Experimental Endoscopic Endovascular Cannulation: A Novel Approach to Thrombolysis in Retinal Vessel Occlusion

Lars-Olof Hattenbach,1 Joachim Puchta,2 and Ingo Hilgenberg3

PURPOSE. Recent studies suggest that the cannulation of retinal vessels may provide a potential access route for the administration of thrombolytic agents in retinal vessel occlusion. However, the major problem with available techniques is the limited visualization of retinal vessels with conventional surgical microscopes, making it difficult to effectively control the targeted injection of drugs.

METHODS. The authors developed a novel single-piece catheter system for the endoscopically guided puncture of microvessels. Experimental punctures of retinal vessels with injection of fluid were performed in porcine cadaver eyes using a standard high-resolution gradient index microendoscope introduced through the pars plana.

RESULTS. Endoscopically guided punctures were successfully performed in porcine branch retinal veins at various distances from the optic disc. Injection of recombinant tissue plasminogen activator (rt-PA), hypertonic solution (hyper HES), or normal saline solution into the vessel lumen was accomplished under direct endoscopic view in a safe and reliable manner.

CONCLUSIONS. Endoscopically guided puncture of retinal microvessels is feasible and can be performed through a pars plana entry without additional micromanipulation devices. This novel technique may be a safe and effective approach to catheter-directed endovascular thrombolysis in retinal vascular occlusive diseases. (Invest Ophthalmol Vis Sci. 2012;53:42–46) DOI:10.1167/iovs.11-8486

Retinal vessel occlusion (RVO) is the most common form of retinal vascular disease after diabetic retinopathy. The natural course of central retinal vein or artery occlusion is associated with a poor visual prognosis and a high incidence of complications.1,2 Early intervention aimed at restoration of blood flow could be critical for a favorable outcome. Over the past years, numerous surgical techniques with varying degrees of success have been advocated for the treatment of branch (BRVO) or central retinal vein occlusion (CRVO). These include vitrectomy with separation of the posterior hyaloid with or without internal limiting membrane peeling, arteriovenous sheathotomy to separate the artery and vein at the AV crossing in BRVO, or radial optic neurotomy to decompress the central retinal vein at the lamina cribrosa in CRVO.3–5 The intravitreal administration of anti-VEGF agents or corticosteroids for macular edema secondary to RVO has gained widespread acceptance.6–9 However, this therapeutic approach is aimed at treating the complications rather than preventing or stopping the factors involved in the development of RVO.3–14

The finding that thrombus formation is a prominent feature of retinal vascular occlusive disease supports consideration of thrombolysis aimed at early restoration of retinal or capillary blood flow. Several studies suggest that thrombolysis with the fibrinolytic agent recombinant tissue plasminogen activator (rt-PA) is associated with a more favorable visual outcome in retinal vein or artery occlusion.12–17 Unfortunately, the systemic administration of thrombolytic agents carries the risk of life-threatening hemorrhagic complications.18,19 Therefore, rt-PA recently has been used through the intravitreal and retinal venous route. Although intravitreous administration of rt-PA shows outcomes that are similar to the natural history of RVO,20 cannulation and injection of rt-PA into a peripapillary branch retinal vein specifically targets the thrombus at the lamina cribrosa.21,22

Recent evidence suggests that vitrectomy with central venous injection of rt-PA is associated with a high risk for surgical complications.23 A major concern is the relatively large size and form of current devices, which allow the puncture of only retinal microvessels with greater diameters. Moreover, the limited visualization of targeted vessels continues to be a significant problem with current techniques, making the cannulation of retinal vessels extremely difficult. As a result, there is still a lack of clinically applicable methods.

With the advent of high-resolution gradient index microendoscopes,24–25 the implementation of a safe and reliable microsurgical technique for the cannulation of retinal vessels has become technically feasible. The objective of the present study was to investigate a device for the endoscopically guided injection of thrombolytic agents into retinal vessels that may be effective in the treatment of retinal vascular occlusive diseases.

MATERIALS AND METHODS

Endoscopic Microcatheter System

We developed a flexible catheter fabricated of a single-piece quartz glass tubing coated with polyamide attached along a sleeve made of glass. A schematic of the endoscopic catheter system is shown in Figure 1. The size of the sleeve is adapted to the outer diameter of the probe of a particular high-resolution gradient index microendoscope (GRIN Endoscope; Insight Instruments, Stuart, FL) used for vitreoretinal surgery. The single-piece design of the catheter has an advantage over assembled systems with glued or welded components in that it may prevent leakage secondary to the high intraluminal pressures required for the injection of fluids through tubings with extremely small diameters. The end of the catheter is tapered and sharpened and has an...
sleeve (then injected into the lumen of the retinal vein using an automated hydroxy ethyl starch plus 7.2% NaCl, hyper-HES; Fresenius Kabi) was recombinant tissue plasminogen activator (Alteplase rt-PA; Boehringer approximately 0.5 mm into the retinal vessel. A continuous infusion of the microcatheter punctured the vessel wall and was advanced with intraocular pressure lowered to a level of 30 mm Hg, the sharp tip similar to the puncture of major peripheral veins, the sharp end of the catheter was held at a shallow angle, with the bevel facing upward. With the endoscope-catheter system within the vitreous cavity, the sharp end of the vitreous cavity through a sclerotomy at a distance of 3.75 mm from the limbus. Visualization of the vitreous cavity and the retinal target vessel. The endoscope-catheter system was then inserted into the vitreous cavity at a distance of 3.75 mm from the limbus. Visualization of the vitreous cavity and the retinal target vessel. The endoscope-catheter system was then inserted into the vitreous cavity, the sharp end of the catheter was positioned almost parallel to the retinal target vessel. The opposite end of the catheter is angled to allow for optimal visualization and positioning parallel to the target vessel. The opposite end of the catheter is equipped with a Luer lock adapter, resistant to high intraluminal pressures, for the connection of an infusion line. The infusion line is supplied by a fluid-loaded syringe attached to an automated high-pressure infusion of a standard vitrectomy system (Accurus; Alcon, Fort Worth, Texas).

**Porcine Eyes**

Enucleated porcine eyes were used in this study because porcine and human eyes have similar features, such as the diameter of the eye bulb, the manner in which retinal vessels emanate from the optic disc, and the comparable size of the vascular lumen. The eyes were used within 24 hours of enucleation and stabilized in a polystyrene foam mount under an operating microscope (Zeiss, Oberkochen, Germany).

**Endoscopic Intravascular Injection**

In each porcine cadaver eye, a standard three-port pars plana vitrectomy was performed before the puncture of the microvessel. A chandelier light (Insight Instruments) was used to enhance visualization during the procedure. The sleeve carrying the catheter was mounted on the fiber optic probe of the endoscope, and the sharp end of the catheter was positioned in front of the tip of the endoscope probe, allowing for the simultaneous visualization of the catheter and the target vessel. The endoscope-catheter system was then inserted into the vitreous cavity through a sclerotomy at a distance of 3.75 mm from the limbus. Visualization of the vitreous cavity and the retinal target vessel were provided simultaneously by the surgical standard microscope and the endoscopic view, displayed on a monitor. By moving the endoscope-catheter system within the vitreous cavity, the sharp end of the catheter was positioned almost parallel to the retinal target vessel. Similar to the puncture of major peripheral veins, the sharp end of the catheter was held at a shallow angle, with the bevel facing upward.

Injection of fluid was performed under endoscopic visualization. With intraocular pressure lowered to a level of 30 mm Hg, the sharp tip of the microcatheter punctured the vessel wall and was advanced approximately 0.5 mm into the retinal vessel. A continuous infusion of recombinant tissue plasminogen activator (Alteplase rt-PA; Boehringer Ingelheim, Ingelheim, Germany) or normal saline solution (0.9% NaCl; Fresenius Kabi, Bad Homburg, Germany) or hypertonic solution (6% hydroxy ethyl starch plus 7.2% NaCl, hyper-HES; Fresenius Kabi) was then injected into the lumen of the retinal vein using an automated high-pressure infusion of a standard vitrectomy system controlled by a foot pedal. After injection, the tip of the microcatheter was removed from the retinal vessel under endoscopic guidance, and the endoscope-catheter system was pulled out through the sclerotomy.

**RESULTS**

Overall, we performed 25 endoscopic cannulation procedures in 11 porcine eyes. Puncture of a branch retinal vein with injection of fluid was successful in all cases. For each retinal vein cannulation, approximately one to five puncture attempts were made before puncture success. Branch retinal veins were cannulated at various distances from the optic disc. Sites near the nerve head, where the vein had a maximum diameter and was tightly adhered to the optic nerve head, were the easiest to puncture. However, it was possible to puncture branch retinal veins at distances ranging from 1 to 15 disc diameters away from the optic disc, where the vein had a considerably smaller diameter and the underlying retina was less tightly adhered. Puncturing of retinal arteries was more difficult. Because of the tougher vessel wall and postmortem stagnation of blood flow in porcine cadaver eyes, arteries tended to slide under the pressure of the sharp tip of the microcatheter. rt-PA in a concentration of 1 mg/mL or hyper-HES was infused in three eyes each, whereas normal saline solution was infused in the remaining five eyes.

All maneuvers were performed under endoscopic guidance. A pressure of 60 to 80 psi was maintained in the syringe of the automated high-pressure infusion to achieve a continuous injection flow. Using bimanual manipulation of the endoscope, the tip of the catheter was maintained in its intravascular position for 1 to 5 minutes and then removed slowly. Figures 2 to 6 and Supplementary Movie S1 (http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.11-8486/-/DCSupplemental) show the endoscopic view before, during, and after venipuncture of a branch retinal vein approximately 10 disc diameters from the optic disc. Because of postmortem stagnation of blood flow, puncturing and injection of fluid into the intravascular lumen always resulted in visible blood flow toward the optic disc within the first seconds after the start of the injection (i.e., after injection of only a few microliters). Typically, the rapid injection of fluid also resulted in a temporary dilation of the vessel. Occasionally, we noted small traces of blood at the puncture site on removal of the catheter tip. However, no rupture or visible damage of the vessel wall was observed. Moreover, we observed no mechanical damage of retinal tissue such as retinal breaks.
DISCUSSION

In the past, various methods for the puncture of retinal vessels have been proposed. Recent approaches include the cannulation of retinal veins with micropipettes or the catheterization of retinal vessels with a flexible microcatheter for the injection of rt-PA. However, although these methods have demonstrated the feasibility of retinal vessel puncture, there is still a lack of clinically applicable methods for the injection of drugs into the lumen of retinal vessels in a reliable manner. The major problem with available techniques is the limited visualization of the retinal vessel because of insufficient magnification with conventional surgical microscopes, making it difficult to puncture the vessel or to effectively control the targeted injection of drugs. In a recent study, Feltgen et al. reported on a high risk of surgical complications after vitrectomy with central venous injection of rt-PA in patients with CRVO. In this study, successful punctures were made in 10 of 13 patients. Of these, neovascular glaucoma developed in six patients and enucleation was needed in two eyes.

In the present study, all maneuvers were performed through a pars plana approach under endoscopic guidance.

We were able to puncture branch retinal veins at various distances from the optic disc, where the vein had a considerably smaller diameter and the underlying retina was less tightly adhered. Using bimanual manipulation of the endoscope, we injected rt-PA, normal saline solution, or hypertonic solution. Moreover, we were able to maintain the tip of the catheter in its intravascular position until removal after several minutes.

The endoscopic approach provides excellent magnification, thereby managing the challenges of visualization of retinal vessels and holding the microcatheter at an appropriate angle for venipuncture. In our study, a sleeve carrying the catheter was mounted on the fiberoptic tip of the endoscope. This has an advantage over settings with multiple instruments because the bimanual manipulation of a single device allows for precise maneuvers by the surgeon. In addition, the surgeon can obtain pseudo-depth perception from the dynamic movement of the endoscope relative to the retinal vessel that, when fixed, is absent. In previous attempts to facilitate the task of delivering drugs to retinal microvessels, various complex micromanipulation devices or expensive robots have been used. Such micromanipulators require maximum stability, which is usually accomplished by a complex fixation of the patient’s head or
eye, thereby limiting accessibility and operability in a surgical setting.

Another major concern is the size and form of current devices for the puncture of retinal microvessels. Thus far, cannulas and microcatheters have been designed to be insertable into main branches close to the optic nerve head. Usually, these vessels measure at least 100 μm in diameter. However, the puncture of retinal vessels close to the optic disc carries the risk of damaging the optic nerve. Moreover, the management of BRVO would require the proximal injection of a fibrinolytic agent to the occluded portion of the vein (i.e., the puncture of a vessel as small as 50 μm or less in diameter). Several experimental studies have demonstrated that probing and catheterization of the vascular lumen of retinal vessels may be achieved with sutures, glass tubes, or polyimide tubes.18-20 Since the maximally achievable reduction in size of a cannula depends on stability, previous techniques using materials such as borosilicate, metal, or polyamide have been limited to an outer diameter ranging from 100 μm to a minimum of 50 μm.21 In a recent experimental study, Tsilimbaris et al.22 demonstrated that beveling of the catheter tip and diameter of the catheter are the most important factors affecting the ease of vascular catheterization. They achieved the best results with polyimide tubes with internal diameters of approximately 50 μm. Based on their results, they concluded that this size seems to represent the maximum catheter diameter that can be used for microvascular catheterization.23 Other researchers have reported the successful use of a microcatheter instrument and a surgical technique for retinal vein cannulation with prolonged intravascular infusion of a thrombolytic agent in experimentally induced BRVO in dog eyes.24 However, in this study, retinal microvessel puncture was performed at relatively short distances away from the optic disc (1-4 disc diameters), indicating that this approach does not overcome the problem of visualization. The cannulation of smaller branches of the retinal vasculature with conventional surgical microscopes remains a difficult task, regardless of the catheter system used for the targeted injection of drugs. In our study, we used a flexible catheter fabricated of a single-piece quartz glass tubing coated with polyamide and terminating in a sharp distal tip with an outer diameter ranging from 10 to 20 μm. By moving the endoscope-catheter system within the vitreous cavity, it was possible to puncture branch retinal veins at distances up to 15 disc diameters from the optic disc, where the vein had a considerably smaller diameter. Occasionally, we noted small traces of blood at the puncture site on removal of the catheter tip. However, we observed no visible damage to the vessel wall or mechanical damage to retinal tissue.

The finding that arteries tended to slide under the pressure of the sharp tip of the microcatheter reflects the fact that the puncture of retinal arteries is technically more challenging. To date, all clinical studies using endovascular surgery included patients with retinal vein occlusion. However, the difficulties we encountered during the puncture of retinal arteries were mainly related to the experimental setup with emptied retinal arteries in porcine cadaver eyes. Our findings indicate that an endovascular approach to the management of central retinal artery occlusion will require the puncture of main branches, where the retina is attached tightly to the margin of the optic disc.

To date, there is much evidence that thrombolysis is associated with a more favorable visual outcome in retinal vein or artery occlusion.12-17 However, it is a well-established observation that the systemic administration of thrombolytic agents carries the risk of life-threatening hemorrhagic complications.18-19 Because this is a dose dependent problem, the targeted retinal delivery of fibrinolytic agents at low doses should be the ideal approach. In a previous experimental study33 on the percutaneous cannulation of supraorbital arteries, we were able to demonstrate that intravascular volumes of the ophthalmic and the supraorbital artery were 60 μL and 10 μL, respectively, indicating that the retinal intravascular administration of drugs would require relatively small injection volumes. This is consistent with our current observation that puncturing and injection of small volumes of fluid always resulted in a visible rapid blood flow toward the optic disc and a temporary dilation of branch retinal veins in porcine cadaveric eyes. Another critical factor that has to be taken into account when using endovascular surgery to restore retinal blood flow is time to treatment. Given that the process of adherence and organization of a venous thrombus does not begin until 5 to 10 days after thrombus formation, it seems plausible that thrombolytic therapy should be initiated in the early acute stage.16,17

The findings of the present study support the concept of retinal endovascular thrombolysis as a potential therapeutic approach to RVO diseases. The endoscopically guided delivery of drugs to retinal vessels may contribute to improve safety and reproducibility of this treatment strategy. Here, we were able to demonstrate adequate retinal vessel visualization and puncture at various distances away from the optic disc using a novel catheter system mounted on the fiberoptic tip of a high-resolution gradient index microendoscope. Experiments to determine the efficacy of endovascular thrombolysis in retinal vein or artery occlusion were beyond the scope of the present study. However, a greater understanding of the technical feasibility and the identification of appropriate surgical techniques are important prerequisites for future clinical studies to establish endoscopic retinal vessel cannulation as an alternative to systemic thrombolysis.

References


