Research Article

Current Trends in Ophthalmology

Simultaneous Angiography for the Anterior Segment and Posterior Fundus of Eyes with Anterior Segment Neovascularization using Heidelberg Retina Angiograph 2

Sakino Y*, Noda Y, Itotani M, Nakamuro T, Kiyosaki K, Yokoyama K and Kubota T

Department of Ophthalmology, Oita University Faculty of Medicine, Japan

*Correspondence: Yuji Sakino, Department of Ophthalmology, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu-shi, Oita 879-5593, Japan, Tel: +81-97-586-5904; Fax: +81-97-549-6043; E-mail: y-sakino@oita-u.ac.jp

Received date: November 29, 2018; Accepted date: December 31, 2018; Pub date: January 04, 2019

Abstract

Objective: To present a method of indocyanine green angiography (IA) and fluorescein sodium angiography (FA) for simultaneously evaluating anterior segment neovascularization and fundus abnormality.

Participants: We examined 19 eyes of 19 patients suspected of having neovascularization in the anterior segment of the eye. Seventeen eyes of 17 patients suffered from proliferative diabetic retinopathy, and two eyes of 2 patients had central retinal vein occlusion.

Methods: Using Heidelberg Retina Angiograph 2 (HRA2), we performed angiography of the anterior and posterior segment of the eye.

Results: Of the 19 cases, anterior segment neovascularization was clearly observed with slit-lamp examination and gonioscopy in 12 eyes (63.1%). However, anterior segment neovascularization was detected by HRA2 angiography in 18 eyes (94.7%). Posterior segment angiography revealed non-perfusion area in 16 eyes (84.2%) and retinal neovascularization in 10 eyes (52.6%). In one case, the posterior segment findings were not obtained due to vitreous hemorrhaging.

Conclusion: Simultaneous anterior and posterior segment HRA2 angiography using indocyanine green and fluorescein sodium is a useful technique for detecting neovascularization in the anterior segment of the eye as well as non-perfusion areas and neovascularization of the retina.

Keywords: Anterior segment angiography, Rubeosis, Neovascular glaucoma, Fluorescein sodium, Indocyanine green

Abbreviations: HRA: Heidelberg Retina Angiograph; NVG: Neovascular Glaucoma; VEGF: Vascular Endothelial Growth Factor; FA: Fluorescein Sodium Angiography; IA: Indocyanine Green Angiography; PDR: Proliferative Diabetic Retinopathy; VA: Visual Acuity; IOP: Intraocular Pressure; CRVO: Central Retinal Vein Occlusion; PRP: Pan-retinal photocoagulation; PPV: Pars Plana Vitrectomy; TLE: Trabeculectomy; IVR: Intravitreal Ranibizumab; IVB: Intravitreal Bevacizumab; IVA: Intravitreal Aflibercept; OD: Ophthalmic Drug; OM: Oral Medicine

Introduction

Neovascular Glaucoma (NVG) is a serious complication

associated with retinal ischemic disorders, such as diabetic retinopathy and central retinal vein occlusion. The etiology of intraocular pressure elevation in patients

with anterior segment neovascularization is thought to arise from aqueous flow blocking, which may be caused by the development of a fibrovascular membrane covering the anterior surface of the trabecular meshwork or by invasion of newly formed vessels to the intertrabecular spaces [1-3]. The detection of the fibrovascular membrane in the iris and iridocorneal angle is very important for early diagnosis of NVG. These patients sometimes receive treatments such as pan-retinal photoablation and intravitreal injection of anti-VEGF monoclonal antibody. However, the detection of the newly formed vessels in the anterior segment of the eye can be difficult in these patients when performing a slit lamp examination. Jensen et al. reported on the utility of fluorescein iris imaging for the early detection of newly formed vessels in diabetic patients [3]. Since then, anterior segment angiography had been reported to be useful for the early detection of newly formed vessels in the iris and iridocorneal angle [4-13]. Previous studies have reported that FA and IA in the anterior ocular segment are useful for studying the structure and hemodynamic of newly formed vessels [12,14,15]. This study was conducted to evaluate the usefulness of the simultaneous anterior and posterior ocular segment angiography using Heidelberg retina angiography 2 (HRA2) with FA and IA.

Materials and Methods

Study design: Cross sectional study

Nineteen eyes of 19 patients suspected of having neovascularization of the iris or iridocorneal angle associated with ischemic retinal disease were included in the study between July 2014 and July 2015. Thirteen patients were male, and six patients were female. The average age was 58.5 ± 10.9 years old (range: 38 -85 years old). In all patients, blood sampling was performed before the ocular fundus angiographic examination. No particular problems were seen in the kidney or liver function that might prevent performing the examination. The fundamental ischemic retinal diseases included proliferative diabetic retinopathy in 17 eyes and central retinal vein occlusion in 2 eyes. All of the patients underwent a complete ocular examination that evaluated the best-corrected visual acuity and intraocular pressure and included slit lamp biomicroscopy, gonioscopy, and a fundus examination. The mean intraocular pressure before treatment was 32.1 ± 15.3 mmHg (range: 8-63 mmHg). Glaucoma drugs had been used in 15 eyes, and retinal photoablation had been enforced in 17 eyes (Table 1).

Anterior and posterior segment angiography were

simultaneously performed using HRA2 (Heidelberg Engineering Company, Heidelberg, Germany). We used a mydriatic agent just before beginning angiography. Anterior segment angiography was first performed using 0.5% indocyanine green and 10% fluorescein sodium. We observed the presence of newly formed vessels on the pupillary region and the front iris through the center lens of the gonioscope, and observed the entire circumference of the iridocorneal angle through the lens of the gonioscope. After confirming mydriasis, the gonioscope was removed, and we observed the pathological changes to the posterior fundus. If necessary, contrast agents were additionally injected. The existence and area of the iris and iridocorneal angle neovascularization are described in table 2, along with the presence or absence of the non-perfusion area and neovascularization of the retina.

The study was approved by the institutional review board of Oita University Hospital, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. After the nature of the study was explained to the participants, informed consent was obtained from all individual participants included in the study.

Results

Table 1 shows the age, gender, right or left eye, causative disease, best-corrected visual acuity, intraocular pressure before therapy, treatment history, surgical procedure, and preoperative and postoperative use of glaucoma drugs for all 19 cases. We present a representative case in the figure 1 (case 18, 58 years old, female, PDR, right eye). The patient had been treated with pan-retinal photoablation because of proliferative diabetic retinopathy. She was referred to us because of elevated intraocular pressure. The findings of the slit-lamp examination showed unclear neovascularization of the iris and iridocorneal angle (Figure 1A and B). However, anterior segment angiography clearly revealed neovascularization in both (Figure 2). The retinal non-perfusion area and retinal neovascularization were not observed in either eye (Figure 3).

The findings of the iris and iridocorneal neovascularization of all cases are summarized in table 2. Using a slit-lamp examination, the new formation of vessels in the iris in the range of 1 quadrant or more was observed in 8 eyes (42.1%). Using gonioscopy, the new formation of vessels in the iridocorneal angle in the range of 1 quadrant or more was observed in 8 eyes (42.1%).

Table 1: Clinical characteristics of patients with suspected anterior segment neovascularization.

Case	Age	Gender	Eye	Causative disease	VA	IOP	Treatment history	Surgical procedure	Glaucoma drugs	
									Before surgery	After surgery
1	77	female	R	CRVO	1.5	20	none	PRP	none	none
2	41	male	L	PDR	2	45	PRP PPV IVR	PRP PPV	3 Ods OM	none
3	80	male	R	PDR	2	13	none	PRP	none	none
4	50	male	L	PDR	0.8	8	PRP	PRP	none	none
5	73	female	L	PDR	1.3	20	PRP	PRP	none	none
6	57	male	L	PDR	0.4	39	PRP	IVR PRP	2 ODs	none
7	60	male	R	PDR	1.4	48	PRP	IVR PRP PPV	1 OD OM	none
8	74	female	L	PDR	2.3	50	PRP	PRP TLE	3 Ods OM	none
9	62	male	R	PDR	1	31	PRP PPV IVB	PRP TLE	3 Ods OM	none
10	52	female	R	PDR	0.7	35	PRP	TLE	3 ODs	none
11	59	male	R	PDR	0.4	63	none	PRP PPV TLE	2 Ods OM	none
12	38	male	L	CRVO	2	38	PRP IVR	IVR PRP TLE	3 ODs	3 ODs
13	45	male	R	PDR	2	51	PRP	PRP TLE	1 OD	none
14	67	male	L	PDR	0	20	PRP	PRP	3 Ods OM	2 ODs
15	85	male	R	PDR	1.3	28	PRP	PRP TLE	4 Ods OM	none
16	75	male	L	PDR	0.3	24	PRP	PRP TLE	3 Ods OM	none
17	69	female	L	PDR	0.7	16	PRP PPV IVR	PRP TLE	3 ODs	none
18	58	female	R	PDR	0.2	43	PRP PPV IVB	IVR TLE	4 Ods OM	none
19	56	male	L	PDR	0.2	28	PRP	IVA PRP TLE	3 ODs	none

VA: visual acuity; IOP: intraocular pressure; PDR:proliferative diabetic retinopathy; CRVO:central retinal vein occlusion; PRP:Pan-retinal photoablation; PPV:pars plana vitrectomy; TLE:Trabeculectomy; IVR:intravitreal ranibizumab; IVB:intravitreal bevacizumab; IVA:intravitreal aflibercept; OD:ophthalmic drug, OM:oral medicine.

Table 2: Identification of rubeosis, retinal non-perfusion areas, and neovascularization.

Case	Rubeosis				Retinal abnormalities	
	Ophthalmoscope		Anterior segment angiography		Non-perfusion area	Neovascularization
	Iris	Iridocorneal angle	Iris	Iridocorneal angle		
1	tem	tem	all	all	+	+
2	none	sup inf	all	all	Invisible due to vitreous hemorrhage	
3	none	none	none	sup nas	+	-
4	tem	tem	tem	tem inf	+	+
5	none	all	all	all	+	-
6	all	all	all	all	+	+
7	none	none	all	all	+	+
8	all	all	all	all	+	-
9	tem nas	tem nas	all	all	+	+
10	none	none	none	none	-	-
11	all	all	all	all	+	+
12	sup nas	sup nas	all	all	+	+
13	tem	none	all	all	+	+
14	none	sup inf	all	all	+	+
15	none	none	all	all	+	+
16	none	none	all	all	+	-
17	none	none	all	all	+	-
18	none	none	all	all	-	-
19	none	tem inf	tem inf	tem inf	+	-

Sup: superior, neovascularization was observed in the superior quadrant area; inf: inferior; tem: temporal; nas: nasal; all: all quadrants; neovascularization was observed in all quadrants.

Figure 1: Case 18, 58 years old, anterior segment neovascularization associated with proliferative diabetic retinopathy. A: Iris rubeosis is unclear under a slit lamp examination in the right eye. B: Iridocorneal rubeosis is unclear with gonioscopy in the right eye.

Figure 2: Anterior segment angiography in the right eye. In IA (right), the entire blood vessel construction, including the healthy blood vessels are visualized. In FA (left), leakage from neovascularization can be clearly seen.

Figure 3: Neither the retinal non-perfusion area nor retinal neovascularization are seen in either eye.

Peripheral anterior synechia was observed in 6 eyes (31.5%). However, anterior segment angiography revealed neovascularization in 18 eyes (94.7%). Posterior segment angiography revealed retinal non-perfusion area in 16 eyes (84.2%) and retinal neovascularization in 10 eyes (52.6%). In one eye (Case 2), it was impossible to observe the posterior fundus due to vitreous hemorrhaging. We diagnosed neovascular glaucoma in 18 eyes and secondary angle-closure glaucoma accompanied with iridocyclitis in one eye (Case 10). Among the 18 cases, iris and/or iridocorneal angle neovascularization was observed in 12 cases on an ophthalmoscopic examination, resulting in a sensitivity of 66.7% and specificity of 100%. Neovascularization was observed in 12 cases by ophthalmoscope and was detected in all 12 cases by anterior segment angiography. The positive predictive value was 100%. Neovascularization was not observed in 7 cases by ophthalmoscope and in 1 case (Case 10) by anterior segment angiography. The negative predictive value was 14.3%.

Discussion

Many previous reports had been published regarding the usefulness of early rubeosis detection by fluorescence anterior segment angiography [3-13]. Azad et al. [13] reported Retcam fluorescein gonioangiography to be a novel technique for the early detection of angle neovascularization in patients with diabetic retinopathy. They concluded that the technique helped to prevent the progression to neovascular glaucoma. Ishibashi et al. evaluated the effects of the intravitreal injection of bevacizumab on anterior segment neovascularization using anterior segment angiography with HRA2 [12]. They observed anterior segment neovascularization with fluorescein and indocyanine green angiography.

The eyes with anterior segment neovascularization exhibited vascular structure with IA and marked leakage with FA. Fluorescein passes through the fenestration of newly formed vessels, but indocyanine green does not, due to the molecule size [14]. The vascular structures

showing leakage with FA in the anterior segment are believed to represent newly formed vessels. Indocyanine green angiography is suitable for evaluating the detailed structure of newly formed vessels because of the absence of extravasation of indocyanine green.

We performed simultaneous anterior and posterior ocular segment angiography using HRA2 with FA and IA to detect anterior segment neovascularization and fundus abnormalities in eyes suspected of having newly formed vessels in the iris and iridocorneal angle. In this procedure, a mydriatic agent was used just before beginning anterior segment angiography. Anterior segment angiography requires a gonioscope and has a disadvantage, due to the difficulty to evaluation under mydriasis. Sufficient mydriasis is obtained when anterior segment angiography is finished in the present procedure. Therefore, we can easily continue fluorescence fundus angiography and observe retinal pathological changes, including retinal non-perfusion area and neovascularization, using HRA2.

The present study confirmed the results of previous that the anterior segment angiography is more sensitive for early detection of the newly formed vessels in both the iris and iridocorneal angle than biomicroscopy [2-12]. Anterior segment angiography showed that neovascularization had a good correlation with posterior fundus abnormalities (Table 2). The subjects were patients with retinal ischemic disorders suspected of having anterior segment neovascularization. Newly formed vessels in the anterior segment were detected in all patients except for one with secondary angle closure glaucoma accompanied by iridocyclitis. In the present study, many patients had undergone previous treatment, including pan-retinal photoablation, anti-VEGF intravitreal injection, and vitrectomy. The patients with newly formed vessels in the anterior segment had compatible retinal abnormalities in the present study. Biomicroscopic detection of these newly formed vessels is not easy in patients with a history of retinal treatments. Therefore, we highly recommend this method using HRA2 be used for the early diagnosis of neovascular glaucoma in patients with retinal ischemic disorders.

Declarations

Consent for publication

Not applicable

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

All authors have no financial interest in the subjects discussed in this manuscript.

Funding

T. Kubota has received research grants from Pfizer, Inc., and Novartis, Inc.

Authors' contributions

Yuji Sakino, Yoshihiro Noda, Maho Itotani, Takako Nakamuro, and Toshiaki Kubota performed fluorescent ocular fundus angiography examination. Yuji Sakino and Toshiaki Kubota analyzed the examination results. All authors read and approved the final manuscript.

Acknowledgements

No special instructions.

References

1. Gartner S, Henkind P. Neovascularization of the iris (rubeosis iridis). *Survey of Ophthalmology*. 1978;22(5):291-312. doi: [http://dx.doi.org/10.1016/0039-6257\(78\)90175-3](http://dx.doi.org/10.1016/0039-6257(78)90175-3)
2. Kubota T, Tawara A, Hata Y, Khalil A, Inomata H. Neovascular tissue in the intertrabecular spaces in eyes with neovascular glaucoma. *British Journal of Ophthalmology*. 1996;80(8):750-754. doi: <http://dx.doi.org/10.1136/bjo.80.8.750>
3. Jensen VA, Lundbaek K. Fluorescence angiography of the iris in recent and long-term diabetes. *Diabetologia*. 1968;4(3):161-163. doi: <http://dx.doi.org/10.1007/BF01219437>
4. Fetkenhour CL. Anterior Segment Fluorescein Angiography With a Retinal Fundus Camera. *Archives of Ophthalmology*. 1978;96(4):711-713. doi: <http://dx.doi.org/10.1001/archophth.1978.03910050401020>
5. Kimura R. Fluorescein gonioangiography of newly formed vessels in the anterior chamber angle. *The Tohoku Journal of Experimental Medicine*. 1983;140(2):193-196. doi: <http://dx.doi.org/10.1620/tjem.140.193>
6. Sanborn GE, Symes DJ, Magargal LE. Fundus-iris fluorescein angiography: evaluation of its use in the diagnosis of rubeosis iridis. *Ann Ophthalmol*. 1986;18(2):52-58.
7. Bandello F, Brancato R, Lattanzio R, Falcomatà B, Malegori A. Biomicroscopy versus fluorescein angiography of the iris in the detection of diabetic iridopathy. *Graefe's Arch Clin Exp Ophthalmol*. 1993;231(8):444-448. doi: <http://dx.doi.org/10.1007/BF02044229>
8. Ohnishi Y, Ishibashi T, Sagawa T. Fluorescein gonioangiography in diabetic neovascularisation. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 1994;232(4):199-204. doi: <http://dx.doi.org/10.1007/BF00184005>
9. Bandello F, Brancato R, Lattanzio R, Galdini M, Falcomata B. Relation between iridopathy and retinopathy in diabetes. *British Journal of Ophthalmology*. 1994;78(7):542-545. doi: <http://dx.doi.org/10.1136/bjo.78.7.542>
10. Hamanaka T, Akabane N, Yajima T, Takahashi T, Tanabe A. Retinal ischemia and angle neovascularization in proliferative diabetic retinopathy. *Am J Ophthalmol*. 2001;132(5):648-658.
11. Oya Y, Sugiyama W, Ando N. [Anterior segment fluorescein angiography for evaluating the effect of vitrectomy for neovascular glaucoma]. *Nippon Ganka Gakkai Zasshi*. 2005;109(11):741-747.
12. Ishibashi S, Tawara A, Sohma R, Kubota T, Toh N. Angiographic changes in iris and iridocorneal angle neovascularization after intravitreal bevacizumab injection. *Arch Ophthalmol*. 2010;128(12):1539-1545. doi: <http://dx.doi.org/10.1001/archophth.2010.282>
13. Azad R, Arora T, Sihota R, et al. Retcam Fluorescein Gonioangiography: A New Modality for Early Detection of Angle Neovascularization in Diabetic Retinopathy. *Retina*. 2013;33(9):1902-1907. doi: <http://dx.doi.org/10.1097/IAE.0b013e318285cdd6>
14. Kubota T, Aoki R, Harada Y, et al. Trabecular meshwork in neovascular glaucoma eyes after the intravitreal injection of bevacizumab. *British Journal of Ophthalmology*. 2009;93(4):557-558. doi: <http://dx.doi.org/10.1136/bjo.2008.148148>
15. Maruyama Y, Kishi S, Kamei Y, Shimizu R, Kimura Y. Infrared angiography of the anterior ocular segment. *Surv Ophthalmol*. 1995;39 Suppl 1:S40-48.

Copyright: © Sakino et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.