Original Article

25-Gauge Vitrectomy versus Intravitreal Bevacizumab for Macular Edema Secondary to Branch Retinal Vein Occlusion: 1 Year Follow-Up

Tatsuhiko Sato,[1 MD], Kosaku Sawada,[1 MD], Chiharu Iwahashi-Shima,[1 MD], Hajime Bando,[1 MD], Toshihide Ikeda,[1 MD], Kazuyuki Emi,[1 MD]

Abstract

Introduction: This study aims to compare the long-term efficacy of 25-gauge vitrectomy to that of intravitreal bevacizumab (IVB) for the treatment of macular edema (ME) secondary to branch retinal vein occlusion (BRVO). Materials and Methods: The medical records of 46 eyes of 46 consecutive patients were reviewed. Twenty-seven eyes underwent 25-gauge vitrectomy (VIT Group) and 19 eyes received 1.25 mg of IVB (IVB Group). The best-corrected visual acuities (BCVAs) in logarithm of minimum angle resolution units and central macular thicknesses (CMTs) were evaluated before and 3, 6, and 12 months after the initial treatment. Results: There was no significant difference in the pre-treatment BCVA and CMT between the 2 groups. In the VIT Group, the preoperative BCVA was 0.59 and the CMT was 587.3 µm and the BCVA was 0.35 and the CMT was 286.6 µm, 12 months after the vitrectomy. Both values were significantly (P <0.05) better at 12 months than the preoperative values. In the IVB Group, the average number of IVB was 2.4 during the 1-year period. The BCVA was 0.69 and the CMT was 590.9 µm before the IVB, and the BCVA was 0.36 and the CMT was 360.1 µm, 12 months after the initial IVB. The improvements of these 2 parameters were significant (P <0.05) at 12 months after the initial IVB. The differences in the BCVA and CMT at 12 months between the 2 groups were not significant. Conclusion: These results suggest that the 25-gauge vitrectomy and IVB have similar effects in improving the BCVA and CMT in eyes with ME secondary to BRVO. However, IVB often required several injections to preserve the improvement.

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Key words: Eye, Vascular endothelial growth factor

Introduction

Branch retinal vein occlusion (BRVO) is the second most frequent vascular disorder of the eye, and it can lead to a decrease in vision. One of the main causes for the vision decrease is the development of macular edema (ME), which has been reported to be present in 60% of the cases.[1,2] An earlier study on the natural course of BRVO reported that only 14% of the eyes with chronic ME secondary to BRVO retained a visual acuity of 20/40 or better at the end of the follow-up period.[3]

The Branch Vein Occlusion Study Group[4] recommended that grid laser photocoagulation should be used to treat the ME secondary to BRVO. However, grid laser coagulation cannot be used in eyes with intraretinal haemorrhage in the fovea or in the foveal capillary area. In addition, the irreversible destruction of paracentral retinal tissue by the laser photocoagulation can result in parafoveal scotoma. Thus until recently, a number of therapeutic trial studies have been performed retro- or prospectively to determine better ways to treat the ME associated with BRVO.

Vitrectomy has been proposed as an alternative treatment, because it is generally believed that vitreous traction on the macula promotes fluid accumulation in the retina.[5-7] Several studies have reported that vitrectomy with or without inner limiting membrane (ILM) peeling can decrease the ME and improve the visual acuity in eyes with BRVO.[8,9] In addition, the 25-gauge vitrectomy system, introduced by Fujii et al,[10] enables surgeons to perform less invasive vitrectomy, which in turn leads to less discomfort and faster postoperative recovery than the conventional 20-gauge vitrectomy. Thus, 25-gauge vitrectomy appears to be an effective way to treat the ME secondary to BRVO.

On the other hand, vascular endothelial growth factor (VEGF), also known as vascular permeability factor, has been shown to be a key molecule in the pathogenesis of

[1]Osaka Rosai Hospital Clinical Research Center for Occupational Sensory Organ Disability
Address for Correspondence: Dr Tatsuhiko Sato, Department of Ophthalmology, Osaka Rosai Hospital, 1179-3 Nagasone-cho, Kita-ku, Sakai, 591-8025, Japan.
Email: t-satou@orh.go.jp

ME secondary to BRVO. In fact, it has been reported that the intraocular level of VEGF is significantly increased in eyes with BRVO and that its level is correlated with the severity of ME.[11,12] Therefore, pharmacological inhibition of VEGF also seems to be a promising therapy to treat ME secondary to BRVO.

Bevacizumab (Avastin®; Genentech, San Francisco, CA, USA) is a full-length humanised monoclonal antibody that is directed against all isoforms of VEGF. Although bevacizumab is approved for intravenous use for the treatment of metastatic colon cancer,[13] it has been widely used as an "off-label" treatment for ME associated with different ocular disorders including BRVO. Until now, intravitreal injection of bevacizumab has been shown to be effective in resolving the ME secondary to BRVO.[14-17] Furthermore, recent studies have compared the efficacy of intravitreal bevacizumab (IVB) to that of intravitreal triamcinolone[18,19] or of grid laser coagulation[20] for ME secondary to BRVO. However, data for comparison of the efficacy of IVB to 25-gauge vitrectomy in cases with ME secondary to BRVO are not available.

Thus, the purpose of this study was to compare the long-term efficacy of 25-gauge vitrectomy to IVB for the treatment of ME secondary to BRVO.

Materials and Methods

We reviewed the medical records of patients who were initially treated for ME secondary to BRVO at Osaka Rosai Hospital, Sakai, Japan. The procedures used for the treatments conformed to the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board of Osaka Rosai Hospital. The diagnosis of ME secondary to BRVO was based on clinical examination, fluorescein angiography, and optical coherent tomography (OCT; Stratus OCT-3000; Carl Zeiss Meditec, Dublin, CA, USA).

None of the eyes had undergone vitreoretinal surgery, intravitreal injection, and laser treatment before the treatment. Patients with neovascularization before the treatment were excluded. In addition, patients with other ocular diseases, e.g. severe cataract, which could decrease the vision, were excluded.

The inclusion criteria were: (i) presence of BRVO of at least 1 month duration, (ii) presence of macular leakage on fluorescein angiography, (iii) best-corrected visual acuity (BCVA) ≥0.0 in logarithm of minimum angle resolution (logMAR) units or central macular thickness (CMT) >250 μm, and (iv) minimum follow-up period of 12 months. The status of the macular perfusion, i.e. ischaemic or non-ischaemic vein occlusion, was not evaluated because the grade of ischaemia was often difficult to determine due to retinal haemorrhage. In addition, non-ischaemia vein occlusion can occasionally convert to ischaemic occlusion. After the patients were informed of the potential benefits and risks of 25-gauge vitrectomy and IVB, they chose either 25-gauge vitrectomy (VIT Group) or IVB (IVB Group). Signed informed consents were obtained from all. The BCVA and CMT before and 3, 6, and 12 months after the initial treatment were evaluated.

In the VIT Group, standard 3-port pars plana vitrectomy with 25-gauge instruments was performed under local anesthesia. The Accurus® (Alcon Laboratories, Inc. Fort Worth, TX, USA) vitrectomy surgical system was used on all eyes. To preserve the conjunctiva, phacoemulsification and aspiration (PEA) and intraocular lens (IOL) implantation were performed through a 2.5-mm clear corneal incision, and a sutureless contact lens ring was used during the vitrectomy.[21] Core vitrectomy was performed with a high-speed vitreous cutter (2500 cycles/minute; MID-Labs, San Leandro, CA, USA) and a conventional halogen light source. The separation of the posterior hyaloid from the retina was performed if it was still attached. To make the ILM more visible, 1.25 mg/mL indocyanine green (ICG) was injected into the vitreal cavity around the ME.[22] After washing out the ICG, the ILM within the major temporal vascular arcades was peeled off with a vitreous forceps. Follow-up examinations were performed within 1 week, 1, 2, 3, 6, and 12 months after the vitrectomy.

In the IVB Group, bevacizumab (1.25 mg/0.05 mL) was injected into the vitreous in a surgical room of the outpatient clinic. Prior to the injection, 4% lidocaine hydrochloride and 0.625% povidone-iodine solutions[23,24] were dropped onto the eye. A lid speculum was inserted, and the injection of bevacizumab was performed with a 30-gauge needle inserted through the superior pars plana 3.5 to 4.0 mm from the limbus. The patient's vision was tested after the injection to ensure that the retinal arterial perfusion was intact. After the injection, the patients received topical antibiotic treatment with levofloxacin (Cravit®; Santen Pharmaceutical Co Ltd Osaka, Japan) 4 times per day for a week. Follow-up examinations of BCVA and OCT were performed during the first week, 1 month after the first IVB, and in monthly intervals thereafter. Additional IVB was injected when an increase of the CMT was associated with visual decrease.

Statistical analyses were performed with the SPSS program (Sigma Stat; Systat Software, Inc. San Jose, CA, USA). Data are presented as the averages and standard deviations. A significant difference of the ratio between the 2 groups was determined by the chi-square. If the data were normally and equally distributed, one-way repeated measures analysis of variance (ANOVA) was performed to compare 3 or more clinical conditions in

the subjects, followed by Holm-Sidak or Dunn's method to detect significant differences between each time point and pre-treatment. If the data were not normally or equally distributed, Friedman repeated measures ANOVA on ranks is an alternative to one-way repeated measures ANOVA. The differences between 2 groups was tested by t tests if the data were normally and equally distributed and, if not, by Mann-Whitney rank sum test. The correlation between 2 groups was determined by the Pearson product moment correlation. A P value <0.05 was taken to be statistically significant.

Results

The demographics of the patients studied are summarised in Table 1. Twenty-seven eyes of 27 patients belonged to the VIT Group, and 19 eyes of 19 patients to the IVB Group. There was no significant difference in the gender ratio, age, pre-treatment BCVA, pre-treatment CMT, and interval from onset to treatment between the 2 groups.

Table 1. Patient Demographics and Pre-treatment Ocular Status

Parameters	VIT Group	IVB Group	*P* Value
Patients (n)	27	19	
Eyes (n)	27	19	
Sex (female:male)	18:9	11:8	0.767†
Age (years, mean ± SDs)	67.1 ± 6.6	64.3 ± 11.2	0.289*
Pre-treatment BCVA (logMAR, mean ± SDs)	0.59 ± 0.41	0.69 ± 0.46	0.562*
Pre-treatment CMT (μm, mean ± SDs)	587.3 ± 179.2	590.9 ± 190.8	0.982*
Duration from onset to treatment (days, mean ± SDs)	86.1 ± 45.6	69.1 ± 33.6	0.246*

†Chi-square or *Mann-Whitney Rank Sum test was performed to compare between two groups. VIT: vitrectomy, IVB: intravitreal bevacizumab, SD: standard deviation, BCVA: best-corrected visual acuity, logMAR: logarithm of minimum angle resolution, CMT: central macular thickness

In the VIT Group, there were no severe ocular (e.g. infectious endophthalmitis, choroidal haemorrhage, and rhegmatogenous retinal detachment) or systemic complications. Twenty-six phakic eyes underwent vitrectomy with PEA and IOL implantation.

The BCVA was 0.59 ± 0.41 logMAR units before the vitrectomy and 0.35 ± 0.34 logMAR units at 12 months after the vitrectomy (Table 2). There was a positive correlation between the pre- and post-vitrectomy BCVA (r = 0.77, P =2.80 x 10^{-6}; Fig. 1A). There was a significant difference in the BCVA among the four time points (P = 7.58 x 10^{-6}), and the BCVA at 6 and 12 months after the vitrectomy was significantly (P <0.05) better than the pre-vitrectomy BCVA (Fig. 2).

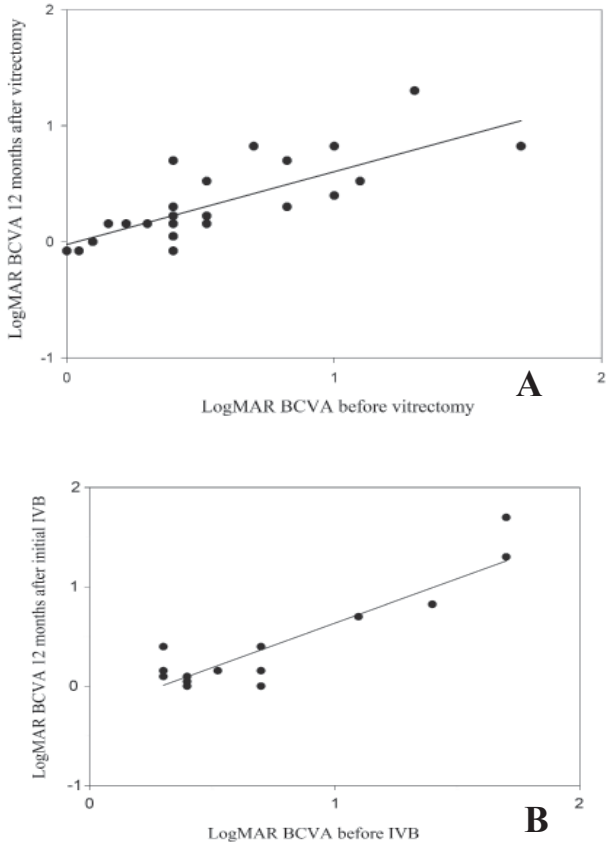

Fig. 1. Correlation between pre- and post-treatment BCVA. The abscissa represents the BCVA in logMAR units before and the ordinate represents the BCVA 12 months after the treatment.
(A). Correlation between baseline and post-vitrectomy BCVA in logMAR units. Statistical analyses were performed by Pearson product moment correlation (r = 0.769, P = 2.80e^{-6}).
(B). Correlation between pre- and post-IVB BCVA in logMAR units. Statistical analyses were performed by Pearson product moment correlation (r = 0.875, P = 9.47e^{-7}).
logMAR: logarithm of minimum angle resolution, BCVA: best-corrected visual acuity; IVB: intravitreal bevacizumab

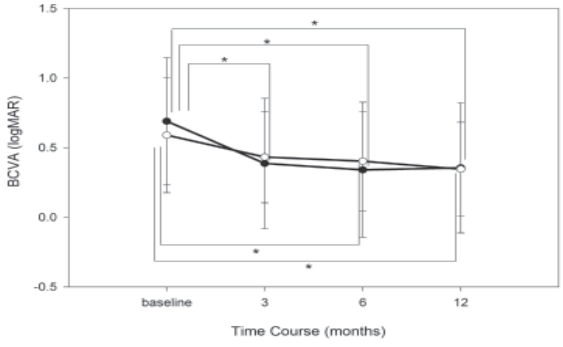

Fig. 2. Time course of best-corrected visual acuity (BCVA) in logarithm of minimum angle resolution (logMAR) units. The abscissa represents the time point and the ordinate represents the BCVA in logMAR units. Statistical analyses were performed by one way repeated measures analysis of variance (ANOVA) followed by Holm-Sidak in IVB Group and Friedman repeated measure ANOVA on ranks followed by Dunn's method in VIT Group (*P <0.05). ○: VIT Group, ●: IVB Group. VIT: vitrectomy, IVB: intravitreal bevacizumab.

Table 2. Time Course of Visual Acuity and Central Macular Thickness

Parameters	VIT Group (n = 27)	IVB Group (n = 19)	*P* Value
BCVA (logMAR, mean ± SDs)			
Pre-treatment	0.59 ± 0.41	0.69 ± 0.46	0.562*
3 months after initial treatment	0.43 ± 0.33	0.39 ± 0.47	0.279*
6 months after initial treatment	0.40 ± 0.36	0.34 ± 0.49	0.241*
12 months after initial treatment	0.35 ± 0.34	0.36 ± 0.47	0.441*
CMT (μm, mean ± SDs)			
Pre-treatment	587.3 ± 179.2	590.9 ± 190.8	0.982*
3 months after initial treatment	363.2 ± 134.9	286.3 ± 135.1	0.041*
6 months after initial treatment	348.2 ± 157.6	395.9 ± 207.4	0.380†
12 months after initial treatment	286.6 ± 113.5	360.1 ± 193.4	0.174*

*Mann-Whitney Rans Sum test or †t-test was performed to compare between two groups. VIT: vitrectomy; IVB: intravitreal bevacizumab; BCVA: best-corrected visual acuity; logMAR: logarithm of minimum angle resolution; SD: standard deviation; CMT: central macular thickness

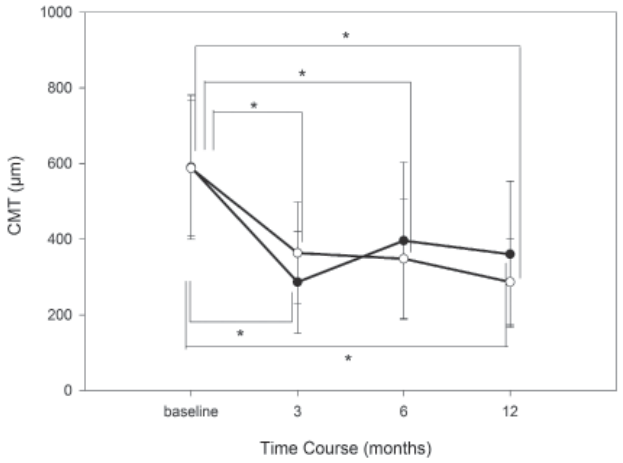

Fig. 3. Time course of central macular thickness (CMT). The abscissa represents the time point and the ordinate represents the CMT. Statistical analyses were performed by Friedman repeated measure analysis of variance on ranks, followed by Dunn's method (*P <0.05). ○: VIT Group; ●: IVB Group; VIT: vitrectomy; IVB: intravitreal bevacizumab

The CMT was 587.3 ± 179.2 μm before the vitrectomy and 286.6 ± 113.5 μm at 12 months after the vitrectomy (Table 2). There was a significant reduction (P =7.00 x 10^{-10}) in the CMT for the four time points, and the CMT at 3, 6, and 12 months after the vitrectomy was significantly (P <0.05) decreased compared to the CMT before the vitrectomy (Fig. 3).

In the IVB Group, there were no severe ocular (e.g. infectious endophthalmitis, rhegmatogenous retinal detachment, and cataract) or systemic (e.g. thrombotic events) complications during the follow-up period. The average number of IVBs was 2.4 ± 1.1 with a range of 1 to 5 during the 1-year follow-up period. Three of 19 eyes (15.8%) had a single IVB.

The BCVA was 0.69 ± 0.46 logMAR units before the IVB and 0.36 ± 0.47 logMAR units at 12 months after the initial IVB (Table 2). There was a positive correlation (r = 0.88, P = 9.47 x 10^{-7}) between the 2 time points BCVA (Fig. 1B). There was a significant difference (P = 5.67 x 10^{-11}) in the BCVA among the 4 time points, and the BCVA at 3, 6, and 12 months after the initial IVB was significantly (P <0.05) improved compared to the pre-IVB BCVA (Fig. 2).

The CMT was 590.9 ± 190.8 μm before the IVB and 360.1 ± 193.4 μm at 12 months after the initial IVB (Table 2). There was a significant reduction (P = 4.47 x 10^{-5}) in CMT among the 4 time points and the CMT at 3 and 12 months after the initial IVB was significantly (P <0.05) decreased compared to the CMT at pre-IVB (Fig. 3).

There was no significant difference in the BCVA and CMT at 12 months after the initial treatment between the IVB and VIT Groups (Table 2).

Discussion

In this study, the long-term efficacy of 25-gauge vitrectomy to IVB for the treatment of ME secondary to BRVO was investigated. The major findings were: the BCVA was significantly improved in both VIT and IVB Groups at 12 months after the initial treatment. In addition, there were positive correlations between the pre-treatment BCVA and the BCVA at 12 months after the treatment in both the VIT and the IVB Groups. Second, the CMT was significantly decreased in both VIT and IVB Groups at 12 months after the initial treatment. Third, at 12 months after the initial treatment, the differences in the BCVA and CMT between the VIT and IVB Groups were not significant.

In the VIT Group, 25-gauge instruments were used to minimise the surgically-induced trauma. A recent study has shown that the clearance of VEGF is increased after vitrectomy,[25] suggesting that vitrectomy may lead to the resolution of the ME by reducing the level of the intravitreal VEGF. In addition, ILM peeling was performed in all cases in the VIT Group, and this procedure has been reported to release tangential traction to help resolve the ME.[9] ILM removal has also been reported to facilitate the diffusion of macromolecules from the retina to the vitreous cavity including mediators such as VEGF.[9] Furthermore, removing the ILM at the time of vitrectomy may reduce the risk of postoperative epiretinal membrane proliferation.[26] Through these mechanisms, vitrectomy with ILM peeling could achieve a long-term resolution of the ME associated with

BRVO. In concurrence, our findings showed that the reduction of the ME and subsequent improvement of BCVA was sustained for at least 12 months after the vitrectomy.

In the IVB Group, a similar effectiveness for improving BCVA and CMT was found during the 12 months follow-up period. Three of 19 eyes (15.8%) had a single IVB while the others needed multiple IVB. The average number of IVB was 2.4 (range, 1 to 5) during the 1-year period. Earlier clinical trials of IVB for cases of ME due to BRVO needed a mean of 2 (Kondo et al[15]) or 3.4 (Jaissle et al[14]) injections to preserve the BCVA improvement during a 1-year period.

The optimal protocol for IVB for the treatment of ME secondary to BRVO has not been determined. We injected 1.25 mg of IVB while other researchers injected 1.0 mg (Kriechbaum et al[27]) or 2.5 mg (Hoeh et al[28]) of IVB. Wu et al[29] reported that IVB at a dose up to 2.5 mg was effective in improving the BCVA and CMT in ME secondary to BRVO, and that there were no significant differences between the 1.25 mg and 2.5 mg dose groups with regard to the number of injections.

We selected a single primary injection of bevacizumab with additional injections when needed, while Prager et al[16] used the 3 primary IVB at monthly intervals just as is done to treat age-related macular degeneration. It remains to be determined which of the 2 schedules is better. However, it seems likely that a single primary IVB may be sufficient. One of the reasons is that 3 of our 19 eyes (15.8%) were successfully treated by a single injection during the 1-year follow-up period. Another reason for selecting a single injection of 1.25 mg bevacizumab is that an experimental study on the pharmacokinetics of IVB demonstrated that bevacizumab is retained in the retina for 3 months after the IVB.[30] Although a recurrence of the ME can be treated effectively by re-injection, the number of IVB injections may be important because the benefit of IVB must be carefully weighed against the possible adverse effects of IVB.[31]

The results of our study are limited because this was a retrospective, non-randomised, single-center study. Thus, the number of the patients was smaller in the IVB Group than in the VIT Group. In addition, we cannot eliminate the possibility that there may have been a bias in the choice of treatment. A prospective randomised study with a larger number of patients is needed.

Conclusion

In summary, we compared the efficacy of 25-gauge vitrectomy with that of IVB for the treatment of ME secondary to BRVO and demonstrated that 25-gauge vitrectomy may be as effective as IVB in improving the BCVA and CMT during the 1-year follow-up period.

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