·Clinical Research·

Effects of two different doses of intravitreal bevacizumab on subfoveal choroidal thickness and retinal vessel diameter in branch retinal vein occlusion

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Abstract

• AIM: To investigate the effects of two different doses of intravitreal bevacizumab on subfoveal choroidal thickness (SFChT) and retinal vessel diameter in patients with branch retinal vein occlusion.

• METHODS: An interventional, restrospective study of 41 eyes of 41 patients who had completed 12mo of follow-up, divided into group 1 (1.25 mg of bevacizumab, 21 eyes of 21 patients) and group 2 (2.5 mg of bevacizumab, 20 eyes of 21 patients). Complete ophthalmic examination, fluorescein angiography, enhanced depth imaging optical coherence tomography and measurement of retinal vessel diameter with IVAN software were performed at baseline and follow-up.

• RESULTS: The SFChT changed from 279.1 (165-431) μm at baseline to 277.0 (149-413) μm at 12mo in group 1 (P= 0.086), and from 301.4 (212-483) μm to 300.3 (199-514) μm in group 2 (P=0.076). The central retinal arteriolar equivalent (CRAE) changed from 128.8 ±11.2 μm at baseline to 134.5±8.4 μm at 12mo in group 1, and from 134.6±9.0 μm to 131.4±12.7 μm in group 2 (P =0.767). The central retinal venular equivalent (CRVE) changed from 204.1±24.4 μm at baseline to 196.3±28.2 μm at 12mo in group 1, and from 205.8±16.3 μm to 194.8±18.2 μm in group 2 (P=0.019). The mean central macular thickness (P<0.05) and average best -corrected visual acuity (BCVA; P<0.05) improved in both groups

• CONCLUSION: Changes in the SFChT are not statistically significant and not different according to the doses of bevacizumab. The CRAE did not show significant change, however, the CRVE showed significant decrease regardless of the dose.

• **KEYWORDS:** bevacizumab; retinal vein occlusion; choroids tomography; optical coherence; intravitreal injections; retinal vessels

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INTRODUCTION

Branch retinal vein occlusion (BRVO) is the second most common retinal vascular disease after diabetic retinopathy, and macular edema is the most frequent cause of visual impairment in BRVO[1-2].

Vascular endothelial growth factor (VEGF) plays a main role in breakdown of the blood-retinal barrier, increasing vascular permeability and developing macular edema[3-4]. Therefore the anti-VEGF agents, which bind and inhibit VEGF, seem to be a promising therapeutic modality in macular edema. Also in BRVO, retinal ischemia is one of the most important upregulators of VEGF, which contribute to the development of macular edema[1-2,5-8].

VEGF is known to induce vessel dilatation and hence increases ocular blood flow *via* a mechanism involving nitric oxide [9]. Also anti-VEGF agents are known to affect the retinal vasculature after intravitreal injection. Previous studies have noted changes of retinal vascular caliber, following intravitreal anti-VEGF injection[10-12].

Spaide *et al* [13] used spectral domain-optical coherence tomography (SD-OCT) and developed a method termed enhanced depth imaging (EDI), which enables *in vivo* measurement of the thickness of choroid. Some reports noted changes in subfoveal choroidal thickness (SFChT) after treatment, and especially, changes of it after intravitreal bevacizumab, were appreciated as predictive factor[14-15].

The aim of this study is to investigate how SFChT changes and how retinal vessel caliber changes after two different doses of intravitreal bevacizumab and compare the changes in central macular thickness (CMT) and best-corrected visual acuity (BCVA) after injecting two different doses. Along with several reports that have demostrated efficacy of intravitreal bevacizumab at doses of 1 to 2.5 mg causes an improvement in CMT and BCVA, we also investigated SFChT and retinal vascular caliber changes, as well as CMT and BCVA [5-6]. Also to evaluate whether SFChT and retinal

vessel caliber changes have a predictive value in treating BRVO.

SUBJECTS AND METHODS

We conducted an interventional retrospective study of 41 consecutive patients (41 eyes) with macular edema secondary to BRVO, treated primarily with intravitreal bevacizumab between January 2011 and December 2013, and had at least 12mo of follow-up. The patients were divided into two groups according to two different doses of intravitreal bevacizumab: group 1 (1.25 mg, 21 eyes) *vs* group 2 (2.5 mg, 20 eyes). Written informed consent was obtained from each patient. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board at Gyeongju hospital of Dongguk University.

Patients were asked of past medical history, and underwent clinical examination, including BCVA, intraocular pressure, slit-lamp examination, fundus examination, fluorescein angiography and SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany).

The visual acuity was measured with the Snellen chart, and converted to logarithm of minimal angle of resolution (logMAR) visual acuity for statistical analysis. Exclusion criteria included patients with severe central corneal opacity, cataract, vitreous hemorrhage and macular edema secondary to other causes such as diabetic retinopathy and central retinal vein occlusion. Also patients with more than 3mo of onset of visual symptoms, and patients who were treated with grid laser photocoagulation or posterior subtenon triamcinolone injection, pars plana vitrectomy were excluded. Choroidal image was obtained using SD-OCT according to the EDI technique[13]. Each image was measured independently by 3 trained ophthalmologists (Park J, Son Y, Lee S). The discrepancies were resolved by open adjudication between the authors.

The retinal vessel diameters were measured using semi-automatic computer-assisted software, IVAN (Computer-assisted software, University of Wisconsin, Madison, USA). The measurement was done as described by Chang *et al*[16]. Excluding the quadrant, where the BRVO occurred and retinal vessels were obscured by retinal hemorrhage, one trained grader, masked to participant characteristics, performed vessel measurements at the other three quadrants. The central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) were calculated using the revised Parr-Hubbard formula developed by Knudtson *et al*[17].

Patients were examined every 4wk. At each visit, patients underwent clinical examination, including BCVA, intraocular pressure, slit-lamp examination, fundus examination, and OCT for CMT and SFChT. Fluorescein angiography was performed at 4mo and 12mo after initial bevacizumab injection.

Patients were reinjected when there was increase of ≥100 μm in CMT on OCT or decrease in BCVA of ≥2 ETDRS lines, after patients consent. The decrease in BCVA was only attributable to macular edema. Decreased visual acuity, related with vitreous hemorrhage, macular ischemia, and neovascular glaucoma secondary to BRVO were excluded.

Statistical Analysis Statistical analysis was performed using R-statistics (version 2.9.2, R Foundation for Statistical Computing, Vienna, Austria). For comparison of baseline datas, Mann-Whitney *U* test and Chi-square test was used. The mean logMAR BCVA, mean CMT, and mean SFChT in both groups were compared using nonparametric repeated-measure analysis of variance (ANOVA) with the Mann-Whitney *U* test. The interval changes of BCVA, CMT and SFChT in both groups were compared using Wilcoxon signed-rank test. The time course of retinal vascular caliber in each group and intergroup differences were analyzed with repeated-measure ANOVA test. A *P* value of <0.05 was considered significant.

RESULTS

Group 1 (1.25 mg) comprised of 21 patients (10 males, 11 females). The average age was 62.43±9.80 (range, 41-85)y, and average follow-up period was 14.3 ±2.5mo, with a minimum of 12mo. The baseline BCVA was 0.78 ±0.54 logMAR units, baseline CMT was 516.1 ±157.4 μm, and baseline SFChT was 279.1±96.4 μm on OCT. Duration from onset of visual symptom was average 21.4 (range 3-78)d, and the average number of injections was 3.0 (range, 1-6). Group 2 (2.5 mg) comprised of 20 patients (9 males, 11 females). The average age was 58.80 ±8.61 (range, 44-74)y and average follow-up period was 15.7±1.9mo, with a minimum of 12mo. The baseline BCVA was 0.57 ±0.24 logMAR units, baseline CMT was 508.7±128.2 μm, and baseline SFChT was 301.4± 91.5 μm on OCT. Duration from onset of visual symptom was average 23.2 (range 5-81)d, and the average number of injections was 3.5 (range, 1-9) (Table 1).

The BCVA at 12mo were 0.20±0.11 logMAR units in group 1, and 0.21 ±0.12 logMAR units in group 2. Statistically significant improvements in logMAR BCVA were seen in both groups at 3mo after initial bevacizumab injection (*P*= 0.000). And these significant changes continued throughout the 12mo follow-up (*P* =0.000). But there were no statistically significant differences between both dose groups in final BCVA outcome (*P* =0.989) (Figure 1).

The CMT at 12mo were 288.6 ±14.9 μm in group 1, and 284.0 ±29.8 μm in group 2. Like BCVA, statistically significant improvements in CMT were seen in both groups at 3mo after initial bevacizumab injection (*P* =0.000). And these significant changes continued throughout the 12mo follow-up (*P* =0.000). But, there were no statistically significant differences between both dose groups in final CMT outcome (*P* =0.824) (Figure 2).

Table 1 Patient's demographic data and baseline characteristics

Variables	Group 1 (1.25 mg) (n=21)	Group 2 (2.5 mg) (n=20)	P
Age (a)	62.43±9.80 (41-85)	58.80±8.61 (44-74)	0.24[a]
Sex (M/F)	10/11	9/11	0.86[b]
Laterality (OD/OS)	10/11	8/12	0.62[b]
Hypertension (%)	5 (23.8)	9 (45)	0.15[b]
Diabetic mellitus (%)	2 (9.5)	2 (10)	0.96[b]
Mean baseline BCVA (logMAR)	0.78±0.54	0.57±0.24	0.34[a]
Means baseline IOP (mm Hg)	14.9±2.6	14.7±2.3	0.75[a]
Mean baseline CMT (μm)	516.1±157.4	508.7±128.2	0.75[a]
Mean baseline SFChT (μm)	279.1±96.4	301.4±91.5	0.43[a]
Duration from onset (d)	21.4 (3-78)	23.2 (5-81)	0.23[a]
Total no. of injections	3.0±1.3	3.5±2.1	0.69[a]

BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimal angle of resolution; IOP: Intraocular pressure; CMT: Central macular thickness; ChT: Choroidal thickness. [a]Statistical significance was calculated by Mann-Whitney U test; [b]Statistical significance was calculated by Chi-square test.

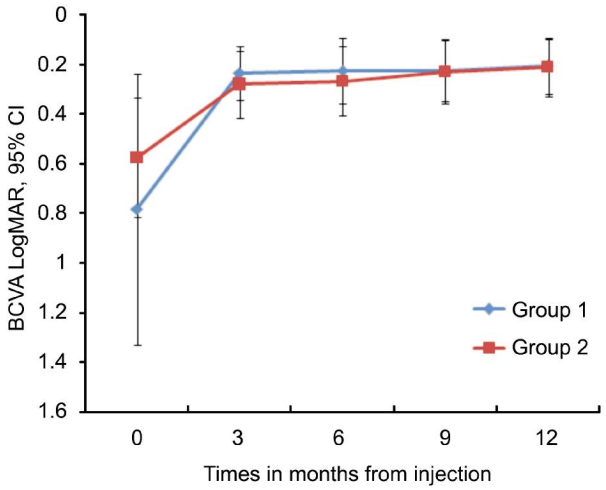

Figure 1 Change in BCVA from baseline to 12mo The logMAR BCVA improved significantly in both groups at 3mo after initial bevacizumab injection, and the changes continued to be significant at 12mo (P=0.000). However, the difference in the final BCVA outcome between the dose groups was not significant (P= 0.989).

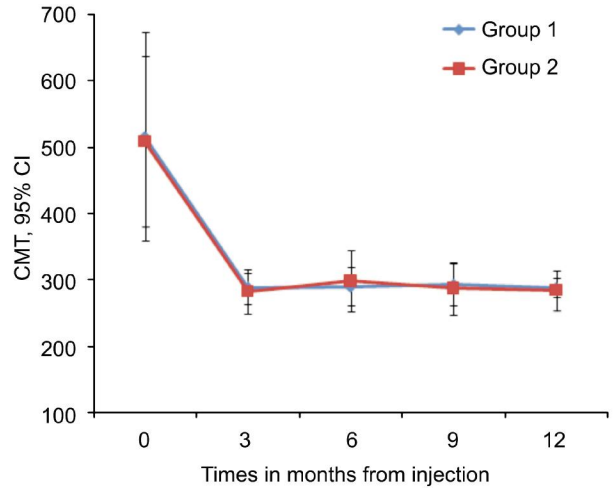

Figure 2 Change in CMT from baseline to 12mo The CMT was significantly improved in both groups at 3mo after initial injection and the changes continued to be significant at 12mo (P= 0.000); there were no significant differences between the dose groups in the final CMT outcome (P=0.824).

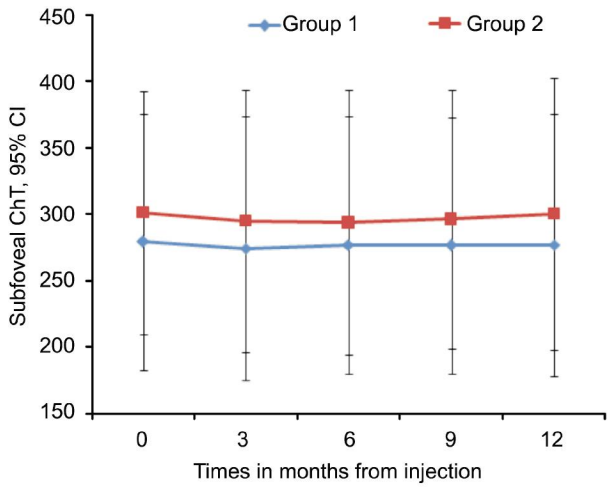

Figure 3 Change in SFChT from baseline to 12mo In group 1, the SFChT significantly decreased at 3mo (P=0.051) and at 6mo (P=0.043), and then did not change significantly at 9mo (P=0.116) or 12mo (P=0.086). In group 2, the SFChT decreased significantly at 3mo (P=0.048), and did not change significantly at 6mo (P= 0.064), 9mo (P=0.254), and 12mo (P=0.076). There were no significant differences in the final SFChT outcome between the dose groups (P=0.540).

In group 1, the SFChT changed from 279.1 ±96.4 μm at baseline to 274.3±99.2 μm at 3mo (P=0.051) and 277.2± 97.0 μm at 6mo (P=0.043), showing significant decrease. But it changed to 276.6±96.8 μm at 9mo (P=0.116) and 277.0±98.5 μm at 12mo (P=0.086), not showing statistically significance. In group 2, the SFChT decreased from 301.4± 91.5 μm at baseline to 294.8±99.0 μm at 3mo (P=0.048), showing statistical significance. But it changed to 293.8 ± 99.9 μm at 6mo (P=0.064), 296.3±97.3 μm at 9mo (P= 0.254) and 300.3 ±102.2 μm at 12mo (P=0.076), not showing statistically significance. And, there were no statistically significant differences between both dose groups in final SFChT outcome (P=0.540) (Figure 3).

In group 1, the CRAE changed from 128.8 ±11.2 μm at baseline to 131.4±15.8 μm at 3mo, 129.6±18.3 μm at 6mo,

130.3±14.5 μm at 9mo, and 134.5±8.4 μm at 12mo. In group 2, the CRAE changed from 134.6±9.0 μm at baseline to 134.8±12.2 μm at 3mo, 131.0±13.4 μm at 6mo, 137.0±14.2 μm at 9mo, and 131.4±12.7 μm at 12mo. The repeated-measure ANOVA revealed that the changes in CRAE from baseline measurements to post-injection times were not statistically significant in both groups (P=0.767). And, there were no statistically significant intergroup differences in CRAE (P=0.652) (Figure 4).

In group 1, the CRVE changed from 204.1±24.4 μm at baseline to 197.6±24.8 μm at 3mo, 203.2±23.7 μm at 6mo, 200.4±27.5 μm at 9mo, and 196.3±28.2 μm at 12mo. In group 2, the CRVE changed from 205.8±16.3 μm at baseline to 196.2±12.0 μm at 3mo, 198.7±18.0 μm at 6mo, 195.0±15.3 μm at 9mo, and 194.8±18.2 μm at 12mo. The repeated-measure ANOVA revealed that the CRVE significantly decreased from baseline measurement to post-injection times in both groups (P=0.019). Also, the repeated-measure ANOVA revealed no statistically significant intergroup differences in the time course of CRVE (P=0.834) (Figure 5).

Intraocular complications, such as increased intraocular pressure, retinal detachment and endophthalmitis, and systemic complications did not occur.

DISCUSSION

Macular edema is an important complication causing visual loss in BRVO. Intravitreal injection of anti-VEGF agents is recognized as a promising treatment modality, not only reducing macular edema, and improving visual acuity, but also preventing retinal neovascularization [5-8]. Among the anti-VEGF agents, bevacizumab is widely used for economic reasons, although, it is currently off-label in ophthalmology. However the optimum timing, dosing and sequence of intravitreal bevacizumab in BRVO are still undetermined. The Pan American Collaborative Retina Study (PACORES) Group reported that, intravitreal bevacizumab at doses up to 2.5 mg seems to be effective in improving BCVA and reducing CMT in macular edema secondary to BRVO in the short term. However, they reported that number of injections, CMT, change in BCVA are not significantly different between two different doses of intravitreal bevacizumab in long-term follow-up (1.25 mg *vs* 2.5 mg) [18-19]. Also in this study, number of injections, BCVA and CMT at last follow-up did not show statistically significant differences between the two dose groups. Both 1.25 mg and 2.5 mg seemed to have similar treatment efficacy. It is not clear whether a higher dose (2.5 mg) can provide better outcomes, a longer disease-free interval or reduce the burden of more frequent injections than a lower dose (1.25 mg). Although both doses were not associated with any adverse events in this study, the 2.5 mg dose is reported to cause inflammatory reaction in the vitreous, and acute posterior vitreous detachment with peripheral retinal hemorrhage [20]. Unless data to support improved efficacy and secure safety for the 2.5 mg dose becomes available, the authors favor the lower dose.

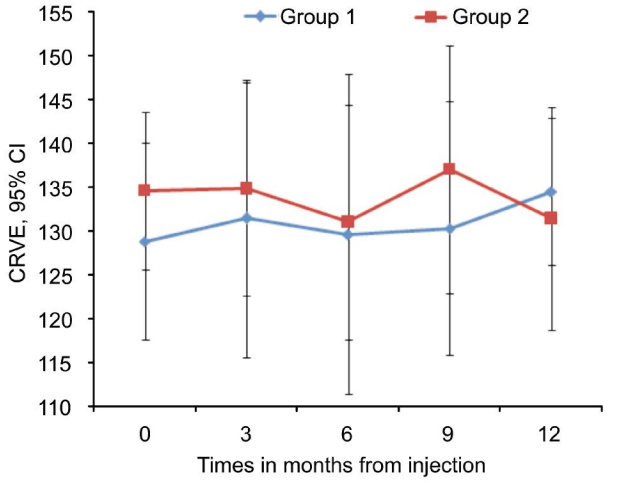

Figure 4 Change in CRAE from baseline to 12mo The changes in CRAE from baseline measurements to post-injection times were not statistically significant in both groups (P=0.767). And, there were no statistically significant intergroup differences in CRAE (P=0.652).

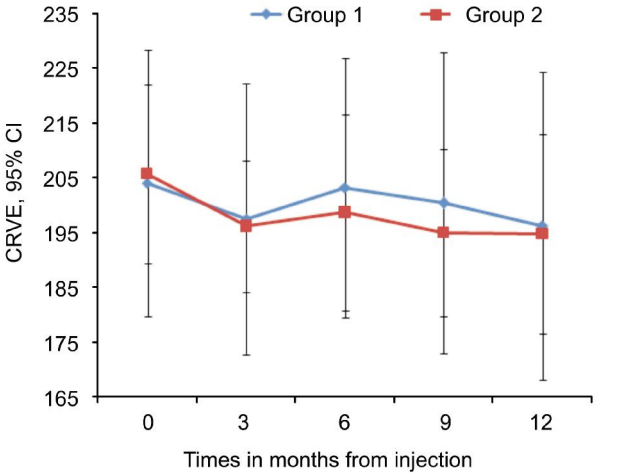

Figure 5 Change in CRVE from baseline to 12mo The repeated-measure ANOVA revealed that the CRVE significantly decreased from baseline measurement to post-injection times in both groups (P=0.019). And, the repeated-measure ANOVA revealed no statistically significant intergroup difference (P=0.834).

Bevacizumab is known to affect the retinal and choroidal circulation after intravitreal injection. Some studies have reported changes of retinal vascular caliber after intravitreal bevacizumab injection. Sacu *et al* [21] reported vasoconstriction in retinal vessels, and significant reduction in flow velocities in the retrobulbar central retinal artery, after three intravitreal injections of ranibizumab in eyes with BRVO. In this study, after intravitreal bevacizumab injection in patients with BRVO, changes of retinal arteriolar diameter did not reach statistical significance. However significant vasoconstriction in the retinal venules was noted, regardless of doses of

intravitreal bevacizumab. As Papadopoulou *et al* [10] noted, this may be interpreted that decrease in retinal venular diameter reflects a return to the normal diameter from a previously vasodilated state. It is known that VEGF has effects in vessel diameter and its down-regulation secondary to bevacizumab is expected to induce vessel constriction[22-23]. In one study of nonhuman primates, VEGF induced capillary endothelial cell proliferation within veins, leading to intussusceptions and endothelial cell wall bridging within venules [24]. If VEGF contributes to venous flow decrease in humans, as in nonhuman primates, the reduction in venous diameter might mean that the flow through the vein was improved after intravitreal bevacizumab injection in BRVO.

We conducted further analysis of variables affecting total number of injections during the follow up period. The patients were divided into two subgroups, considering that the average number of injections was three; subgroup A (≤3 injections, 28 eyes) *vs* subgroup B (≥4 injections, 13 eyes). First, the repeated-measure ANOVA revealed that the changes in SFChT from baseline measurements to post-injection times were not statistically significant in both subgroups (P=0.151). Also there were no statistically significant intergroup difference (P=0.130) (Figure 6). Second, the baseline CRVE in both subgroups did not show significant difference (P=0.868). However in the final CRVE outcome, subgroup A showed a significantly greater decrease in CRVE than did subgroup B (P=0.049). This revealed that a greater decrease in retinal venular diameter was associated with a lesser numbers of intravitreal injection, required. In other words, changes of retinal venular diameter may help predict which patients with BRVO will respond more favorably to intravitreal bevacizumab. The CRVE is an easily available marker, to predict patients who will be more responsive to bevacizumab. It seems important to check the changes of CRVE during intravitreal bevacizumab treatment, to aid in clinical decision making. To our knowledge, this is the first study to show the relation between changes of retinal venular diameter and the numbers of required intravitreal injection.

Choroidal vasculature is supplied by sympathetic innervation both anatomically and physiologically, and there is lack of autoregulation, but rich of receptors for VEGF [25]. After intravitreal injection, bevacizumab is delivered to choroid passing through retina, and is accumulated in the vascular wall of choroid [26]. Thus, inhibition of VEGF, by intravitreal injection of anti-VEGF agents may affect the permeability of choroidal vasculature and choroidal thickness. Tsuiki *et al* [27] reported that SFChT of CRVO eyes was significantly greater than that of fellow eyes and decreased significantly after intravitreal bevacizumab treatment. In this study, SFChT of BRVO eyes was significantly greater than that of fellow eyes in 15 patients, in which baseline SFChT was measured in both eyes. The mean SFChT of BRVO eyes was 322.75±101.3 μm, which was significantly thicker than the mean SFChT of the fellow eyes, 284.1±109.2 μm (P=0.036).

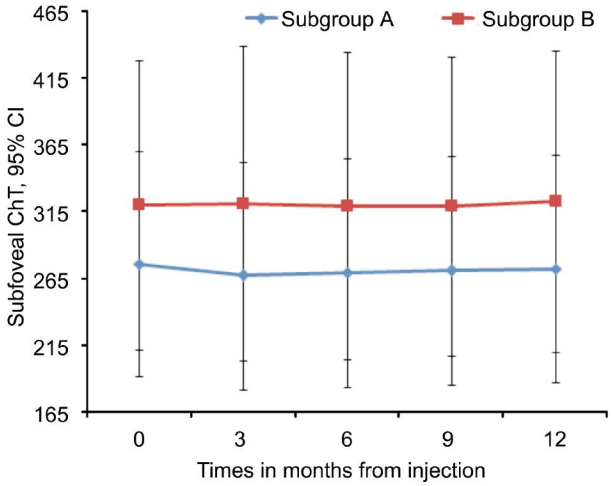

Figure 6 Subgroup analysis –change in SFChT in two subgroups differing in total numbers of intravitreal injections In both subgroup, the repeated-measure ANOVA revealed that the changes in SFChT from baseline measurements to post-injection times were not statistically significant (P=0.151). Also there were no statistically significant intergroup differences (P=0.130).

Decrease in SFChT was seen in both groups for the first 6mo, after the initial bevacizumab injection. But SFChT of the next 6mo did not show change from the baseline. The decrease during the first 6mo might be related with frequent bevacizumab injections, performed during the period. This might have affected intravitreal VEGF level [22]. This may be related with short duration of drug action of bevacizumab, in pharmacokinetic aspect. Considering that, the vitreous half-life is about 9.8d [28], and significant VEGF binding activity lasts for 4wk to 5wk [29], after a single intravitreal bevacizumab injection, most patients need more than 2 reinjections. Actually in this study, 39 eyes of total 41 eyes (95%) needed reinjection of bevacizumab within 6mo after initial intravitreal bevacizumab injection. And the mean time of reinjection was 2.4mo. This is similar to the report of other study, revealing that macular edema secondary to BRVO relapses in average 2.1mo [2].

The final SFChT did not show statistically significant differences from the baseline in both groups. As VEGF level much decreased at last follow-up from the baseline, it might have least effects on choroidal thickness. As VEGF level is known to be related with macular edema and retinal ischemia, VEGF level is much decreased in last follow-up[22,30]. This might be attributable to the facts, as below. First, as shown in the study of natural history of BRVO, without diffuse macular ischemia, macular edema spontaneously resolves, and visual acuity improves to some degree without any treatment in 6-9mo. Also, unlike CRVO, in which, anatomic obstruction occurs at or just posterior to laminar

cribrosa, causing diffuse retinal ischemia, BRVO only affects relatively small areas. In that regard, after intravitreal bevacizumab, vitreous VEGF level is well maintained under physiologic level[22].

This study has some limitations of being retrospective nature, and small sample size. Even though EDI-OCT provides high-resolution imaging of choroid, there might have been some artifacts that affected SFChT measurement, and the measurements were obtained manually, not by automated software. Also fluorescein angiography was performed at the discretion of the examiner during follow-up, not at every postinjection evaluation. So the degree of retinal ischemia was not checked at every postinjection evaluation.

Further large studies with long-term follow-up, analyzing variable factors, including retinal ischemia, which affect choroidal thickness and retinal vessel diameter might be needed. In conclusion, SFChT decreased during the first 6mo after initial bevacizumab injection, and did not show significant change during the last 6mo. Also change in SFChT was not significantly different according to different doses of intravitreal bevacizumab. CRVE significantly decreased after bevacizumab injection, and changes of retinal venular diameter may help predict which patients with BRVO will respond more favorably to intravitreal bevacizumab pharmacotherapy.

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Conflicts of Interest: Park J, None; **Lee S,** None; **Son Y,** None.

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