visual acuity (BCVA) were measured and statistically compared. Results: All patients had no application of anti-VEGF drugs before and after operations. Intraoperatively, the active bleeding was stopped by increasing intraocular pressure in 5 eyes and by using cutter compression in 3 eyes. These methods successfully stop all bleeding. The rest of 42 eyes had no obvious bleeding during operation and follow-up time. No retinal detachment happened in these patients. They had improved visual acuity (χ²=34.69, P<0.05) after operation. The IOP change after surgeries was not statistically significant (preoperative 16.29 ± 3.15 mmHg, and postoperative 15.55 ± 3.80 mmHg; t = -1.228, P = 0.228). Conclusion: 23G MTV is a feasible and safe treatment for proliferative diabetic retinopathy. Intraocular hemorrhage during and after the operation may be avoided without anti-VEGF injection.


Keywords: proliferative diabetic retinopathy; 23G microincision total vitrectomy; vitreous hemorrhage; retinal bleeding

Introduction

Diabetic retinopathy (DR) is one of the important complications of microvascular diseases in diabetes mellitus. Proliferative diabetic retinopathy (PDR) is the severe stages of diabetic retinopathy, which include vitreous hemorrhage, neovascularization or tractional retinal detachment. Three-port pars plana vitrectomy can clean the vitreous hemorrhage and membrane, relax or destroy the tracting fibres. As a main surgical management of PDR, the inroperative bleeding is the intractable complication(1). To reduce the complication and increase the rate success of operation, different methods have been used to reduce the bleeding during and post operation. Recently the focused on the anti-VEGF medication perioperation. Anti-VEGF can induce regression of retinal neovascularization and is suggested that it can reduce the bleeding during performing vitrectomy of proliferative diabetic retinopathy(2,3). Many studies also suggested that the vitrectomy of PDR without anti-VEGF could be difficult, time-consuming and resulted in high rate of bleeding in the operation and surgical failure. In our method, the study used the 23-gauge microincision total vitrectomy (23G MTV) combined with a set of perioperative hemostasis to reduce the inroperative and postoperative bleeding. The total vitrectomy is a technique of cutting all vitreous including on the vitreous base and pars plana which can prevent anterior proliferative vitreoretinopathy (APVR) (6), while APVR is a common cause of vitreous hemorrhage postoperatively(7-10). The perioperative hemostatic measures also played an important roles in the investigations. By using this series of management, vitreous hemorrhage could be prevented without using anti-VEGF medication. The present study evaluates effeteness of 23G MTV without administration of anti-VEGF before surgery. The result of the surgery was still satisfactory. We report our cases as follow:

Methods

General information

This was a retrospective uncontrolled interventional case-series performed in Zhengzhou Second Hospital (Zhengzhou, China). 42 consecutive eyes of 33 patients with PDR who underwent 23G MTV were studied. Participants included 13 male and 20 female patients. Their average age was 53.48 ±
14.02 years. 9 patients had both eyes treated. All 33 patients had 11.88±8.34 years long Type II diabetes. The average time with decreased visual acuity was 17.4±20.84 months. 26 eyes had carried out part or retinal photocoagula- tion. The average number of photocoagulation therapy was 1.65±0.85 times. The inclusion criteria was PDR without other retinal diseases and ocular operative history. The blood sugar levels were controlled in the normal range before operation. The exclusion criteria were prior scleral buckling, prior trauma, and a follow-up period of less than 6 months. All of the surgeries were performed at the Surgical Retina Service of Zhengzhou Second Hospital from May 2013 to December 2013. All 23G MTV procedures were performed by a single surgeon (W.L.). After the purpose and procedures of the operation were explained to patients, informed consents were obtained. This study conformed to the tenets of the Declaration of Helsinki and was by the Institutional Review Board of the Zhengzhou Second Hospital.

**Surgical methods**

All surgeries were performed under retrobulbar anesthesia and were performed using the Constellation Vitrectomy System (Alcon Laboratories; Fort Worth, Texas, USA) and Alcon 23G surgery package. A 23-23-gauge stiletto blade was inserted at a 15° to 30 ° angle through the conjunctiva, sclera, and pars plana, mm from the limbus, at the superotemporal, superonasal, and inferotemporal quadrants, respectively. The epiretinal fibrovascular membrane was peeled using the cutter as far as possible after the vitreous gel excised. The periphery, basal and pars plana vitreous were cut through scleral indentation the help of the assistant. A standard phacoemulsification before vitrectomy and intraocular lens (IOL) implantation at the end of vitrectomy were performed if the lens was opaque. A laser endophotocoagulation was performed to the places without previous laser and retinal detachment. In tractional rhegmatogenous retinal detachment, fluid air exchange or heavy liquid were used to flatting the retina befor intraocular laser and silicone oil tamponade was used. During operation, the following hemostatic measures were used to prevent intraoperative intraocular hemorrhages including epinephrine 0.5 mg added into 500 ml perfusion solution, short-duration intraocular pressure raised to 60 mmHg or cutter pressing bleeding spots beyond optic disk and macula. The epiretinal membranes were peeled as possible with segmentation and of 23G cutter and all tractions were relaxed. The 23-23-gauge sclerotomy sites were sutured with a 7-0 absorbable suture. corticosteroids (2.5 mg dexamethasone) was subconjunctivally injected at the end of operation.

**Postoperative treatment**

Patients were immediately kept by a half position for one day after coming back ward. Adrenosin 5mg (tid, po.), dicynone 500 mg (bid, im.) and p-aminomethylbenzoic acid (PAMBA) 600mg (qd, iv) were prescribed at once. Hemostatic drugs were discontinued until there was no active bleeding.

**Measurements of clinical findings.**

Best-corrected visual acuity (BCVA), IOP, slit light examinations and fundus images were evaluated, type-B ultrasonic scanning was used when necessary. BCVA was measured using the standard visual acuity chart. Success of the 23G MTV procedure was defined as improvement or maintenance of BCVA and maintenance of IOP ≤ 21 mmHg with or without the use of topical glaucoma medication, with no need for additional surgery. The procedure was recorded as a failure if there was a decrease in BCVA, additional surgery was required, or IOP could not be maintained ≤ 21 mmHg with the use of topical glaucoma medication during the postoperative short-term period.

**Follow-up time**

The follow-up time was about 10.25 ± 2.29 months with a range of 6 to 14 months.

**Statistical analysis.**

The data are presented as the mean ± standard deviation, the SPSS 17.0 Microsoft was used to analyzed the data. The significance of the difference between the pre-23G MTV BCVA and last visit of BCVA was determined by the chi-square test. The independent student -test was used for comparing the IOP between the pre-operation and the last visit of post-operation. A P value of less than 0.05 was considered to be statistically significant.

**Results**

The mean operative time was 77.74 ± 38.48 minutes. 36 eyes had BCVA less than 0.05, 6 eyes between 0.05 and 0.3 before surgery. 14 eyes had BCVA than 0.3, 18 eyes between 0.05 and 0.3, 10 0.05 or less at the last visit. The pre-operative and BCVA showed statistic significance with chi-square test ($\chi^2 = 34.69, \ P< 0.05$). The final IOPs were 16.29 ± 3.15 mmHg, not statistically different from pre-operative IOPs, 15.55 ± 3.80 mmHg ($t = -0.228$). 9 eyes with high IOPs (>21mmHg), the medication decreased IOPs to normal levels. Two eyes developed neovascular glaucoma, their IOPs were controlled through the transscleral diode laser cyclophotocoagulation (CTDC). 6 eyes with silicone injection had oil removed in 4.02 ± 0.65 months, all without new complications.
Figure 1. Pre-operative vitreous hemorrhage and postoperative fundus. A: Blurring fundus before surgery; B: The fundus in the first day after 23G MTV, showing the laser spots.

Figure 2. Before and after treatment for PDR with tractional retinal detachment. A: Vitreous hemorrhage with fibrovascular membranes made retina unintelligible. B: B ultrasonic scanning showed the tractional retinal detachment; C: On the third day after 23G MTV, clear vitreous, flat retina with scattering bleeding spots.
There were 2 eyes carrying out phacoemulsification for the PDR with vitreous hemorrhage only during the surgery. There were 16 eyes with bigger than two quadrants detachment for the PDR with traction retinal detachment, 8 eyes with retinal holes. 5 eyes carried out phacoemulsification and 4 eyes had IOL implantation. No anti-VEGF drug was used pre-/post-operative periods. Increased short-duration intraocular pressure to 60 mmHg was used to stop the retinal bleeding of 5 eyes during operation. Cutter tips pressuring was used in 3 cases of intraoperative retinal bleeding. A summary of the Operation situation in different strains PDR is shown in Table 1. One sample image of PDR and vitreous hemorrhage only treated eyes is showed in Figure 1. One sample image of PDR with traction retinal detachment treated eyes is showed in Figure 2.

We achieved success with 23G MTV in all cases (100%) and did not observe surgical complications, such as bacterial endophthalmitis.

Discussion

Microincision vitrectomy cutter has opener close to the tip. The epiretinal membrane can be cut without additional membrane peeler, forceps, and scissors. We set out to evaluate the feasibility of using 23G MTV to treat vitreoretinal diseases in DR eyes. The micro-incisor is good at membrane segmentation and membrane delamination during the PDR surgery(11). Without the additional instruments such as membrane peeler, forceps, and scissors, the times of entering into eye decreased significantly(12,13). The operation time was shortened, the complications decreased (though our patients had relatively complicated conditions of retina, the operative time was still decreased). In our study, 30 eyes with fibrovascular membrane had membrane peeled with 23G micro-incisor, 20 eyes had complete membrane-peeling, 10 eyes partly membrane-peeling. We tried to cut all the loosed membrane and left the close sticking membrane to avoid the bleeding and retinal tears. Most cases did not induce bleeding. One case had iatrogenic retinal hole. The average operative time was 77.74 ± 38.48 minutes.

Total vitrectomy was carried out in our study, including pars plana and basal vitreous(6). The residual vitreous in the basal part could provide the conditions for neovascular formation, which is one cause of postoperative hemorrhage. Studies reported that the residual and puncture site vitreous in the basal and pars plana part have proliferative diseases, the APVR lead to recurring vitreous hemorrhage(7-10). Total vitrectomy can effectively prevent these complications. In the 42 eyes of our study had only 2 eyes (5%) with sequent vitreous hemorrhage, but medication stopped the bleeding. No case had anterior vitreoretinal pathology and vitreous hemorrhage that caused the surgery failure. The total vitrectomy looks necessary in managing PDR.

It is a controversy for the anti-VEGF to prevent vitreous hemorrhage in the operation. Some reports proved the administration of anti-VEGF decreased the bleeding during or after vitreous surgery(14-16). Another reports showed no significant decreases of postoperative hemorrhage and no improved visual acuity after the use of anti-VEGF drugs(17-19). The anti-VEGF drugs are expensive, need to be injected before surgery, which increase the surgery manipulation and the waiting time. Patients suffer much more(20). In this investigation, no anti-VEGF drugs were used before and after operation. A series of measurements, such as the controlled blood sugar level, 1:1000 epinephrine perfusion, 23G total vitrectomy, the suturing closure of sclerotomy sites at the end of operation, special positioning and combined hemostatic drugs, could effectively control and prevent the intro- and posto- vitreous hemorrhage. Additional hemostatic methods included increasing the perfusion pressure during operation and using cutter to hemostasis by compression. These methods resulted in our 100% success rate of one-time operation, no intraoperative bleeding and no early bleeding after operation. 38 eyes (90.48%) had improved visual acuity after surgery. Our results are obviously better than those reports which depended on anti-VEGF drugs in treating PDR(16,21,22).

The sclerotomy sites need be sutured after total operation.

Table 1. Operation situation in different types of PDR

<table>
<thead>
<tr>
<th>PDR classification</th>
<th>Eye number</th>
<th>PRP eyes</th>
<th>PRP during operation</th>
<th>BCVA improved eyes</th>
<th>Membrane completely peeled</th>
<th>Membrane partly residue</th>
<th>Silicone injection</th>
<th>Iatrogenic hole eye</th>
<th>Increasing IOP hemostatic</th>
<th>cutter compression hemostatic</th>
<th>Average operative time (Mean ± SDs) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A*</td>
<td>12</td>
<td>6</td>
<td>7</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>57.92±21.58</td>
</tr>
<tr>
<td>B*</td>
<td>10</td>
<td>8</td>
<td>5</td>
<td>9</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>76.00±26.25</td>
</tr>
<tr>
<td>C*</td>
<td>20</td>
<td>12</td>
<td>12</td>
<td>18</td>
<td>13</td>
<td>7</td>
<td>6</td>
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<td>2</td>
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<td>93.50±45.37</td>
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<tr>
<td>total</td>
<td>42</td>
<td>26</td>
<td>24</td>
<td>38</td>
<td>20</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>77.74±38.48</td>
</tr>
</tbody>
</table>

*A: Patients with PDR and vitreous hemorrhage only.
B: Patients with PDR and fibrovascular membranes but no tractional retinal detachment.
C: Patient group with PDR and traction retinal detachment.
vitrectomy, otherwise the leakage of intraocular
taponade materials usually leads to low ocular
and second intraocular hemorrhage postoperatively.
We routinely closed three sclerotomy sites to prevent
the postoperative bleeding.

There were limitations to our study, including the
retrospective nature of the analysis, a relatively short
follow-up period, and a small number of patients. If
we carried out a comparative, prospective cohort study
of two random patient groups, defining the group
according to part or total vitrectomy, with or without
anti-VEGF drugs. Our results should be more
scientific and more valuable. Anyway, our 100%
success rate of surgery and hemostasis during and
after operation proved 23G MTV treatment for PDR
safe, effective and of high success rate.

Further investigation is needed to evaluate
postoperative visual quality and complications in the
late postoperative period before a final determination
can be made of the efficacy of this procedure. In
conclusion, 23G MTV is a technique that can feasibly
be used to treat vitreoretinal diseases of PDR.

Conflict of Interests
The authors declare that there is no conflict of
interests regarding the publication of this paper.

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