Original Article
Effect of intravitreal conbercept vs triamcinolone acetonide at the end of surgery on macular structure and function in patients with severe proliferative diabetic retinopathy

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Abstract: Objective: This study is to compare the efficacy of vitrectomy combined with intravitreal injection of triamcinolone acetonide (IVTA) versus intravitreal injection of conbercept (IVC) at the end of surgery in patients with severe proliferative diabetic retinopathy (S-PDR). Methods: A retrospective study of the medical records of 44 eyes diagnosed as S-PDR between November 2014 and December 2015 was performed. The patients underwent 23G vitrectomy combined with retinal laser photocoagulation and drug intravitreal injection at the end of surgery. They were divided into 2 groups: 22 eyes undergone IVC while 20 eyes undergone IVTA. Best-corrected visual acuity (BCVA), foveal thickness (FT), and macular volume (MV) were compared at baseline and 1, 3, and 6 months after surgery were recorded and compared. Results: The values of BCVA, FT and MV at 1, 3, and 6 months were significantly improved from baseline in both groups (p < 0.05). The extent of FT and MV reduction during the first month after surgery was greater in IVC group than in IVTA group (p = 0.024). The values of FT and MV in IVTA group were better than that in IVC group at the last follow-up examination. An increase in IOP was noted in 0/22 eyes in IVC group and 3/20 eyes in IVTA group at different follow-up, and the IOP of all three eyes was controlled using topical medication. Conclusions: Vitrectomy combined with IVC and IVTA at the end of surgery both were beneficial to S-PDR. The effects of IVC were more obvious in the early period after surgery, however, the effect of IVTA was more stable in the long period follow-up.

Keywords: Diabetic retinopathy, vitrectomy, intravitreal injection, conbercept, triamcinolone acetonide

Introduction
Diabetic retinopathy (DR) is a significant source of visual morbidity among the older adults in the developed world and is one of the three major causes of blindness in the developing countries [1]. Complications of DR include ischemic maculopathy, macular edema, neovascular glaucoma, and sequelae of fibrovascular proliferation [2, 3]. The sequelae of fibrovascular proliferation includes vitreous hemorrhage (VH), severe proliferative diabetic retinopathy (S-PDR), and tractional retinal detachment (TRD).

In China, many patients with S-PDR need surgery therapy, and pars plana vitrectomy (PPV) combined with panretinal photocoagulation (PRP) is traditionally performed for non-clearing VH, significant fibrovascular proliferation, refractive macular edema, and/or TRD, particularly if macula-involving exists. PRP itself is a destructive therapy. Previous studies have shown that 25-43% of eyes with PDR treated with PRP will develop into macular edema (ME) or experience an exacerbation in ME, resulting in visual disturbances [4-6]. Although retinal thickness and macular edema can be reduced obviously and photo sensitive and conductive function of the retina can be improved effectively after vitrectomy [7, 8], persistent and recurrent ME sometimes occurs in eyes after vitrectomy of PDR and DME [9]. For many patients, the vitrectomized chronic and recurrent nature of retinal
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It is documented that intravitreal injection of triamcinolone acetonide (IVTA) could significantly decrease central retinal thickness, and for patients with continuous DME after vitrectomy, IVTA is still an effective treatment method [13, 14]. Another study argues that intravitreal bevacizumab injection for persistent DME after vitrectomy could temporarly improve central thickness and visual function [15]. There are some studies about the roles of using anti-VEGF drugs or TA at the end of vitrectomy for preventing postoperative recurrent VH [16, 17].

Recently, conbercept (Chengdu Kanghong Biotech Co., Ltd., Sichuan, China), a kind of anti-VEGF drugs, has been developed and available for clinical application. It is widely used for curing patients with age-related macular degeneration (AMD) and macular edema due to various causes. In China, a large proportion of the DR patients are not aware of their retinal conditions until the development of VH. Conbercept is effective for VH, but some patients give up choice to take it because of economical questions.

IVTA and conbercept are both applied in clinic, however, to our knowledge, there are no reports about macular structure and function evaluation after vitrectomy combined with IVTA and conbercept at the end of surgery. Therefore, in the present study macular structural and the function after conbercept or triamcinolone acetonide injection at the conclusion of surgery in S-PDR were investigated so as to compare the effectiveness and difference of the two drugs, and further support the guidance for clinical application.

**Patients and methods**

**Participants**

We retrospectively reviewed the medical records of 44 patients with 44 eyes (15 were male and 29 were female) diagnosed as S-PDR with VH or TRD. These patients had undergone 23G vitrectomy combined with retinal laser photoagulation and intravitreal injection at the end of surgery between November 2014 and December 2015. We divided the patients into 2 groups: eyes with vitrectomy plus conberceptintravitreal injection (IVC group), and eyes had undergone vitrectomy plus triamcinolone acetonide intravitreal injection (IVTA group). The IVC group received injection of conbercept (0.5 mg in 0.05 ml) at the end of vitrectomy, whereas the IVTA group received injection of triamcinolone acetonide (4 mg in 0.1 ml). Baseline characteristics of study eyes are listed in **Table 1**.

The exclusion criteria is listed as follows: patients that were with prior history of vitreoretinal surgery; patients that were with prior history of intravitreal drugs injections; patients with uncontrolled systemic disease, glaucoma, elevated intraocular pressure; patients that were with evidence of any retinal disease that might affect visual acuity or macular microstructure; patients who had undergone cataract extraction with vitrectomy; and patients who had recurrent vitreous hemorrhage after surgery. Prior written and informed consent were obtained from the patients and the study was approved by the ethics review board of Chengdu Second People's Hospital.

**Preoperative examinations**

Preoperative ocular examinations included best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure measurement, funduscopic, ocular B ultrasonic, and Optical coherence tomography (OCT). BCVA was examined using Snellen visual acuity charts. OCT examinations were completed with

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<th>Table 1. Preoperative characteristics of baseline in patients</th>
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<td><strong>No. of eyes</strong></td>
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<td>Age (year)</td>
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<td>Male/Female</td>
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<td>Types of diabetes (type 1/type 2)</td>
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<td>BCVA logMAR</td>
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dilated pupils using the Zeiss Stratus OCT system (Carl Zeiss Meditec, USA). OCT measurements of the macula were generated from 6-mm linear scans in a spoke-like radial configuration with each line centred in the fovea and angled 30° apart. Automatic delineation of the inner and outer boundaries of the neurosensory retina generated by built-in OCT software was verified for each of the 6 scans using the retinal thickness (single eye) analysis protocol. All OCT evaluations were performed in the afternoon (between 13:00 and 18:00). For this study, FT was defined as the average thickness of the macular area with a diameter of 1000 µm centred on the patient’s foveola. The outcomes of FT and MV were obtained from OCT reports. Fluorescein angiograms and fundus photographs before surgery were not obtained clearly because VH had not been cleared.

**Therapeutic regimen**

In all 44 patients, a 3-port 23-G PPV was performed by a single surgeon. Vitrectomy, retinal laser photocoagulation and IVC or IVTA were sequentially performed. Vitrectomy with removal of the fiber proliferative membrane was conducted in all of the patients. Retinal endolaser photocoagulation was performed intraoperatively in cases with apparent high risk characteristics. All patients received fluorescein angiography within four weeks after operation and supplementary of retinal photocoagulation was performed when there was extensive retinal capillary dropout. At the conclusion of the operation, patients in the IVC group received an intravitreal injection of conbercept (10 mg/mL, 0.5 mg in 0.05 ml), and the control group received an intravitreal injection of TA (40 mg/mL, 4 mg in 0.1 ml). Patients of IVTA were instructed to maintain a sitting position for approximately six hours in the immediate postoperative period to facilitate inferior sedimentation of the injected triamcinolone acetonide.

**Postoperative examination**

All patients were followed up for 6 months with return visits in the first, third and sixth month. Postoperative examination including BCVA, slit-lamp biomicroscopy, intraocular pressure measurement and fundus examinations, was conducted at two days, one week, and one month after vitrectomy. Fluorescein angiography was performed within four weeks after operation and subsequent examinations were generally scheduled every one to three months.

As outcome measures, BCVA, FT and MV were recorded at one, three, and six months after the administration of surgical therapy. BCVA was then transformed to a logarithmic scale for statistical analysis. Additionally, we compared the differences in BCVA, FT and MV after surgery between the two groups at different follow-up time.

**Main outcome measures**

BCVA was analyzed on a logarithm of minimal angle of resolution (logMAR) scale. Counting fingers vision was defined as 0.01 (2.0 logMAR) and hand movement was defined as 0.001 (3.0 logMAR). As for primary outcome measurement, changes in BCVA, FT and MV were compared between patients of the two groups at 1, 3, and 6 months after surgery. And as for secondary outcome measurement, BCVA, FT and MV were compared within each group before surgery and at each follow-up time.

**Statistical analysis**

Statistical analyses were performed using the software program SPSS19.0 (SPSS Inc, Chicago, IL, USA). Data were expressed as mean ± SD for continuous variables. Mean changes in BCVA from baseline at months 1, 3 and 6 were assessed using the paired t test or rank-sum test with 95% confidence intervals. Changes in BCVA, FT and MV measurements between
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Results

General situation of the eyes included in the study

In order to make sure that there were no differences in eyes between the two groups before the study, comparison was performed at the beginning of the experiment. During the inclusion period of the study, S-PDR that had undergone vitrectomy, retinal laser photocoagulation and IVC or IVTA were identified in 44 patients. Of these patients, 42 patients with 42 eyes were finally enrolled in the study. Two eyes were excluded because they have recurrent vitreous hemorrhage after vitrectomy. As detailed in Table 1, baseline characteristics of the study eyes, such as patients’ age, sex, types of diabetes, years of diabetes, IOP, TRD, BCVA, FT and MV were compared. The comparison result argued that there was no difference between the two groups pre-examination.

Primary outcome measurement

To compare the effect of IVC and IVTA at the end of surgery to macular, BCVA, FT, and MV were investigated. The values of BCVA, FT, and MV in the two groups before and after operation were shown in Table 2. The macular OCT images of the two groups before and after the operation were illustrated in Figure 1. Comparison of IVC group and IVTA group showed no statistically significant differences in BCVA at any time during the study. FT (μm) measurements showed a statistically significant difference between the two groups at the 6-month follow-up. And the mean ± SD was 479.9 ± 100.5 in IVC group and 463.3 ± 79.6 in IVTA group at baseline (p = 0.061). During the following time, the mean FT of IVC group versus IVTA group were 238.3 ± 94.6 versus 240.2 ± 98.3 at 1 month (p = 0.124), 287.5 ± 102.4 versus 256.8 ± 90.5 at 3 months (p = 0.09), and 320.1 ± 86.3 versus 283.4 ± 77.9 at 6 months (p = 0.037), respectively.

At the 1-month and 6-months follow-up, MV (mm³) showed a statistically significant difference between the two groups from 1 month to 6 month follow up. IVTA group showed more stable effect at the 6 months follow up. The mean ± SD was 16.83 ± 7.5 in IVC group and 17.91 ± 9.2 in IVTA group at baseline (p = 0.477) and IVC group versus IVTA group were 8.64 ± 2.05 versus 9.23 ± 1.88 at 1 month (p = 0.022), 10.01 ± 2.17 versus 10.30 ± 2.65 at 3 months (p = 0.08), and 13.70 ± 4.73 versus 10.64 ± 3.19 at 6 months (p = 0.015). To sum
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The results indicated that the effects of IVC were more obvious in the early period after surgery, however, the effects of IVTA were more stable in the long period follow-up.

Secondary outcome measurement

In order to learn the change of macular function of preoperation and postoperation suffer from vitrectomy versus TA or conbercept, BCVA, the preoperation and postoperation FT and MV were compared. In IVC group, as illustrated in Figure 2, BCVA (logMAR) increased significantly from 1.57 ± 1.1 at baseline to 0.64 ± 0.11 at 1 month (p = 0.001), 0.78 ± 0.19 at 3 months (p = 0.013), and 0.94 ± 0.30 at 6 months (p = 0.028). In IVTA group, BCVA increased significantly from 1.66 ± 0.8 at baseline to 0.70 ± 0.18 at 1 month (p = 0.011), 0.73 ± 0.33 at 3 months (p = 0.03), and 0.84 ± 0.23 at 6 months (p = 0.041). The result demonstrated that there were statistically significant differences between the baseline and every follow-up in both groups.

FT reduced significantly in IVC group with a mean ± SD value (um) of 479.9 ± 100.5 at the baseline to 238.3 ± 94.6 at 1 month (p < 0.001), 287.5 ± 102.4 at 3 months (p = 0.017) and 320.1 ± 86.3 at 6 months (p = 0.042). In IVTA group, FT reduced from baseline of 463.3 ± 79.6 to 240.2 ± 98.3 at 1 month (p < 0.001), 256.8 ± 90.5 at 3 months (p = 0.011) and 283.4 ± 77.9 at 6 months (p = 0.035) (Figure 3). Together, the results suggested statistically significant differences in both groups when baseline values were compared to the data at each follow-up period.

MV reduced significantly in IVC group from a baseline of 16.83 ± 7.5 to 8.64 ± 2.05 at 1 month (p = 0.029), 10.01 ± 2.17 at 3 months (p = 0.03), and 13.70 ± 4.73 at 6 months (p = 0.066). And in IVTA group, MV reduced from baseline of 17.91 ± 9.2 to 9.23 ± 1.88 at 1 month (p = 0.032), 10.30 ± 2.65 at 3 months (p = 0.040), and 10.64 ± 3.19 at 6 months (p = 0.048) (Figure 4). Statistically significant difference was observed when baseline values were compared to measurements at 1- and 3-month follow-up in both groups; however, no significant difference was observed in the IVC group at 6 months follow-up examination.

Three eyes (15%) IOP increased transitorily in the IVTA group after surgery, and all reduced to normal by dropping anti-glaucoma drugs; however, no such situation occurred in the IVC group. Together, the results indicated that IVC
(0.5 mg) and IVTA (0.4 mg) at the end of vitrectomy all had benefits for patients with PDR. The effect of TA is more persistent, and conbercept was more safety.

**Discussion**

In china, vitrectomy is the most common surgery therapy for PDR patients, especially for patients with VH and TRD. Many researchers have paid close attention to the complication of intraoperative bleeding and postoperative recurrent VH. With the improvement of surgery technology and the increasing application of anti-VEGF drugs, the incidence of intraoperative bleeding and postoperative recurrent VH have reduced significantly [18-20]. A randomized clinical study reported that intravitreal injection of anti-VEGF drug one week prior to vitrectomy was effective in reducing intraoperative bleeding and early postoperative vitreous hemorrhage in PDR patients [18, 21]. However, for many smoothly vitrectomized eyes, macular edema (ME) sometimes persists or recurs in eyes with PDR and DME after vitrectomy.

Conbercept, as a kind of anti-VEGF drugs, is a recombinant and soluble protein composed of VEGF receptorand the Fc portion of immunoglobulin G [22, 23]. Once binding to VEGF, conbercept could competitively inhibit the binding VEGF to VEGF receptors and thereby blocking the activation of VEGF receptors. A Phase I study demonstrated that conbercept can lead to improvements in BCVA, reduction in central retinal thickness, and decrease in the area of choroidal neovascularization (CNV) in patients with neovascular age-related macular degeneration [23]. Recently, conbercept had been used widely in China.

It is well established by clinical studies that treatment of both anti-VEGF drugs and TA could decrease macular thickness for DME, and even for DME after vitrectomy [24, 25]. However, the use of the drugs is either preoperative or postoperative while refractory DME occurs, and there is no joint application of Conbercept or TA at the end of PPV and no analysis of the comparison of the structure and function of the macular. To address this issue, in this study, the effects of IVC and IVTA at the end of vitrectomy were compared, and as for the consolidation of PPV, reduction in FT and MV was observed in both groups. Both the IVC group and the IVTA group caused a significant reduction in FT and MV at different follow-up period while compared to the base line. Two groups both decreased FT appeared at 1 month, and a rising trend at 3 months and 6 months was found. The FT of IVTA group was more stable than IVC group with a small rising trend during our follow up period. In the period of 6-months follow-up visit, a different increase in FT was noted, and there was significant difference between the two groups studied at the last examination. The FT of IVTA group was lower obviously than the one of IVC group. By comparing the effects of both drugs, triamcinolone showed a greater reduction power. The data were similar to that of Fernando Marcondes Penha [26]. They found that triamcinolone seems to be more effective to reduce CMT up to 6 months when compared with bevacizumab in DME. However, the subjects of previous studies were patients with DME but without PPV, and MV wasn’t observed. These observations suggested that both drugs had limited effect on reducing macular edema after surgery, and both had an upward trend in FT and MV in periods longer than 6 months.

Regarding BCVA, both medications resulted in significant visual improvement at different follow up time comparing with the base line. Jirawison C et al. [27] have conducted a retro-
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A frequent adverse effect described for the intraocular use of triamcinolone is corticosteroid glaucoma. In our study, three eyes (15%) of IVTA group showed an increased IOP, and fortunately all could be controlled by dropping antiglaucoma drugs and the IOP finally decreased to normal.

Vitrectomy combined with IVC and IVTA at the end of surgery both had a beneficial effect on anatomical and functional outcomes in eyes with S-PDR. Conbercept had the better effect at the aspect of FT and MV reduction in the short period after vitrectomy than triamcinolone acetonide. The effect of IVTA was more stable in the long period follow-up. Conbercept was safer than triamcinolone acetonide at the aspect of IOP after surgery. The limitation of our current study was that it was a retrospective study only examined a small number of patients. In addition, there was only a fairly short follow-up period for this study. Thus, further randomized control studies with longer follow-up periods will be performed to confirm the consequences of our study.

Disclosure of conflict of interest

None.

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