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Intravitreal triamcinolone and bevacizumab as adjunctive treatments to panretinal photocoagulation in diabetic retinopathy

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ABSTRACT

Background/aims To evaluate efficacy of intravitreal triamcinolone (IVTA) and bevacizumab (IVB) as adjunctive treatments to panretinal photocoagulation (PRP).

Methods In 91 eyes of 76 patients (clinically significant macular oedema (CSME) 46 eyes; no CSME 45 eyes) with severe diabetic retinopathy, PRP with IVTA (IVTA group, 30 eyes) or PRP with IVB (IVB group, 31 eyes) or PRP only (PRP group, 30 eyes) was performed. Primary outcome measures were changes in best corrected visual acuity (BCVA) and central macular thickness (CMT) at 1 and 3 months. Secondary outcome measures were proportion of visual gain or loss, and decreased or increased CMT.

Results There was significant worsening in BCVA from 0.26 to 0.29 at 1 and 3 months ($p=0.031$) in the PRP group. In eyes with CSME, there was significant improvement of BCVA from 0.33 to 0.27 at 1 and 3 months ($p=0.012$) in IVTA group. In eyes without CSME, PRP group showed significant worsening in BCVA from 0.18 to 0.26 at 1 month ($p=0.008$) and 0.27 at 3 months ($p=0.005$). There was significant improvement in CMT in IVTA and IVB groups: in eyes without CSME, there was significant increase in CMT from 209.75 to 259.00 μm at 1 month ($p=0.023$) and to 276.14 μm at 3 months ($p=0.011$) in the PRP group; in eyes with CSME, the proportion of eyes with visual gain and decreased CMT was significantly higher in the IVTA group (75% and 100%, respectively) than in the IVB group (37.5% and 62.5%, respectively).

Conclusions IVTA and IVB may be effective adjunctive treatments to PRP, minimising the risk of PRP-induced macular oedema and visual loss.

INTRODUCTION

Scatter laser panretinal photocoagulation (PRP) has become the mainstay for the management of diabetic retinopathy. The Diabetic Retinopathy Study results demonstrated 50% or more reduction of severe visual loss in patients with high-risk proliferative diabetic retinopathy (PDR) that had received photocoagulation compared with no treatment.¹ PRP was recommended in eyes with severe diabetic retinopathy, including those with severe non-proliferative diabetic retinopathy (NPDR) or non high-risk PDR, and prompt PRP was indicated for the patients with high-risk PDR.^{2,3}

However, macular oedema sometimes develops or increases, at least temporarily, after PRP, and this may be followed by transient or persistent reduction of visual acuity. Previous studies have shown

that 25–43% of eyes with PDR treated with PRP developed increased macular oedema and visual disturbances.^{4–6} The Early Treatment Diabetic Retinopathy Study (ETDRS) recommended treatment of macular oedema with focal/grid photocoagulation before or at the time of initiating PRP.^{7,8} Focal/grid photocoagulation reduced the risk of moderate visual acuity loss for all eyes with diabetic macular oedema by about 50%. However, patients had only minimal visual improvement after laser treatment, and only 3% had visual improvement of three lines at 3 years. Moreover, 12% of eyes developed moderate visual loss at 3 years despite treatment, and 40% of eyes with retinal thickening involving the macula had persistent oedema at 12 months.² The limitations of focal/grid laser photocoagulation for the treatment of post-laser macular oedema have prompted interest in other methods.

The exact pathogenic mechanism for macular oedema following PRP has not been determined. Recently, a series of studies suggested post-laser release of inflammatory factors, accumulation of leucocytes in the non-photocoagulated posterior pole, and upregulation of angiogenic growth factors, such as vascular endothelial growth factor (VEGF), play a role in the pathogenesis of the oedema.^{9–13} Intravitreal triamcinolone acetonide (IVTA) has shown promise for the treatment of macular oedema that failed to respond to conventional laser photocoagulation,¹⁴ and PRP combined with IVTA may be useful in improving the effect of PRP in eyes with PDR by reducing neovascularisation (NV) and macular thickening.^{15,16} However, the adverse events of IVTA including intractable glaucoma and progression of cataract, have limited its use.^{17–20} Bevacizumab (Avastin; Genentech Inc., San Francisco, California, USA) is a full-length humanised monoclonal antibody that competitively inhibits all isoforms of the VEGF-A family. Recent studies have demonstrated the usefulness of intravitreal bevacizumab (IVB) in the improvement of visual acuity, reduction of macular oedema, fibrovascular proliferation in retinal NV and resolution of vitreous haemorrhage secondary to high-risk PDR.^{21–23} More recently IVB before PRP has been reported to be effective also in preventing PRP-induced visual dysfunction and foveal thickening,^{24,25} and promoting greater reduction in the area of active leaking of NV in PDR patients.^{26,27} Therefore, in the present study, we aimed to compare and evaluate the efficacy and safety of IVTA and IVB as adjunctive treatments to PRP in reducing PRP-related short-term vision loss and macular oedema.

MATERIALS AND METHODS

Patient enrolment

The present study was designed as a prospective, comparative, interventional case series. Patients from very severe NPDR to high-risk PDR with or without clinically significant macular oedema (CSME) were considered for enrolment into the study. Patients were enrolled in the study after undergoing systemic evaluation including medical history, blood pressure, serum HbA1c (glycated haemoglobin) levels, renal profiles and complete ocular examination. Ocular examination included best corrected visual acuity (BCVA), intraocular pressure (IOP), presence of lens opacities using the Lens Opacities Classification System III (LOCS III), fundus examination, and macular thickness measurement by the optical coherence tomography (OCT; Stratus OCT, Carl Zeiss, Dublin, California, USA). The central macular thickness (CMT) reported in the central 1 mm macular thickness map was taken as the mean retinal thickness of the macula. Criteria for inclusion into the study were age ≥ 18 years, very severe NPDR to high-risk PDR, and Snellen BCVA of ≥ 0.3 . Exclusion criteria consisted of systemic and diastolic blood pressures of higher than 180 and 110 mm Hg, respectively, HbA1c levels exceeding 9.5%, chronic renal failure, major surgery within 1 month, or previous systemic steroid or anti-VEGF treatment. We also excluded patients with ocular conditions other than diabetic retinopathy, which might affect macular oedema or limit visual acuity during the course of this study (eg, retinal vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.). Patients with a history of treatment for diabetic macular oedema in the previous 3 months, previous PRP or focal/grid laser photocoagulation, previous intraocular surgery and uncontrolled glaucoma were also excluded.

Study design

The study protocol is shown in figure 1. Ninety-one eyes of 76 patients were eligible for the study. In 46 eyes with CSME and 45 eyes without CSME, the enrolled eye randomly received PRP with IVTA (IVTA group) or PRP with IVB (IVB group) or PRP only (PRP group). There were 30 eyes in the IVTA group, 31 eyes in the IVB group and 30 eyes in the PRP group. In the 15 patients who had bilateral eyes eligible for the study, one eye of each patient was randomly chosen to receive PRP with IVTA or PRP with IVB or PRP only and the other eye received the other procedure.

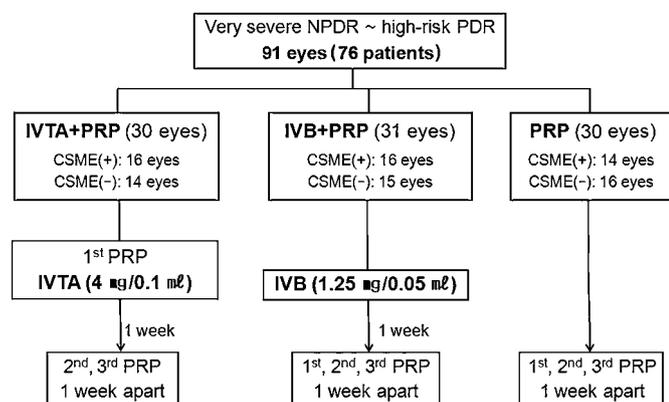


Figure 1 Study protocol. CSME, clinically significant macular oedema; IVB, intravitreal bevacizumab; IVTA, intravitreal triamcinolone acetonide; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation.

Treatment

IVTA (4 mg/0.1 ml) was given 1 day after first session of PRP because triamcinolone particles could hide the inferior retina and disturb PRP. IVB (1.25 mg/0.05 ml) was given about 1 week prior to initial PRP. After the eye had been prepared in a standard fashion using 5% povidone–iodine, an eyelid speculum was used to stabilise the eyelids, and intravitreal injection of bevacizumab or triamcinolone acetonide was given with a 30-gauge needle with topical anaesthesia. After injection intraocular pressure was checked, and patients were instructed to administer topical antibiotics for 7 days. All enrolled eyes underwent a scatter laser treatment using a 532-nm argon-green laser (Visulas 532s/LSL 532s Laser Slit Lamp; Carl Zeiss Meditec) at three time-points (1 week intervals). Focal/grid laser photocoagulation was performed at the time of initiation PRP in patients with CSME.

Follow-up protocol

Follow-up visits were scheduled at 1 day after injection, and 1 week, 1 month and 3 months after the final session of PRP. Measurement of BCVA, IOP by using Goldmann applanation tonometer, slit lamp biomicroscopy and fundus examination were performed at all of those visits. At each visit, the patients were also asked about adverse events. At month 1 and month 3, OCT and fluorescein angiography was also performed. At the time of follow-up, the investigators and the study coordinators were masked to the treatment.

Outcome measures

The primary outcome measures were the changes in BCVA (logarithm of the minimum angle of resolution ((logMAR)) and CMT at 1 and 3 months. The secondary outcome measures were the proportion of eyes with visual gain and decreased CMT at 3 months in eyes with CSME, and the proportion of eyes with visual loss and increased CMT at 3 months in eyes without CSME. The potential injection-related complications, such as ocular hypertension and lens opacity progression, were studied for the evaluation of ocular safety, and arterial thromboembolic events for systemic safety.

Statistical analysis

The results were analysed using SPSS statistical software (version 11.0 for Windows; SPSS, Inc., Chicago, Illinois, USA). Visual acuities were converted to the logMAR before the statistical analysis. The Mann–Whitney test was performed for comparing baseline values between three groups. Changes in BCVA and CMT on within-group or between-group analyses were assessed by means of repeated measures ANOVA. Proportions of the patients with visual loss or gain, and with increase or decrease in CMT, between-groups were analysed by using χ^2 test.

RESULTS

Patients at baseline

Between March 2007 and August 2008, 91 eyes of 76 patients were enrolled in the study. There were 30 eyes were in the IVTA group, 31 eyes in the IVB group and 30 eyes in the PRP group (figure 1). The three groups were well balanced overall for demographic and baseline ocular characteristics (table 1). The mean age was 50.8 ± 36.8 years in the IVTA group, 50.9 ± 46.0 years in the IVB group and 51.0 ± 26.0 years in the PRP group. The mean BCVA (logMAR) was 0.27 ± 0.25 in the IVTA group, 0.28 ± 0.31 in the IVB group and 0.26 ± 0.28 in the PRP group. Mean CMT was 343.89 ± 330.79 μm in the IVTA group, 328.02 ± 335.29 μm in the IVB group and 326.27 ± 315.17 μm in the PRP group.

Table 1 Baseline characteristics of patients with/without clinically significant macular oedema (CSME)

	Eyes with CSME				Eyes without CSME			
	IVTA group	IVB group	PRP group	p Value	IVTA group	IVB group	PRP group	p Value
Number of eyes (n)	16	16	14		14	15	16	
Systemic								
Age (years)	49.8 (11.1)	51.2 (34.8)	51.1 (21.7)	0.231	52.0 (13.2)	50.5 (10.1)	50.9 (19.3)	0.132
Female (%)	31.25	37.5	35.71			28.57	33.33	31.25
Duration of DM (months)	168.2 (25.4)	153.7 (22.1)	158.7 (21.1)	0.658	154.5 (21.1)	160.8 (19.3)	155.5 (24.1)	0.832
HbA1c (%)	6.91 (0.21)	7.81 (0.32)	7.31 (0.41)	0.815	7.12 (0.13)	7.21 (0.23)	7.18 (0.09)	0.651
Systolic BP (mm Hg)	141 (21)	143 (15)	140 (18)	0.258	138 (18)	140 (16)	145 (19)	0.815
Diastolic BP (mm Hg)	96 (14)	91 (17)	98 (15)	0.543	98 (15)	98 (13)	100 (21)	0.983
Ocular								
BCVA (logMAR)	0.33 (0.16)	0.34 (0.16)	0.34 (0.17)	0.814	0.20 (0.15)	0.22 (0.28)	0.19 (0.21)	0.715
IOP (mm Hg)	17.2 (3.5)	16.0 (1.9)	15.3 (2.1)	0.758	16.8 (2.7)	15.9 (4.1)	16.7 (3.3)	0.427
CMT (μ m)	463.50 (227.47)	443.22 (169.72)	459.43 (168.85)	0.654	207.20 (30.77)	205.15 (25.30)	209.75 (38.85)	0.681
PRP								
Power (mW)	242 (20.8)	238 (21.7)	243 (20.7)	0.578	251 (19.1)	244 (22.1)	248 (20.5)	0.310
Number of burns (n)	1329 (45.2)	1351 (35.6)	1339 (28.8)	0.719	1335 (31.8)	1381 (41.8)	1348 (35.8)	0.618

Values are mean \pm SD.

There were no statistically significant differences between the three groups.

BCVA, best corrected visual acuity; BP, blood pressure; CMT, central macular thickness; CSME, clinically significant macular oedema; DM, diabetic mellitus; HbA1c, glycated haemoglobin; IOP, intraocular pressure; IVB, intravitreal bevacizumab; IVTA, intravitreal triamcinolone acetonide.

Primary outcome measures

Mean BCVA (logMAR) in the PRP group worsened significantly from 0.26 to 0.29 at 1 month ($p=0.031$) and 0.29 at 3 months ($p=0.030$). However, in the IVTA and IVB groups, there were no significant changes in BCVA within-group and between-groups analyses (figure 2A). In eyes with CSME, only the IVTA group showed significant improvement of BCVA during 3 months (figure 2B). In eyes without CSME, there was significant worsening of BCVA only in the PRP groups (figure 2C). There was significant difference in mean BCVA between the IVTA and IVB groups only in eyes with CSME.

Considering all eyes with PRP, there were significant decreases in CMT during the follow-up period in both IVTA and IVB groups (figure 2D). In eyes with CSME, there were significant decreases in CMT in both IVTA and IVB groups (figure 2E). However, in eyes without CSME, CMT increased significantly from $209.75 \pm 27.47 \mu\text{m}$ at baseline to $259.00 \pm 58.28 \mu\text{m}$ at 1 month ($p=0.023$) and $276.14 \pm 47.38 \mu\text{m}$ at 3 months ($p=0.011$) in the PRP group, while there were no significant changes in both IVTA and IVB groups (figure 2F). There was no significant difference in CMT at 1 month and 3 months between IVTA and IVB groups.

Secondary outcome measures

In eyes with CSME, the proportion of eyes with visual gain ≥ 0.1 logMAR was significantly higher in the IVTA group than in the IVB group and the PRP group. The proportion of eyes with visual gain ≥ 0.2 logMAR was significantly higher in the IVTA group than in the PRP group (figure 3A). The proportion of eyes with visual loss ≥ 0.1 logMAR and visual loss ≥ 0.2 logMAR was significantly higher in the PRP group than the IVTA group (figure 3B).

In eyes without CSME, the proportions of eyes with visual gain ≥ 0.1 logMAR was significantly higher in the IVTA and the IVB groups than in the PRP group. The proportions of eyes with visual gain ≥ 0.2 logMAR was not statistically different among the three groups (figure 3C). The proportions of eyes with visual loss ≥ 0.1 logMAR and visual loss ≥ 0.2 logMAR was significantly higher in the PRP group than in the IVTA group and the IVB group (figure 3D).

In eyes with CSME, the proportion of eyes with a decrease in CMT was significantly lower in the PRP group than in the IVTA group and the IVB group. The proportion of eyes with a decrease in CMT was significantly higher in the IVTA group than in the IVB group (figure 4A). In eyes without CSME, the proportion of eyes with an increase in CMT was significantly higher in the PRP group than in the IVTA group and the IVB group (figure 4B).

There were four patients with increased proliferation and development of vitreous haemorrhage during follow-up in the PRP group. However, none of the patients in the IVTA and the IVB groups showed an increased proliferation process and development of vitreous haemorrhage.

Injection-related complications

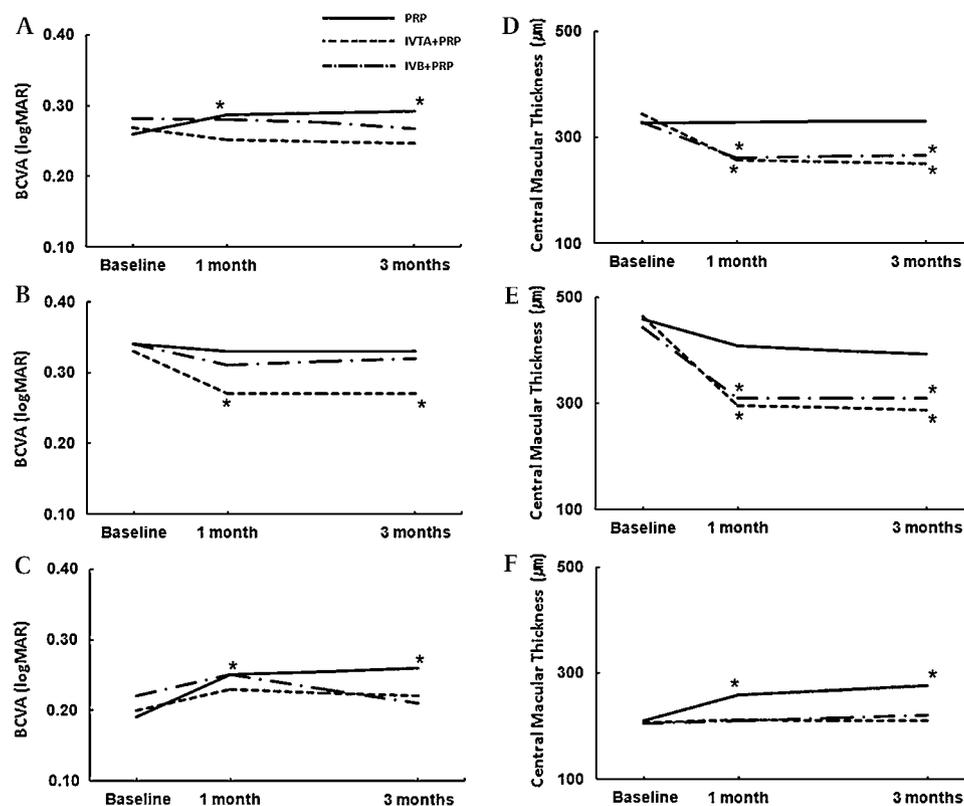
There was one eye with cataract progression, that is, two-grade progression of cataract according to LOCS III. There were four eyes (three eyes with CSME and one eye with no CSME) with increased IOP (15 ± 3 mm Hg at 1 month) in the IVTA group. There were no complications in the IVB group.

DISCUSSION

For eyes with coexistent PDR and macular oedema, the ETDRS have recommended focal/grid photocoagulation for macular oedema before or at the time of initiating PRP.^{7 8} However, treating macular oedema first in those patients would delay the initiation of PRP and place the patients at risk for severe visual loss from PDR. Conversely, initiating PRP prior to focal/grid laser photocoagulation would exacerbate existing CSME. Under these circumstances, an adjunctive treatment to PRP seems to be feasible to overcome this dilemma.

At present, IVTA is one of the most common methods for reducing diabetic macular oedema. However, the adverse events of IVTA, including intractable glaucoma and progression of cataract, have limited its use.^{17–20} Previous studies have shown the efficacy of IVB in diabetic retinopathy.^{21–23} We aimed to evaluate the efficacy and safety of IVB as an adjunctive treatment to PRP, and have shown that IVB seems to be a promising adjunctive treatment to PRP in the treatment of high-risk PDR, especially if there is no CSME. The results of our study demonstrated that IVB appears to stabilise or improve diabetic

Figure 2 Changes in best corrected visual acuity (BCVA) (logarithm of the minimum angle of resolution (logMAR)): (A) all eyes with panretinal photocoagulation; (B) eyes with clinically significant macular oedema (CSME); (C) eyes without CSME. Changes in central macular thickness: (D) all eyes with panretinal photocoagulation; (E) eyes with CSME; (F) eyes without CSME. Statistically significant change from baseline. * $p < 0.05$.



macular oedema in conjunction with PRP, at least in the short term.²⁴

In the present study, we aimed to compare the efficacy and safety of IVTA and IVB as adjunctive treatments to PRP in reducing PRP-related vision loss and macular oedema. During the follow-up period, there was a significantly higher proportion of eyes with visual loss and increased CMT in the PRP group than in the IVTA and IVB groups, and there was a significantly lower proportion of eyes with visual gain and decreased CMT in the PRP group than in the IVTA and IVB groups. This result suggests that both IVTA and IVB may be effective as adjunctive treatments to PRP in the prevention or improvement of visual loss and PRP-induced macular oedema in the short term.

In eyes with CSME, there were significant changes in mean BCVA, and the proportion of visual gain and eyes with decreased CMT were significantly higher in the IVTA group than in the IVB group. These results demonstrated that IVTA had better efficacy in relation to visual gain and reduction of PRP-induced macular oedema than IVB. The results of our study are consistent with those of previous studies, which compared the effects of IVTA and IVB in diabetic macular oedema.^{28 29} Better results for IVTA in reducing macular oedema and in the improvement of BCVA than that for bevacizumab suggest that the pathogenesis of PRP-induced macular oedema is not only attributable to VEGF dependency, but is also attributable to other mechanisms suppressed by corticosteroids.

Diabetic macular oedema results from the breakdown of the blood-retina barrier and increased vascular permeability over the compensatory ability of retinal pigment epithelium (RPE). Theoretically, pre-existing macular oedema prior to PRP results in overburdened RPE, so PRP could aggravate macular oedema. However, if there is no macular oedema prior to PRP, it is hard to predict accurately whether the load resulting from PRP will

exceed the remaining function of RPE or not. Hence, presence of CMSE may be a primary yardstick for judging the treatment needed. If CSME has already developed in patients who need PRP, IVTA, with the more potent effect of resolving macular oedema, is more appropriate than IVB. However, the risk of IOP elevation associated with IVTA has been reported in previous studies.^{14 30} In our study, there were only four eyes with increased IOP in the IVTA group, although IOP was normalised with topical glaucoma medications. In our study, there was one eye with cataract progression, despite receiving just a single injection. Although there were no significant differences in IOP elevation and cataract progression between two groups in this study, the risks involved with IVTA treatment can limit its use. In this situation, IVB may be a better treatment option for steroid-responders and phakic patients.

It has been reported that about 60% of patients with PDR respond to PRP with regression of NV within 3 months of treatment according to ETDRS guidelines.^{31 32} However, many of the patients in our study, especially in the IVB group, showed complete regression of NV within 3 months of follow-up period, although the statistical analysis was not performed. Regression of NV might result from the pharmacological inhibition of triamcinolone acetonide or bevacizumab in conjunction with PRP. Tonello *et al*²⁵ have already reported that the adjunctive use of IVB with PRP was associated with a greater reduction in the area of active leaking NV than PRP alone in patients with high-risk PDR. Francesco *et al*¹⁵ also reported a beneficial effect of IVTA before PRP for deducing NV. Long-term follow-up studies with statistical analysis will be required to compare the beneficial effects of IVTA and IVB reducing NV and to elucidate the reactivation of NV.

In conclusion, IVTA and IVB are effective as adjunctive treatments to PRP, minimising the risk of macular oedema and

Clinical science

Figure 3 The proportions of eyes with visual gain or visual loss at 3 months in eyes with clinically significant macular oedema (CSME): (A) the proportions of eyes with visual gain ≥ 0.1 minimum angle of resolution (logMAR) and visual gain ≥ 0.2 logMAR; (B) the proportions of eyes with visual loss ≥ 0.1 logMAR and visual loss ≥ 0.2 logMAR. In eyes without CSME: (C) the proportions of eyes with visual gain ≥ 0.1 logMAR and visual gain ≥ 0.2 logMAR; (D) the proportions of eyes with visual loss ≥ 0.1 logMAR and visual loss ≥ 0.2 logMAR. IVB; intravitreal bevacizumab, IVTA; intravitreal triamcinolone acetate; PRP, panretinal photocoagulation. * $p < 0.05$, ** $p < 0.01$.

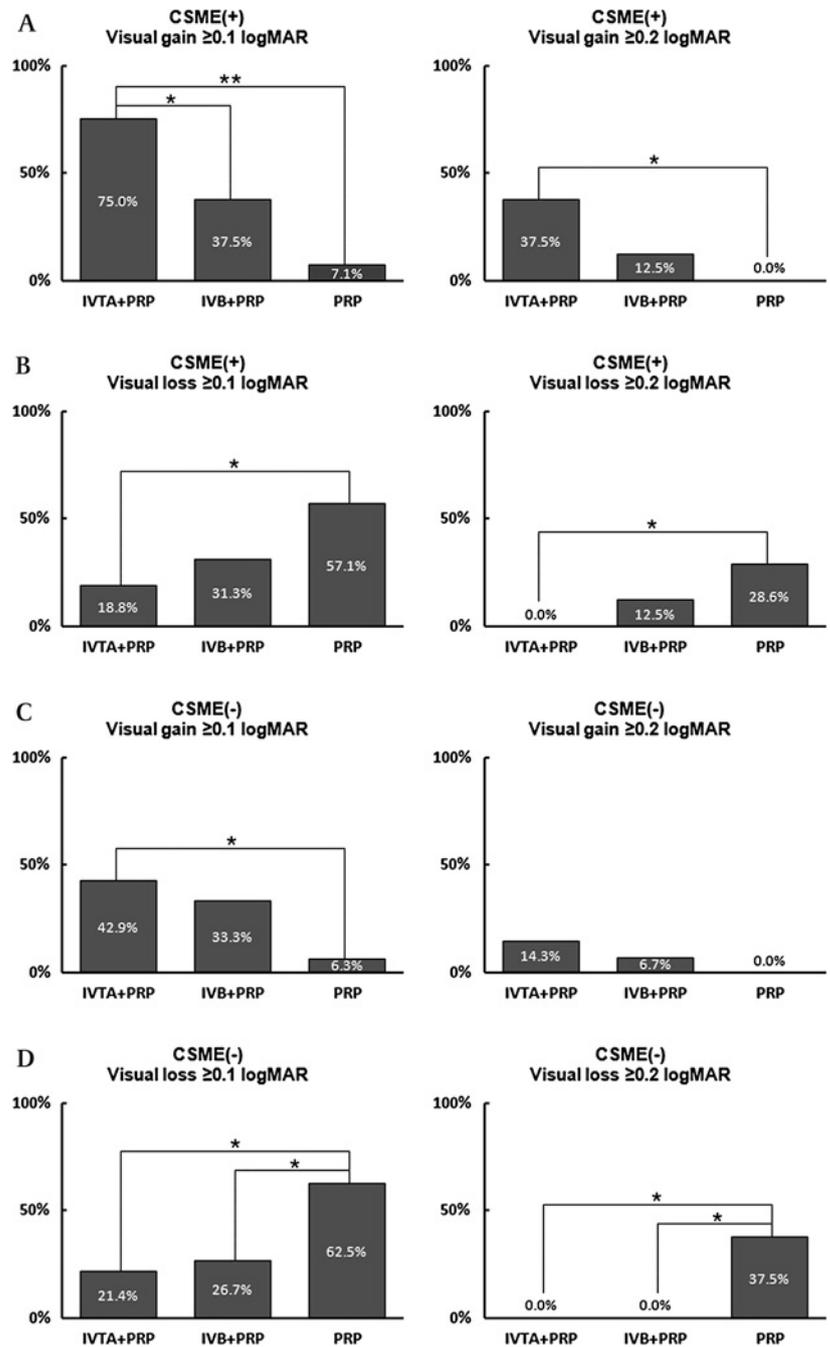
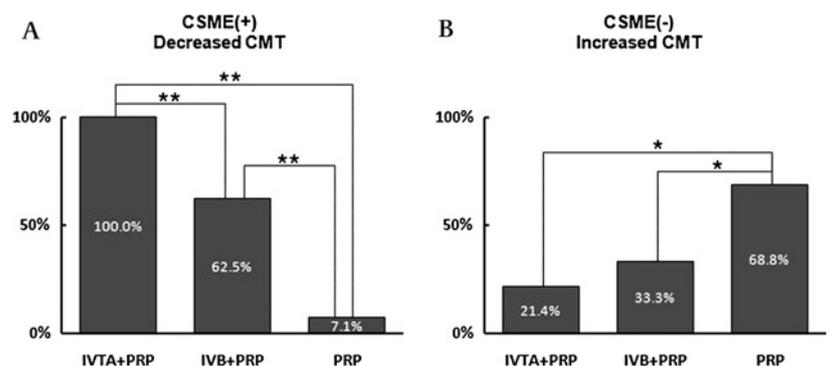


Figure 4 (A) The proportions of eyes with decreased central macular thickness (CMT) at 3 months in eyes with clinically significant macular oedema (CSME). (B) The proportions of eyes with increased central macular thickness at 3 months in eyes without CSME. IVB; intravitreal bevacizumab, IVTA; intravitreal triamcinolone acetate; PRP, panretinal photocoagulation. ** $p < 0.05$, ** $p < 0.01$.



visual loss. IVTA is more effective than IVB in improving visual acuity and macular oedema in eyes with CSME, while both IVTA and IVB are effective in preventing visual loss and macular oedema in eyes without CSME. In patients with cataract or glaucoma, IVB can be another treatment option in conjunction with PRP.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Ethical Committee of Konkuk University College of Medicine. The study followed the tenets of the Declaration of Helsinki.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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