황반하출혈의 망막하 Tenecteplase 주입술

Subretinal Tenecteplase Injection for Submacular Hemorrhage in Age-related Macular Degeneration

김양재, 김주영, 성산, 유용성, 권오웅, 김순현

Yang Jae Kim, Ju Young Kim, San Seong, Yong Sung You, Oh Woong Kwon, Soon Hyun Kim

누네안과병원 망막센터

Retina Center, Nune Eye Hospital, Seoul, Korea

Purpose: To investigate the efficacy and safety of a surgical procedure with subretinal tenecteplase (TNK) injection for displacement of thick submacular hemorrhage in patients with age-related macular degeneration (AMD).

Methods: A retrospective, non-comparative, interventional case study was conducted. Medical records of patients with submacular hemorrhage secondary to AMD who underwent subretinal TNK injection were reviewed. Best-corrected visual acuity (BCVA) and spectral domain optical coherence tomography (SD-OCT) at baseline, 1 month, 3 months, and final follow-up after initial treatment were measured. Postoperative complications were identified.

Results: Eleven eyes of eleven patients who underwent subretinal TNK injection for submacular hemorrhage were included. Mean BCVA at baseline was 1.85 ± 0.90 logarithm of the minimum angle of resolution (logMAR), which improved to 1.17 ± 0.63 logMAR at 3 month follow-up and 0.94 ± 0.58 logMAR at final follow-up ($p = 0.011$). SD-OCT results, including central foveal thickness ($495.7 \pm 410.7 \mu\text{m} \rightarrow 230.5 \pm 166.4 \mu\text{m}$) and submacular hemorrhage thickness ($263.3 \pm 196.0 \mu\text{m} \rightarrow 0 \mu\text{m}$), significantly improved ($p = 0.028$). Complications included retinal detachment ($n = 2$), epiretinal membrane ($n = 1$), and vitreous hemorrhage ($n = 1$).

Conclusions: Vitrectomy with subretinal TNK injection may be a good treatment option for displacement of submacular hemorrhage leading to functional and anatomical improvement.

Keywords: Age-related macular degeneration; Submacular hemorrhage; Subretinal injection; Tenecteplase (TNK)

Introduction

The natural prognosis of submacular hemorrhage resulting from age-related macular degeneration (AMD) is generally poor [1-4]. Submacular hemorrhage interferes with retinal function through several mechanisms. Iron released from hemoglobin is toxic to retinal microcirculation and choriocapillaris. Shearing forces exerted by the contracting clot are

involved in photoreceptor damage. Thick hemorrhages are physical barriers to the exchange of nutrients, oxygen, and metabolites between photoreceptors and the choroid [5,6].

Several procedures have been proposed to displace submacular hemorrhage away from the fovea, including pneumatic displacement with or without tissue plasminogen activator (tPA) [7-9], pars plana vitrectomy (PPV) with subretinal tPA [10-12], and intravitreal anti-vascular endothelial growth

Address reprint requests to Soon Hyun Kim, MD, PhD

Retina Center, Nune Eye Hospital, #404 Seolleung-ro, Gangnam-gu, Seoul 06198, Korea
Tel: 82-2-1661-1175, Fax: 82-2-2086-7779
E-mail: kim1441@gmail.com

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factor (VEGF) injection with or without pneumatic displacement [13,14]. However, there remains no gold standard treatment for submacular hemorrhage in AMD.

tPA is a recombinant plasminogen activator that binds to the fibrin component of thrombus. It converts bound plasminogen to plasmin to initiate local fibrinolysis. As mentioned earlier, tPA has been used to facilitate clearance of submacular hemorrhage [8-14]. However, dose-dependent retinal toxicity in animal and human eyes have been reported with tPA [15-18].

More recently, a new third-generation thrombolytic agent, tenecteplase (TNK, Metalyse; Boehringer Ingelheim, Ingelheim, Germany), has been developed to overcome the limitations of tPA. TNK has a 6-fold prolonged plasma half-life, 15-fold higher fibrin specificity, and 80-fold reduced binding affinity to physiological plasminogen activator inhibitor (PAI-1) [19]. Another advantage of TNK is that its vehicle has less than one-third of the potentially toxic L-arginine content than the equivalent dose of tPA [20]. The penetration and toxicity of TNK has been reported in previous studies [20-23]. We recently reported a case of thick submacular hemorrhage resulting from polypoidal choroidal vasculopathy (PCV) that was successfully treated with subretinal TNK injection [24].

We previously reported the result of intravitreal TNK injection for acute submacular hemorrhage [25]. Even though it is an effective and safe treatment strategy, submacular hemorrhage is not removed by intravitreal pharmacological injection with gas tamponade followed by additional intravitreal injections in some patients. The objective of this study was to evaluate the efficacy and safety of PPV with subretinal TNK injection for submacular hemorrhage resulting from AMD in these patients.

Materials and Methods

We performed a retrospective case series study for eleven eyes from eleven patients who underwent PPV with subretinal TNK injection for submacular hemorrhage secondary to AMD at Nune Eye Hospital (Seoul, Korea) from November 2010 to August 2015. This study adhered to the ethical standards in the Declaration of Helsinki. Subretinal TNK injection for submacular hemorrhage secondary to AMD was approved by the Nune Eye Hospital Institutional Review Board

(IRB No. 2010-NEH-001). Informed consent was obtained from all individual participants included in the study.

The inclusion criteria were as follows: 1) patients without displacement of subretinal hemorrhage in macula 1-2 weeks after previous intravitreal TNK injection with pneumatic displacement for submacular hemorrhage and/or previous anti-vascular endothelial growth factor (VEGF) agent injection for AMD, 2) patients who had significant vitreous hemorrhage and submacular hemorrhage in AMD diagnosis, and 3) patients who were followed up for at least 5 months after PPV with subretinal TNK injection. Patients with submacular hemorrhage secondary to any condition other than AMD were excluded from this study. Patients with evidence of end-stage AMD with severe scarring or atrophy at initial presentation and those with duration of symptoms resulting from submacular hemorrhage longer than one month or who had eyes with an old, whitish discolored submacular hemorrhage were also excluded. In addition, patients who had previously undergone ocular trauma, PPV, or ocular surgery except cataract surgery were also excluded.

All patients received comprehensive ophthalmic examinations, including anterior segment examination and dilated biomicroscopic fundus examination. Best-corrected visual acuity (BCVA) was determined using a Snellen visual acuity (VA) chart. Patients who could not visualize the largest Snellen line were shown a 10/400 eye chart at a shorter test distance and then successively asked to count fingers or determine hand movements under bright illumination. BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. According to the Holladay method, hand movement was set at 3.0, and counting fingers at 2.0 [26]. Color fundus photography and fluorescein angiography (FA) with indocyanine green angiography (ICGA) (Spectralis HRA; Heidelberg Engineering; Heidelberg, Germany) were performed before vitrectomy with subretinal TNK injection. Spectral-domain optical coherence tomography (SD-OCT, Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) was performed before surgery and during follow-up visit. In eyes without a view of the retina because of vitreous hemorrhage, B-scan ultrasonography was used to identify the extent of hemorrhage.

Diagnosis for neovascular AMD and submacular hemorrhage were based on the results obtained from FA and ICGA at either initial presentation or after the resolution of submacular hemorrhage. Patients were classified as PCV or

typical exudative AMD. PCV was diagnosed based on ICGA findings, the presence of a branched vascular network, and evidence of terminal polypoidal lesions. Other cases were classified as typical exudative AMD.

Operations were performed by experienced vitreoretinal surgeons (Y.S.Y, O.W.K, and S.H.K). Patients with a visually significant cataract precluding adequate intraoperative visualization underwent phacoemulsification. PPV and posterior vitreous detachment formation were performed using an Alcon Accurus or Constellation 23-gauge system (Alcon Laboratories, Fort Worth, TX, USA). TNK was diluted with buffered saline solution (100 µg/0.1 mL) (concentration was based on previous reports by Rowley et al. [20] and McAllister et al. [27] and our previous report [24]) and injected into the subretinal space via a 40-gauge needle to create bullous retinal detachment of the posterior pole. Retinal detachment induced by subretinal injections of TNK involved the fovea. Partial or total air/fluid exchange was performed. C3F8 gas or silicone oil was used for tamponade. Thereafter, the face-down position was maintained for 48 hours.

The main outcome measures included BCVA, central foveal thickness (CFT), thickness of submacular hemorrhage, and the extent of submacular hemorrhage at baseline, 1 month, 3 months, and final follow-up after initial operation. CFT was defined as the distance between the internal limiting membrane and the Bruch membrane at the foveal center. The thickness of submacular hemorrhage was defined as the distance between the inner segment–outer segment line and the inner border of RPE. The extent of hemorrhage was measured in square millimeters on a reference scan image obtained with SD-OCT using built-in caliper function. All measurements were conducted by a single retinal specialist (J.Y.K).

Statistical analyses were performed with a commercially available software package (PASW Statistics v. 18.0; IBM Corp., Armonk, NY, USA). Wilcoxon's matched pairs signed ranks test was used to compare BCVA between baseline and postoperative time points (1 month, 3 months, and final follow-up). Additional analysis was conducted for six patients whose submacular hemorrhage size and thickness could be identified preoperatively. A Wilcoxon signed rank test was performed to determine changes in the size and the thickness of submacular hemorrhage. Statistical significance was defined as a *p*-value less than 0.05.

Table 1. Summary of patient characteristics

Case No./ Age/Sex	Dx	VH	SMH duration (day)	Amount of TNK (mL)	Tamponade	Preop Tx	Preop VA (logMAR)	Postop 3 months VA (logMAR)	Final VA (logMAR)	F/U duration (months)	Postop anti-VEGF injection
1/62/M	PCV	(+)	27	0.05	SO	(-)	3	2	1.4	5	2
2/68/F	CNV	(-)	10	0.05	C3F8	A + TNK + gas	1.3	1.3	1.4	47	4
3/65/M	PCV	(+)	19	0.05	C3F8	(-)	3	2	1.4	30	6
4/62/M	CNV	(-)	13	0.05	C3F8	L + TNK + gas	1.4	1	0.52	13	7
5/58/M	PCV	(+)	10	0.05	C3F8	TNK + gas	3	1.3	1	14	0
6/57/F	PCV	(-)	21	0.05	C3F8	A	0.7	0.1	0	27	10
7/69/F	CNV	(-)	30	0.05	C3F8	A + TNK + gas	1.6	0.52	0.52	23	17
8/66/M	PCV	(-)	20	0.05	C3F8	A + TNK + gas	0.4	0.7	0.4	5	0
9/52/F	PCV	(+)	22	0.05	SO	(-)	2	2	2	10	0
10/76/F	CNV	(-)	28	0.05	C3F8	L + TNK + gas	2	1	0.7	7	0
11/69/F	CNV	(+)	3	0.05	C3F8	(-)	2	1	1	7	9

Dx = diagnosis; VH = vitreous hemorrhage; SMH = submacular hemorrhage; TNK = tenecteplase; Preop = preoperative; Tx = treatment; VA = visual acuity; Postop = postoperative; F/U = follow up; VEGF = vascular endothelial growth factor; M = male; F = female; PCV = polypoidal choroidal vasculopathy; CNV = choroidal neovascularization; SO = silicone oil; A = Avastin (bevacizumab); L = Lucentis (ranibizumab).

Results

Eleven eyes of 11 patients who underwent surgery for submacular hemorrhage were included. There were 5 men (45.5%) and 6 women (54.5%). They had a median age of 65 years, ranging from 52 to 76 years. Three eyes (27.3%) had been previously treated with intravitreal anti-VEGF injections for neovascular AMD. The median number of previous injections in these eyes was 20, ranging from 2 to 42. There were nine phakic eyes and two pseudophakic eyes.

The median time between onset of symptoms and surgery was 20 days, ranging from 3 to 30 days. Six eyes had been previously treated with intravitreal TNK injection (50 µg/0.05 mL) with C3F8 gas injection (0.3 mL) for submacular hemorrhage. There were five eyes with vitreous hemorrhage. Procedures performed during initial surgery included subretinal injection of TNK (n = 11), C3F8 gas tamponade (n = 9), silicone oil tamponade (n = 2), intravitreal bevacizumab injection (n = 5), and cataract extraction (n = 8).

Median follow-up time was 13 months, ranging from 5 to 47 months. During postoperative follow-up, 8 (72.7%) patients received additional intravitreal anti-VEGF injections. The median number of additional postoperative injections in these patients was 4, ranging from 2 to 17. Five eyes (45.5%) were diagnosed with typical neovascular AMD and six eyes (54.5%) were diagnosed with polypoidal choroidal vasculopathy (PCV) (Table 1). Mean BCVA of all eyes at baseline was 1.85 ± 0.90 logMAR, ranging from 0.4 to 3.0 logMAR. Mean BCVA at 1 month after initial surgery was 1.49 ± 0.68 logMAR, ranging from 0.15 to 2 logMAR. Mean BCVA at 3 months after surgery was 1.17 ± 0.63 logMAR, ranging 0.1 to 2.0 logMAR. At final follow-up, mean BCVA was 0.94 ± 0.58 logMAR, ranging from 0 to 2.0 logMAR. BCVA was significantly improved at 1 month ($p = 0.049$), 3 months ($p = 0.010$), and final follow-up ($p = 0.011$) after the initial operation. Eight of 11 eyes had improved BCVA.

In six eyes that were available for SD-OCT preoperatively, mean CFT, mean thickness of submacular hemorrhage, and mean extent of submacular hemorrhage were 495.7 ± 410.7 µm, 263.3 ± 196.0 µm, and 28.7 ± 24.8 mm², respectively. At one month after the initial operation, mean CFT, mean thickness of submacular hemorrhage, and mean extent of submacular hemorrhage were 210.2 ± 123.5 µm, 52 ± 66.7 µm, and 3.81 ± 6.99 mm², respectively. At 3 months after the initial operation, mean CFT was 230.5 ± 166.4 µm, with clearly re-

Table 2. Summary of OCT data of submacular hemorrhage without vitreous hemorrhage cases

Case No.	Extend of Preop SMH (mm ²)	Preop SRHT (µm)	Preop CFT (µm)	Extend of SMH at Postop 1 month (mm ²)	SRHT at Postop 1 month (µm)	CFT at Postop 1 month (µm)	Extend of SMH at Postop 3 months (mm ²)	SRHT at Postop 3 months (µm)	CFT at Postop 3 months (µm)
2	31.39	593	864	3.78	180	441	0	0	481
4	3.74	231	260	0.64	47	124	0	0	73
6	35.59	400	1,159	0	0	211	0	0	217
7	4.25	101	234	0.64	52	127	0	0	97
8	71.11	114	206	0	0	121	0	0	132
10	26.09	141	251	7.78	33	237	0	0	383

OCT = optical coherence tomography; Preop = preoperative; SMH = submacular hemorrhage; SRHT = thickness of subretinal hemorrhage; CFT = central foveal thickness; Postop = postoperative.

solved submacular hemorrhage. At the final follow-up, mean CFT was $193.7 \pm 86.4 \mu\text{m}$. CFT was decreased significantly at 1 month ($p = 0.028$), and 3 months ($p = 0.028$) after the initial operation. However, it did not change significantly at final follow-up ($p = 0.116$). The thickness of submacular

hemorrhage and extend of submacular hemorrhage were significantly decreased at 1 month (both $p = 0.028$), and 3 months ($p = 0.028$, $p = 0.027$, respectively) after the initial operation (Table 2, Fig. 1).

Following surgery, VA remained stable or deteriorated in 3 (27.3%) patients and was improved by at least 1 line in 8 (72.7%) patients. Complications in the study included retinal detachment ($n = 2$, 18%), epiretinal membrane ($n = 1$, 9%), vitreous hemorrhage ($n = 1$, 9%), and recurrent submacular hemorrhage ($n = 1$, 9%) (Table 3).

Discussion

tPA has been used to treat submacular hemorrhage [8-12]. However, tPA has not been shown to penetrate the retina in experimental studies, and there are reports of tPA dose-related retinal toxicity [15-18]. Johnson and colleagues reported dose-related retinal toxicity of tPA in rabbits [15]. They suggested that the L-arginine vehicle in the commercially available solution rather than tPA itself was responsible for the retinotoxicity. It has been reported that tPA can increase N-Methyl-D-aspartate (NMDA)-induced retinal cell damage [28,29]. Chen et al. reported that the toxicity of tPA in human eyes can induce diffuse RPE perturbations, poor recovery of visual acuity, and decreased photopic and scotopic a-waves and b-waves in the electroretinogram (ERG) [17].

TNK is a variant of tPA that was produced by recombinant DNA technology after tPA underwent multiple point mutations. This new thrombolytic agent was developed to overcome several tPA limitations for treating myocardial infarctions. Compared to tPA, TNK has a longer half-life and greater fibrin specificity with greater efficacy in thrombus

Figure 1. Illustrative case. Fundus photography (A) and spectral-domain optical coherence tomography (SD-OCT) (B) of submacular hemorrhage in case 7 at first visit before intravitreal tenecteplase (TNK) and avastin injection with gas tamponade. One week after the primary treatment, fundus photography (C) and SD-OCT (D) of the left eye of case 7 showed aggravated submacular hemorrhage. Post-operative fundus photography (E) and SD-OCT (F) taken 3 months after vitrectomy with subretinal TNK injection showed that the submacular hemorrhage had mostly disappeared.

Table 3. Summary of postoperative complications

Case No.	Cx	Secondary procedure	Term between primary operation and secondary procedure
2	VH	TPPV	6 weeks
5	RD	SB + gas	2 months
6	ERM	TPPV + membranectomy + ILM	8 months
7	Submacular hemo	Intravitreal TNK + gas	7 months
9	RD	TPPV + SE + SO exchange + endolaser	5 weeks

Cx = complications; VH = vitreous hemorrhage; TPPV = trans pars plana vitrectomy; RD = retinal detachment; SB = scleral buckling; ERM = epiretinal membrane; ILM = internal limiting membrane; TNK = tenecteplase; SE = scleral encircling; SO = silicone oil.

dissolution [19]. Furthermore, the vehicle of TNK has less than one-third of the L-arginine content used for tPA. These characteristics could provide significant advantages for treatment of submacular hemorrhage [20]. In human eyes, McAlister et al. reported that intravitreal TNK injection had a safe and favorable effect on submacular hemorrhage [22,23].

We recently reported a case of subretinal TNK injection in a submacular hemorrhage from PCV [24]. In this case, we identified the efficacy and safety of direct subretinal TNK injection for submacular hemorrhage secondary to PCV. The patient's vision fully recovered without retinal pigment epithelium change. Scotopic and photopic ERG showed no prolongation of implicit time with slightly decreased a-wave and b-wave amplitude.

Several studies have recently shown that anti-VEGF treatment with or without gas tamponade for submacular hemorrhage from neovascular AMD had positive results. Kim et al. reported that anti-VEGF monotherapy was a useful treatment option for exudative AMD accompanied by submacular hemorrhage [13]. Shin and colleagues have shown that anti-VEGF therapy with gas tamponade may yield better treatment outcomes than anti-VEGF monotherapy for eyes with thick subretinal hemorrhage [14]. However, surgery is unavoidable if there is accompanying vitreous hemorrhage or if pharmacological treatment with or without gas tamponade has failed.

In our clinic, the primary treatment for submacular hemorrhage from neovascular AMD is intravitreal TNK injection with C3F8 gas tamponade. Intravitreal TNK injection with gas tamponade may be an effective treatment for submacular hemorrhage [25]. However, submacular hemorrhage can remain in some patients at the macula or more severe submacular hemorrhage can be found even after primary intravitreal TNK and/or anti-VEGF injection with gas tamponade. In this study, 6 of 11 eyes received intravitreal TNK injection with C3F8 gas tamponade preoperatively. However, the results of intravitreal TNK injection in these cases were unsatisfactory. When intravitreal TNK injection with gas tamponade failed, surgery including pars plana vitrectomy, subretinal TNK injection, and gas tamponade may have good results. Therefore, in our clinic, indications for subretinal TNK injection for submacular hemorrhage include accompanying vitreous hemorrhage and unsatisfactory results from intravitreal TNK injection with gas tamponade.

A direct comparison between subretinal TNK and tPA

injection is difficult because different procedures are used in different cases. However, results of subretinal TNK injection in this study may not be inferior to previous results of subretinal tPA injection for submacular hemorrhage. In previous studies, improved visual acuity was observed in 45-82% of eyes after subretinal tPA injection [10,11,30]. In this study, 9 of 12 (75%) eyes had improved BCVA. In addition, submacular hemorrhage of all eyes improved 3 months after subretinal TNK injection. Complications in the study included retinal detachment (n = 2, 18%), epiretinal membrane (n = 1, 9%), vitreous hemorrhage (n = 1, 9%), and recurrent submacular hemorrhage (n = 1, 9%). Complications after subretinal TNK injection were similar to subretinal tPA injection complications reported in the literature. Surgical removal of submacular hemorrhage with tPA has been associated with significant complications, including retinal detachment (4.0-19.3%), vitreous hemorrhage (1.9-40%), and glaucoma (6%) [10,11,12,30]. Recurrence of submacular hemorrhage (5.9-27%) has also been reported [10,11,30].

This study has several limitations. First, it was a small, retrospective case series study without a control group. Second, although visual acuities were best corrected, Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuities were not available. Third, unlike our previous case report, we did not perform both preoperative and postoperative ERG for all cases. Therefore, we could not exactly evaluate the retinal toxicity of TNK. It was also difficult to discriminate the causes of complications between TNK and surgical technique. In addition, data obtained in this study were not from a single surgeon and that could be a confounding factor.

In conclusion, vitrectomy with subretinal TNK injection may be a good treatment option for submacular hemorrhage secondary to neovascular AMD if submacular hemorrhage has accompanying vitreous hemorrhage or if primary intravitreal pharmacological injection and/or gas tamponade is unsatisfactory. To our knowledge, this is the first study on the efficacy and safety of subretinal TNK injection for submacular hemorrhage. Large, long-term, prospective, and comparative clinical trials are needed to evaluate the efficacy and safety of this procedure in the future.

Conflicts of Interest

The authors have no conflicts to disclose.

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