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ORIGINAL PAPER

Effects of kallidinogenase in patients undergoing vitrectomy for diabetic macular edema

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Abstract

Purpose To evaluate the effectiveness of the combination of vitrectomy with kallidinogenase for diabetic macular edema (DME).

Methods This study was designed as a prospective, randomized, multicenter study comparing 19 eyes of 19 patients who received 150 units of kallidinogenase administered a day for 52 weeks from the day after vitrectomy (study group) with 20 eyes of 20 patients who received no kallidinogenase (control group). The main outcome measurements included logMAR visual acuity and central foveal thickness (CFT) before surgery and at 3, 6, 9, and 12 months after vitrectomy.

Results During follow-up, 11 patients dropped out (six in the study group and five in the control group), leaving 28 eyes in 28 patients for analysis (13 in the study group and 15 in the control group). Visual acuity improved significantly at 12 months in both groups compared with before surgery. The degree of improvement did not differ significantly between the groups. At 12 months, the mean CFT decreased significantly in both groups, with no significant difference in the rate of change between the two groups. In the study group, the visual acuity and CFT significantly improved from 3 to 12 months and from 6 to 12 months, whereas these parameters did not continue to improve in the control group after 6 months (for visual acuity) or 3 months (for CFT).

Conclusion After vitrectomy for DME, visual acuity and CFT improved significantly in both groups, but only patients treated with kallidinogenase continued to have significant improvement throughout the study period.

Keywords Diabetic macular edema ·
Kallidinogenase · Central foveal thickness ·
Vitrectomy · Optical coherence tomography ·
Vascular endothelial growth factor

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Introduction

According to the International Diabetes Federation, the number of people with diabetes is estimated to exceed 400 million worldwide, with the prevalence expected to continue to increase year after year.

Diabetic retinopathy is one of the three major complications of diabetes. Diabetic retinopathy is a major cause of visual impairment in Japan [1]. Diabetic macular edema (DME) develops on the background of simple retinopathy and can cause moderate to severe visual impairment [2].

DME is thought to arise because of impaired retinal microcirculation that results in retinal ischemia, hypoxia, and the subsequent release of vascular endothelial growth factor (VEGF) and increased vascular permeability. Anti-VEGF drugs have been demonstrated to be effective in treating DME [3, 4], and they have in recent years become the first line of treatment. Other approaches include steroids and laser treatment, but some cases do not respond [5]. In large-scale clinical trials, the anti-VEGF medications have required frequent dosing, imposing a burden on patients who may find it difficult to persist with the treatment [6, 7].

Vitrectomy has also been performed to treat DME and appears to be particularly effective in cases with vitreomacular interface abnormalities [8–10]. It has been reported to benefit DME in patients with or without posterior vitreous detachment [11–14]. Yamamoto et al. attributed its utility to mechanisms such as decreased mechanical traction in the macular region, removal of VEGF in the vitreous cavity, and elevation of oxygen partial pressure in the vitreous cavity after vitrectomy [15]. However, they also noted that rapid disappearance of edema and recovery of visual acuity were not obtainable in all cases.

Recently, Suzuki and colleagues reported that oral administration of kallidinogenase alone was effective in improving central foveal thickness (CFT) in DME [16]. Kallidinogenase acts on plasma kininogen to liberate kinin, which is thought to improve microcirculation in the eye through the production of nitric oxide or prostaglandin. Kallidinogenase is used to improve disorders of retinal circulation, such as diabetic retinopathy [17].

In addition, kallidinogenase has been reported to have anti-VEGF activity [17–19]. In a rat model of streptozotocin-induced diabetes, Kato et al. reported that kallidinogenase significantly suppressed VEGF levels in the intraocular fluid as well as retinal vascular permeability [17].

Ise et al. reported on the effect of vitrectomy combined with kallidinogenase to treat DME. According to them, administration of kallidinogenase is useful to improve retinal morphology after vitrectomy and a synergistic effect with vitrectomy can be expected; however, it was a short study of only 6 months [20]. To clarify the effectiveness of this approach over a longer period, we conducted a multicenter, prospective, open-label, randomized controlled trial.

Subjects and methods

Subjects

Between August 2012 and December 2014, 39 patients underwent vitrectomy for DME at Tsukazaki Hospital and Hiroshima University Hospital. Vitrectomy was performed on cases resistant to drug therapy or laser treatment, cases in which medication could not be treated due to anamnesis, and cases with macular traction. A study group comprising 19 eyes of 19 patients was compared with a control group of 20 eyes of 20 patients. This study was approved at Tsukazaki Hospital and Hiroshima University Hospital with approval by each Ethics Committee, and all patients gave written informed consent.

Using simple randomization, patients were assigned either to the study group, with oral administration of 50 units of kallidinogenase three times a day after every meal for 12 months from the day after surgery, or to the control group, treated with surgery alone.

Surgery

Pars plana vitrectomy was performed using a 23-gauge or 25-gauge system, and the phakic eye received surgery when simultaneous cataract surgery was required. In all cases, internal limiting membrane exfoliation was performed. Air tamponade was carried out as necessary. Neither gas such as C3F8 nor silicone oil was used in case. During surgery, 1 mg triamcinolone was used only for vitreous dyeing purposes. Triamcinolone was eliminated as much as possible during surgery. After surgery, no additional treatment for DME, such as anti-VEGF drugs or macular photocoagulation, was given.

Outcomes

The outcomes of the study were logMAR visual acuity and CFT. They were evaluated preoperatively, and at 3, 6, 9, and 12 months after vitrectomy. CFT was the distance from the foveal retinal surface layer of the fovea to the retinal pigment epithelium of the image measured using optical coherence tomography (OCT, SPECTRALIS OCT, Heidelberg Engineering Company or RTVue OCT, Optovue). Images were taken in 3D mode with center 6 mm × 6 mm for SPECTRALIS OCT and in 6 mm × 6 mm cross-mode for RTVue OCT.

Patients were excluded from the study if they had previously experienced severe adverse reactions to kallidinogenase, had a recent history of hemorrhage, had been treated with kallidinogenase within 1 month before vitrectomy, had an HbA1c of 10% or more, were on dialysis, used steroids or anti-VEGF drugs within 3 months before surgery, had a grade III or higher cataract by the Emery-Little classification, had a history of intraocular surgery other than cataract surgery, were pregnant or breastfeeding, or if their physician considered it inappropriate for them to participate in the study.

Statistical analysis

Differences between the two groups were evaluated with Tukey's honestly significant difference test using SAS software, JMP 10. Data are reported as mean ± SE. A P value of < 0.05 was considered to indicate a significant difference.

Results

Of the original 39 patients in the study, 28 were available for final analysis (13 in the study group and 15 in the control group). The other 11 patients did not complete the study, six because of loss to follow-up, two who developed exclusion criteria during the study, two with other illnesses that prevented the continuation of kallidinogenase administration, and one who died during follow-up.

Cataract surgery was performed in eight of the 13 patients in the study group and seven of the 15 patients in the control group.

Macular traction or thick posterior hyaloid was observed in seven of the 13 patients in the study group and nine of the 15 patients in the control group. We detected the presence of macular traction using the OCT image.

The distribution of the retinopathy stage in the groups is as follows. In study group, eight cases were proliferative and five were nonproliferative. In the control group, nine cases were proliferative and six cases were nonproliferative.

The study group included six men and seven women and the control group five men and ten women. There were no significant differences between the groups in terms of age, preoperative visual acuity, preoperative CFT, HbA1c, or serum creatinine value (Table 1). During the study period, there were no serious adverse reactions due to kallidinogenase.

Changes in visual acuity

Although we excluded patients with advanced cataract, those with mild cataract underwent cataract surgery at the same time as vitrectomy, which might have affected visual acuity.

At each postoperative evaluation, the mean visual acuity in the study group improved significantly from the preoperative value (Table 2). The differences in the mean visual acuity between 3 and 12 months ($P = 0.002$) and 6 and 12 months ($P = 0.02$) were also significant.

In the control group, significant improvement was noted at 6 months after surgery (Table 3), but the visual acuity in this group did not continue to improve significantly after that (3 vs. 12 months, $P = 0.29$; 6 vs. 12 months, $P = 0.39$).

The mean visual acuities of the two groups did not differ significantly from each other preoperatively or at any of the postoperative evaluations (preoperative, $P = 0.71$; 3 months, $P = 0.86$; 6 months, $P = 0.82$; 9 months, $P = 0.70$; 12 months $P = 0.51$; Figs. 1, 2).

Changes in CFT

The mean CFT of the study group showed a continual decrease over the study period (Table 4). In addition, it improved significantly between 3 and 12 months ($P = 0.003$) and 6 and 12 months ($P = 0.02$) postoperatively.

Table 1 Patients with diabetic macular edema before vitrectomy

| Item	Study group (mean ± SE) n = 13	Control group (mean ± SE) n = 15	P value
Age (years)	65.0 ± 10.8	67.5 ± 5.5	0.43
Preoperative visual acuity (logMAR)	0.62 ± 0.10	0.67 ± 0.11	0.09
Preoperative CFT (μm)	540.7 ± 50.4	553.9 ± 43.9	0.84
HbA1c NGSP (%)	6.70 ± 0.15	7.20 ± 0.24	0.71
Serum creatinine (mg/dl)	0.93 ± 0.11	0.88 ± 0.09	0.73

There was no significant difference in the patient background before surgery with Tukey's honestly significant difference (HSD) test

Table 2 Mean visual acuity in the study group

	Before surgery	3 months	6 months	9 months	12 months
Visual acuity	0.62 ± 0.10	0.47 ± 0.12	0.43 ± 0.10	0.40 ± 0.10	0.35 ± 0.09
P value		0.02	0.01	0.0004	< 0.001

Table 3 Mean visual acuity in the control group

	Before surgery	3 months	6 months	9 months	12 months
Visual acuity	0.67 ± 0.11	0.49 ± 0.10	0.47 ± 0.10	0.46 ± 0.11	0.44 ± 0.11
P value		0.06	0.03	0.02	0.02
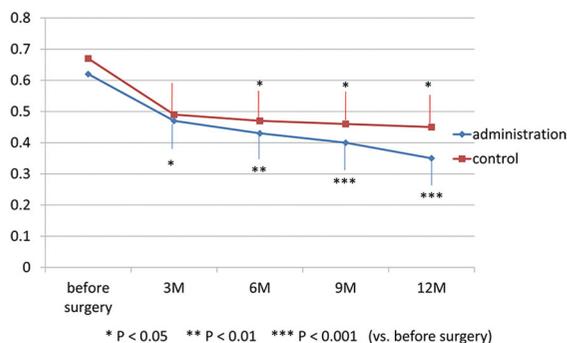
Fig. 1 Visual acuity by logMAR

The mean CFT of the control group was as shown in Table 5. Although the decrease between the preoperative and the 3-month postoperative value was significant, there was no further significant decrease (3 vs. 12 months, $P = 0.78$; 6 vs. 12 months, $P = 0.65$).

As with visual acuity, the mean CFT values did not differ between the two groups either preoperatively ($P = 0.84$) or at any of the postoperative evaluations
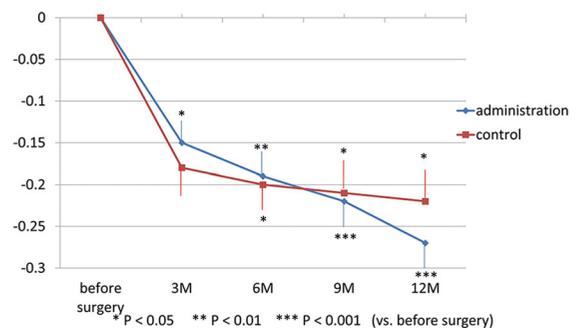
Fig. 2 Degree of change in visual acuity by logMar

(3 months, $P = 0.57$; 6 months, $P = 0.86$; 9 months, $P = 0.59$; 12 months, $P = 0.11$; Figs. 3, 4).

Discussion

In our randomized controlled trial, we did not observe any significant difference in visual acuity and CFT changes with oral administration of kallidinogenase in
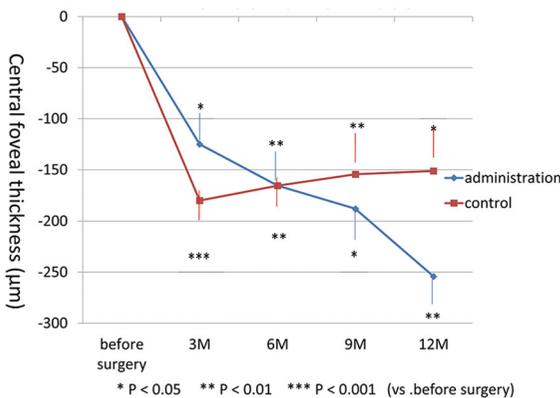
Table 4 Mean CFT in the study group

	Before surgery	3 months	6 months	9 months	12 months
CFT (μm)	541 ± 50	415 ± 56	375 ± 53	352 ± 73	286 ± 38
P value		0.04	0.005	0.02	0.001

Table 5 Mean CFT in the control group

	Before surgery	3 months	6 months	9 months	12 months
CFT (μm)	554 ± 44	374 ± 46	388 ± 53	399 ± 51	403 ± 57
P value		0.0005	0.003	0.008	0.01
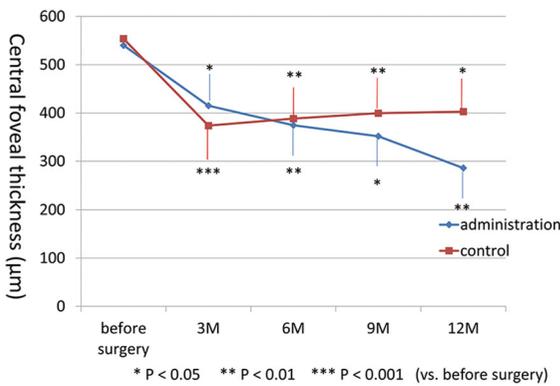
Fig. 3 Central foveal thickness

Fig. 4 Degree of change of central foveal thickness

the 12 months following vitrectomy, although the differences in the mean values did appear to become greater. Values for both outcomes continued to improve significantly at each postoperative evaluation in the study group but not in the control group.

In 1992, Lewis and colleagues reported the effectiveness of vitrectomy for DME that was caused by traction by thickened posterior vitreous membranes [8]. This procedure has, therefore, continued to be recommended for DME [21]. However, some reports suggest that the effect of surgery is observed only in cases with macular traction or with serous retinal detachment, and it does not appear to be uniformly successful [22–25]. There is, therefore, no definitive opinion on the effectiveness of vitrectomy for DME.

Currently, intravitreal administration of anti-VEGF drugs is the primary treatment for DME. However, in vitrectomized eyes, the effect of anti-VEGF drugs was diminished [26]. Vitreous injection is also accompanied by the risk of infection, is very expensive, and places a substantial burden on patients [27].

Kallidinogenase is used by ophthalmologists to improve choroidal circulation in such disorders as retinal vein occlusion and diabetic retinopathy. Kato et al. reported that kallidinogenase significantly suppresses an increase in the VEGF content in intraocular fluid and retinal vascular permeability in diabetic rats [17]. Fukuhara and colleagues reported that kallidinogenase fragmented recombinant VEGF-164 in a murine model of choroidal neovascularization model mice [19]. Because kallidinogenase is a drug that can be delivered long term by oral administration, it is an attractive treatment option for a chronic disease such as DME.

As noted above, Suzuki and colleagues reported a prospective trial of oral kallidinogenase for 28 patients

(33 eyes) with DME, reporting that CFT decreased significantly 3 months beginning kallidinogenase [16]. Ise et al. prospectively examined the effect of oral kallidinogenase on vitrectomy in 25 eyes of 25 patients with DME but found no significant difference in CFT after 6 months between patients treated with kallidinogenase and controls who only underwent vitrectomy. They reported that CFT improved continuously over the study period only in the oral administration group, suggesting that administration of kallidinogenase is useful to improve retinal morphology after vitrectomy and that a synergistic effect with vitrectomy can be expected [20].

In our study, we did find a continuous improvement in visual acuity and CFT in the study group, demonstrating that kallidinogenase was associated with long-term improvement. Similar to the results of Ise and colleagues, the CFT in the control group decreased significantly at 3 months after surgery, but no further improvement was observed thereafter, in contrast to the continued improvement in the study group. Although we could not demonstrate statistically significant differences between the two groups over time, our results suggest that long-term administration of kallidinogenase might indeed have a synergistic effect with vitrectomy. It may be that a similar study over a longer period and with a larger study population would demonstrate a significant difference.

Our study may, therefore, be limited both by its relatively small size and the length of follow-up. Also, because it was a multicenter study, different surgeons operated on the patients; therefore, the surgical technique, such as the degree of internal limiting membrane peeling and the number of laser irradiations, may have differed. This might have affected the vitrectomy results.

Although we could not demonstrate statistically significant differences between the two groups, the fact that significant improvement throughout the study period was seen in patients receiving oral kallidinogenase is very suggestive that its effects persist over time. We, therefore, believe further study with longer follow-up, and a larger study population is warranted.

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