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FOREFRONT REVIEW

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Endovascular surgery in the field of ophthalmology

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Abstract

In this article, we provide an overview of the current perspectives on endovascular surgery in ophthalmology, including a description of the various approaches, recent clinical results and future prospects. Experimental studies of endovascular surgery in ophthalmology started in the 1980s; since then, a considerable amount of research has been done to develop the procedure for clinical use. During the past two decades endovascular surgery has been performed on eyes with retinal vascular disorders, including central retinal vein occlusion and central retinal artery occlusion. The first endovascular surgery on human eyes was performed in 1998 on a patient with central retinal vein occlusion (CRVO). The most recent techniques used in retinal endovascular surgery involve manual injection of liquid agents such as tissue plasminogen activator into major retinal vessels using a 47 or 48-gauge micro-needle. New technology using a bimanual procedure and digitally assisted vitrectomy systems enables surgeons to perform this delicate procedure more effectively. Recent results reported from a number of researchers corroborate the effectiveness of the procedure. Endovascular surgery is one of the latest techniques in the field of ophthalmology and has garnered significant interest from vitreoretinal surgeons. However, it is also at the limit of what surgeons are able to accomplish with manual precision. There is still much to learn and improve to maximize the potential of this approach. The combination of skills as a surgeon, sound science, objective clinical evidence and cutting edge technology will lead to improvements in this field.

Keywords Vitrectomy · Endovascular surgery · Central retinal vessels occlusion · tPA

Introduction

Endovascular surgery is a new avenue in ophthalmology [1, 2]. There is a variety of eye diseases such as retinal vein occlusion [3] and retinal artery occlusion [4, 5], caused by occlusion of major retinal vessels. The ideal course of treatment for retinal vascular disorders is cannulation, a direct procedure aimed at flushing out occluded vessels. However, cannulation for retinal vascular diseases has not yet been accepted as a conventional procedure. The main reason for this is the difficulty of the procedure. Current acceptable treatments for these retinal vascular disorders include laser treatment, anti-vascular endothelial growth factor (VEGF) injections, steroid injections and vitrectomy.

Several researchers in the field have been making efforts to develop effective surgical procedures for endovascular surgery (Table 1). Some of the surgical results obtained are still considered controversial. We would like to review recently published reports on endovascular surgery, and present the latest results of these studies.

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Table 1 Surgical results reported for CRVO from a variety of surgical settings

Authors/Year/# of eyes	Needle type	Surgical equipment	VA improvement more than 3 lines (%)
Weiss [6] / 2001 / 30	Glass pipette	PPV with chandelier	50
Bynoe [7] / 2005 / 25	Micro-cannula	PPV with chandelier	72
Kadonosono [8] / 2013 / 11	47G micro-needle	PPV with chandelier	74
Van Overdam [9] / 2015 /12	Angled glass cannula	PPV with twin chandelier	50
Hayashi [10] / 2017 /16	47G micro-needle	PPV with chandelier	50

Year year published, *PPV* pars plana vitrectomy, needle; instrument used for cannulation, *47G* 47 gauge; *VA* visual acuity

Past attempts at retinal endovascular surgery

Groundbreaking efforts in endovascular surgery include the surgeon who re-anastomosed blood vessels with outer diameters of 500 μm [11], renal physiologists who cannulated 15 μm renal cortical vessels [12] and a researcher who cannulated retinal vessels in enucleated eyes in the 1950s [13].

An experimental study on retinal endovascular surgery was started during the 1980s, and was considered the first endovascular surgery in ophthalmology. Representing a significant step forward, a study involving experimental cannulation of retinal vessels in rabbit retinas, was performed at Duke University in 1987 [14]. Researchers created glass micropipettes with a 1.6 mm outer diameter and curved shanks made from standard capillary tubing. Micro-puncture was confirmed by observing spontaneous filling of the micropipette tips with blood. This procedure was assisted with electronic micromanipulators.

In Japan, some researchers reported the results of experimental cannulation with a purpose made glass pipette [15], whereas another group showed that a specifically designed microcatheter enabled successful injection of Tissue plasminogen activator (tPA) into the central retinal vein of a dog for approximately 45 min [16].

In the late 1990s, retinal endovascular surgery first began as insertion of a microcannula into branches of the retinal vasculature with injection of pharmacologic agents such as tPA in human eyes with central retinal vein occlusion [6]. In that report, Weiss performed injection of tPA (20 μm/0.1 ml), into the retinal vein of an 81-year-old woman CRVO patient using a 33-gauge needle assisted with a micromanipulator. Her preoperative visual acuity was 20/400 and remained unchanged postoperatively.

Following Weiss's report [6], further studies on retinal endovascular surgery for central vein occlusion (CRVO) were performed. One study reported the results of retinal endovascular surgery using a microcannula accompanied with injection of tPA which were better than natural course, with 72% of eyes with CRVO obtaining improvement in visual acuity [6]. However, other reports showed little benefit [7], with visual acuity remaining unchanged after surgery. In addition, major surgical complications such as neovascular glaucoma and retinal detachment were seen. These results resulted in a significant amount of controversy over whether retinal endovascular surgery was a good option for occlusive diseases.

Innovations in surgical equipment and techniques for retinal endovascular surgery.

A new and challenging surgical technique requires a lot of steps [17]. Limiting factors in the early studies were the difficulties involved in retinal endovascular surgery. The initially used glass micropipettes were too fragile and difficult to see when inside the retinal vein. Glass micropipettes can be produced with very fine tips and diameters that enable their use for such applications as pressure injection, ion sensing, and microvascular puncture [18, 19]. They are extremely sharp and can pierce the retinal microvasculature easily, thus they have been considered the suitable surgical tools for retinal endovascular surgery. However, micropipettes have the disadvantage of being fragile and delicate, it is, therefore, difficult to maneuver them during cannulation of retinal vessels.

Recently micro-needles have been fabricated modelled on tools from the microelectronics industry, and these needles have proved to be effective in facilitating administration delivery [19, 20]. Micro-needles are sharp and rigid, making them suitable as tools for microvascular surgery. Currently 47- and 48-gauge stainless steel micro-needles are commercially available (Figs. 1, 2).

Other major factors in the development of endovascular surgery are the newly developed three-dimensional operating systems, also known as 3D vitrectomy [8]. This allows surgeons to better observe minute structures in the eye. 3D vitrectomy provides better depth of field (DOF) and higher resolution of images than a conventional operating microscope, and this new visualization system makes it possible to perform precise endovascular surgery.

Endovascular surgery is a very delicate surgical procedure, due to the need for precise piercing of the microneedle into the retinal vessels, and exacting positioning of the surgeon's hand for several minutes during the procedure. It

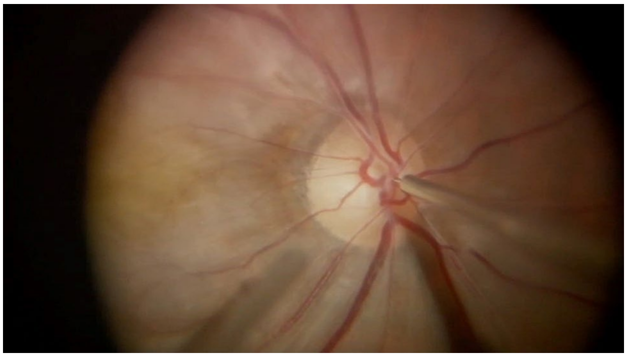

Fig. 1 Intraoperative endovascular surgery for an eye with CRAO. A 47-gauge microneedle pierces the central retinal artery

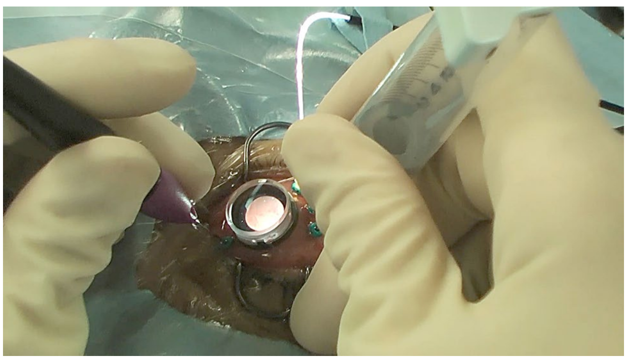

Fig. 2 The operating field of retinal endovascular surgery for an eye with CRAO. A 47-gauge microneedle is connected with a 10 cc syringe for viscous fluid control, allowing surgeons to inject tissue plasminogen activator

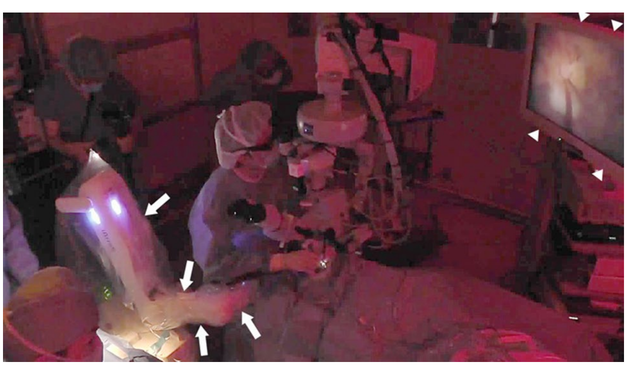

Fig. 3 A surgical robot and 3D system. A robotic arm (arrows) assists a surgeon in performing a delicate surgical procedure to decrease hand's tremor, and 3D system (arrow heads) enbles precise surgery

is reported that robotic devices can assist surgeons during retinal vein cannulation [21, 22]. Further development of these robotic assistants is expected to minimize surgical difficulties (Fig. 3).

Clinical use of endovascular surgery

Endovascular surgery is indicated for several severe eye diseases including retinal vein occlusion and retinal artery occlusion. Central retinal vein occlusion (CRVO), in particular is so difficult to treat that no truly accepted treatments have been developed for it. VEGF agents have proven efficient and are considered the first line treatment option for macular edema due to CRVO. There are several studies of efficacy of anti-VEGF agents [6–8, 17–25]. According to a recent clinical study of ranibizumab for CRVO, there was significant improvement in visual acuity of 12.3 letters, following a mean number of 8.1 injections of ranibizumab in one year [26].

Our team's published data on retinal endovascular surgery for CRVO shows that best corrected visual acuity (BCVA) in 9 out of 12 patients had improved by more than 15 letters at 24 weeks after surgery compared with baseline values [27]. No major complications such as retinal tears, endophthalmitis, retinal detachment, severe vitreous hemorrhage, or recurrence of macular edema were seen during the 24-week follow-up period.

Central retinal artery occlusion (CRAO) causes devastating vison loss and is an ophthalmic emergency [4, 5]. Several treatments have been proposed such as paracentesis [28], systemic drug treatment [29] and hyperbaric therapy [30]. Our published data reveal that at 1 week after cannulation of 13 eyes with CRAO, visual acuity in 11 eyes (85%) had improved by more than 2 lines, however, there was no change in visual acuity in the remaining eyes [31]. A single postoperative complication occurred in one patient with massive vitreous hemorrhage in one eye. Another researcher reports two cases with CRAO with endovascular surgery showing significant improvement of vision after cannulation [32]. Visual acuity improved from counting fingers to 20/250 in one eye, and from counting fingers to 20/200 in the other. There are other papers that describe endovascular surgery.

One paper reports the natural course of CRAO indicating the possibility of spontaneous resolution [10]. Twenty-two percent of eyes with CRAO in which visual acuity was counting fingers or worse spontaneously improved.

One invasive treatment for eyes with CRAO is the use of thrombolysis [33]. The rationale for this treatment is that a fibrin-platelet thrombus or embolus can be lysed with intra-venous or intra-arterial injection of tPA. It is reported that thrombolysis is effective in the treatment of CRAO, with significant improvement in visual acuity [34]. In addition, a meta-analysis study reveals that systemic fibrinolysis is superior to conventinal treatment [35].

Future expectations and needs

Endovascular surgical technique for retinal diseases still has some inherent difficulties, it is a challenging procedure and requires a steep learning curve to master. However, recent advances in technology such as digitally assisted vitreoretinal surgery (3D) are likely to prove beneficial for surgeons in performing this procedure. Moreover, robotic surgery might provide further support in performing these types of surgery in the future.

Endovascular surgery is one of the latest techniques in ophthalmology, and has been garnering significant interest from vitreoretinal surgeons since pioneers had started this kind of surgery. However, endovascular surgery is at the very limit of what surgeons are able to accomplish with manual precision. There is still much to learn and improve to maximize the potential of this approach. The combination of excellent skills as a surgeon, sound science, objective clinical evidence and cutting-edge technology will hopefully improve this field.

Conflicts of interest K. Kadonosono, None; A. Hayashi, None; E. D. Juan Jr., None.

References

1. Hattenbach LO, Puchta J, Hilgenberg I. Experimental endoscopic endovascular cannulation: a novel approach to thrombolysis in retinal vessel occlusion. Invest Ophthalmol Vis Sci. 2012;53:42–6.
2. Pournaras CJ, Petropoulos IK, Pournaras JA, Stangos AN, Gilodi N, Rungger-Brändle E. The rationale of retinal endovascular fibrinolysis in the treatment of retinal vein occlusion: from experimental data to clinical application. Retina. 2012;32:1566–73.
3. Green WR, Chan CC, Hutchins GM, Terry JM. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. Retina. 1981;1:27–55.
4. Hayreh SS, Zimmerman MB. Central retinal arterial occlusion: visual outcome. Am J Ophthalmol. 2005a;140:376–91.
5. Brown GC, Magargal LE. Central retinal artery obstruction and visual acuity. Ophthalmology. 1982;89:14–9.
6. Weiss JN. Treatment of central retinal vein occlusion by injection of tissue plasminogen activator into a retinal vein. Am J Ophthalmol. 1998;126:142–4.
7. Bynoe LA, Huchins RK, Lazarus HS, Friedberg MA. Retinal endovascular surgery for central retinal vein occlusion. Retina. 2005;25:625–32.
8. Eckardt C, Paulo EB. Heads-up surgery for vitreoretinal procedures: an experimental and clinical study. Retina. 2016;36:137–47.
9. Ishida M, Abe S, Nakagawa T, Hayashi A. Short-term results of endovascular surgery with tissue plasminogen activator injection for central retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol. 2017;255:2135–40.
10. Hayreh SS, Zimmerman B. Central retinal artery occlusion: visual outcome. Am J Ophthalmol. 2005b;140:376–91.
11. Urbaniak J. Hand clinics, microvascular surgery. Philadelphia: Saunders; 1985. p. 98–134.
12. Andreucci VE. Manual of renal micropuncture. Naples: Idelson; 1978. p. 32–4.
13. Ashton N. Injection of the retinal vascular system in the enucleated eye in diabetic retinopathy. Br J Ophthalmol. 1950;34:38–41.
14. Allf BE, de Juan E. In vivo cannulation of retinal vessels. Graefes Arch Clin Exp Ophthalmol. 1987;225:221–5.
15. Suzuki Y, Matsuhashi H, Nakazawa M. In vivo retinal vascular cannulation in rabbits. Graefes Arch Clin Exp Ophthalmol. 2003;241:585–8.
16. Tameesh MK, Lakhanpal RR, Fujii GY, Javaheri M, Shelley TH, Danna S, et al. Retinal vein cannulation with prolonged infusion of tissue plasminogen activator (t-PA) for the treatment of experimental retinal vein occlusion in dogs. Am J Ophthalmol. 2004;138:829–39.
17. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374:1105–12.
18. Prausnitz MR. Microneedles for transdermal drug delivery. Adv Drug Deliv Rev. 2004;56:581–7.
19. McAllister DV, Wang PM, Davis SP. Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: fabrication methods and transport studies. Proc Natl Acad Sci USA. 2003;100:13755–60.
20. Kadonosono K, Arakawa A, Yamane S, Uchio E, Yanagi Y. An experimental study of retinal endovascular surgery with a microfabricated needle. Invest Ophthalmol Vis Sci. 2011;52:5790–3.
21. Gijbels A, Smits J, Schoevaerdts L, Willekens K, Vander Poorten EB, Stalmans P, et al. In-human robot-assisted retinal vein cannulation, a world first. Ann Biomed Eng. 2018;46:1676–85.
22. de Smet MD, Meenink TC, Janssens T, Vanheukelom V, Naus GJ, Beelen MJ, et al. Robotic assisted cannulation of occluded retinal veins. PLoS ONE. 2016;11(9):e0162037.
23. Ogura Y, Roider J, Korobelnik JF, Holz FG, Simader C, Schmidt-Erfurth U, et al. Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 18-month results of the phase 3 GALILEO study. Am J Ophthalmol. 2014;158:1032–8.
24. Heier JS, Clark WL, Boyer DS, Brown DM, Vitti R, Berliner AJ, et al. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS study. Ophthalmology. 2014;121:1414–20.
25. Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117:1124–33.
26. Larsen M, Waldstein SM, Boscia F, Gerding H, Monés J, Tadayoni R, CRYSTAL Study Group, et al. Individualized ranibizumab regimen driven by stabilization criteria for central retinal vein occlusion. Twelve-month results of the CRYSTAL study. Ophthalmology. 2016;123:1101–11.
27. Kadonosono K, Yamane S, Arakawa A, Inoue M, Yamakawa T, Uchio E, et al. Endovascular cannulation with a microneedle for central retinal vein occlusion. JAMA Ophthalmol. 2013;131:783–6.
28. Gombos GM. Anterior chamber paracentesis and carbogen treatment of acute CRAO. Ophthalmology. 1996;103:865.
29. Youn TS, Lavin P, Patrylo M, Schindler J, Kirshner H, Greer DM, et al. Current treatment of central retinal artery occlusion: a national survey. J Neurol. 2018;265:330–5.
30. Watanabe I, Miyake Y, Ando F, Sakakibara K, Sakakibara B. The effect of hyperbaric oxygen on ERG. Nippon Ganka Gakkai Zasshi. 1969;73:1920–33 (in Japanese).
31. Kadonosono K, Yamane S, Inoue M, Yamakawa T, Uchio E. Intra-retinal arterial cannulation using a microneedle for central retinal artery occlusion. Sci Rep. 2018. https://doi.org/10.1038/s41598-018-19747-7.
32. Takata Y, Nitta Y, Miyakoshi A, Hayashi A. Retinal endovascular surgery with tissue plasminogen activator injection for central retinal artery occlusion. Case Rep Ophthalmol. 2018;22(9):327–32.

33. Biousse V, Calvetti O, Bruce BB, Newman NJ. Thrombolysis for central retinal artery occlusion. J Neuroophthalmol. 2007;27:215–30.
34. Kattah JC, Wang DZ, Reddy C. Intravenous recombinant tissue-type plasminogen activator thrombolysis in treatment of central retinal artery occlusion. Arch Ophthalmol. 2002;120:1234–6.
35. Schrag M, Youn T, Schindler J, Kirshner H, Greer D. Intravenous fibrinolytic therapy in central retinal artery occlusion: a patient-level meta-analysis. JAMA Neurol. 2015;72:1148–54.