Vitrectomy for Proliferative Diabetic Retinopathy in a Patient with Heparin-Induced Thrombocytopenia

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Key Words
Proliferative diabetic retinopathy · Vitrectomy · Heparin-induced thrombocytopenia · Argatroban hydrate

Abstract
Introduction: In this study, we report a case of proliferative diabetic retinopathy in a patient with heparin-induced thrombocytopenia (HIT) in whom vitrectomy was performed with good results. Case: A 57-year-old man presented with a chief complaint of decreased visual acuity (VA) in the left eye. Corrected VA of the left eye was 0.03, and ophthalmic examination showed fibrovascular membranes along the vascular arcade and a combined rhegmatogenous-traction retinal detachment with a macular hole. The patient began hemodialysis for diabetic nephropathy in March 2014; thrombocytopenia developed after dialysis was started, and HIT was diagnosed after further evaluation. Argatroban hydrate was being used during dialysis. Treatment was switched from warfarin to argatroban hydrate 6 days prior to vitrectomy being performed on the patient’s left eye. Although there was bleeding with somewhat difficult hemostasis during the intraoperative treatment of the fibrovascular membranes, surgery was completed without complications and the postoperative course was good. Discussion: Vitrectomy was performed with good results in this patient with HIT. Treatment with argatroban hydrate during surgery enabled surgery without the danger of intraoperative clotting.
**Introduction**

Heparin-induced thrombocytopenia (HIT) is a serious adverse effect of heparin caused by platelet-activating antibodies [1, 2]. HIT is a paradoxical prothrombotic disorder in which thrombosis is caused by an anticoagulant. The incidence rate of HIT varies depending on the underlying disorder, but it generally affects 0.5–5% of patients treated with heparin [3]. Precautions are required when surgery is performed in patients with HIT, and we have found no previous reports of vitrectomy in a HIT patient. In this present study, we report the case of a patient with HIT in whom vitrectomy was performed for proliferative diabetic retinopathy (PDR).

**Case History**

A 57-year-old male presented with the chief complaint of bilateral decreased visual acuity (VA). He had previously undergone hemodialysis for diabetic nephropathy in March 2014, and after starting hemodialysis, thrombocytopenia was noted, blood clots were found in the hemodialysis circuit, and further evaluation showed elevated anti-HIT antibody levels, thus leading to a diagnosis of HIT. He also had hepatitis C and hypertension. The family medical history was unremarkable.

**Case Report**

The patient had been treated by a local physician for diabetic retinopathy since 2007, and photocoagulation of both retinas was performed in 2011. The patient had not been examined for 1 year after 2013, and PDR had progressed in both eyes by early 2014. He was subsequently referred to the Department of Ophthalmology, Osaka Medical College Hospital, for surgery on his left eye in March 2014.

**Findings upon Initial Evaluation**

Upon initial examination, the patient’s VA was 0.4 (1.0 × S + 1.0 D = C –1.75 A × 90°) in his right eye and 0.03 (uncorrectable) in his left eye. Intraocular pressure was 14 mm Hg in his right eye and 13 mm Hg in his left eye. The patient had an intraocular lens in both eyes. The examination of the anterior eye and optic media was unremarkable. Bilateral fundi showed proliferative fibrovascular membranes along the vascular arcades. In his right eye, there was traction retinal detachment inferiorly and vitreous hemorrhage. In his left eye, there was traction retinal detachment extending superiorly from the macula and a macular hole (fig. 1). Blood tests indicated poorly controlled diabetes with an HbA1c of 9.3%.

**Treatment Course**

In the patient’s left eye, vitrectomy using a 25-gauge system, removal of the fibrovascular membranes, retinal photocoagulation, and gas tamponade with 20% SF6 were performed. Mild bleeding during the removal of the fibrovascular membranes was noted, yet the surgery was successfully completed. Postoperatively, the corrected VA of the patient’s left eye was 0.09. Residual subretinal fluid was gradually decreased and the macular hole was closed (fig. 2).

Perioperative anticoagulation was managed in consultation with the Blood Purification Center at our hospital. His body weight was 63.45 kg on admission. Immediately, warfarin
was stopped, and because heparin could not be used, argatroban hydrate (0.2–0.7 
μg/min/kg) alone was used for anticoagulation. The dose of argatroban hydrate was 
increased to 240 mg/day on day 3 after warfarin was stopped. Blood tests were done daily 
to control the activated partial thromboplastin time to about 50 s. The patient also received 
argatroban hydrate by continuous i.v. infusion during the surgery.

On the day after surgery, warfarin (3 mg/day) was resumed while continuing on ar-
gatroban hydrate (170 mg/day). After his discharge from the hospital, the anticoagulation 
was managed with warfarin (3 mg/day) alone (fig. 3). Finally, prothrombin time-
international normalized ratio has been controlled around 2.5.

Discussion

First introduced in the 1950s, heparin has been used for more than 60 years (e.g., during 
cardiovascular surgery), and is an essential drug for the treatment of thromboembolism in 
the perioperative period. However, heparin can also cause thrombocytopenia by an immu-
nologic mechanism. Thus, the concept of HIT was proposed as a disorder in which thrombo-
embolism rather than bleeding can develop [1, 2]. In 1992, antibodies that recognize the 
heparin-platelet factor 4 complex were reported as the cause of HIT [4, 5].

HIT is classified as either type I or type II based on the mechanism of development [6, 7]. 
HIT type I develops soon after heparin is started (i.e., 2–3 days) due to a direct effect of hepa-
rin on platelet aggregation; thrombocytopenia is mild, and heparin can usually be contin-
ued. HIT type II is more severe and requires treatment. The mechanism involves platelet 
activation by heparin and platelet factor 4 binding to heparin to form an immune complex. 
This complex binds to and crosslinks platelet receptors, leading to strong platelet activation 
and platelet aggregation.

The incidence rate of HIT varies depending on the underlying disease, but it generally 
affects 0.5–5% of patients who receive heparin [3]. The incidence of complications such as 
thrombosis is 25–50% if HIT is not treated, with a mortality rate of approximately 5%. Spe-
cific events that may predispose patients to HIT are those in which heparin is used, including 
coronary artery bypass graft surgery and when starting hemodialysis. HIT is most common 
in Western countries where unfractionated heparin is used to prevent thrombo-
embolism after or-
thopedic surgery. The diagnosis of HIT is based on a combination of detection of HIT anti-

bodies and the following 4 clinical findings: (1) severity of thrombocytopenia, (2) time of 
platelet reduction, (3) presence of thrombosis, and (4) possibilities other than HIT.

However, since antibody testing can take a long time, in actual clinical practice, a platelet 
count ≤50% of the original platelet count or ≤100,000/μl, together with symptoms, suggests 
HIT, and treatment should be initiated. Treatment involves discontinuing to use heparin and 
usually initiating argatroban, an antithrombin drug [8–10]. Reports of ophthalmic complica-
tions in HIT patients include orbital hematomas [11] and retinal vein occlusion [12], but the 
number of reported cases is very small. In fact, we found no previous reports of ophthalmic 
surgery in HIT patients. In the present patient, switching from warfarin to argatroban before 
vitrectomy enabled vitrectomy to be performed safely without any systemic adverse events.

Patients with PDR who also have renal dysfunction often tend to develop clots during 
vitrectomy, but despite renal dysfunction in the present patient, the intraoperative admin-
istration of argatroban hydrate allowed for successful completion of the vitrectomy without 
the danger of clotting. Thus, these findings show that intravenous argatroban hydrate can be 
used prophylactically to easily prevent clotting during vitrectomy in the clinical setting. The 
 drugs half-life is 30 min, and it has an anticoagulant effect for about 15 min after administra-
tion. Therefore, by stopping argatroban as soon as the dissection of the fibrovascular membranes is completed, there is little risk of postoperative bleeding and clotting can be safely controlled [13]. A worsening of PDR with increased platelet aggregation has also been reported [14, 15]. Hence, although HIT activity is suppressed by anticoagulant drugs, careful follow-up is required to observe whether or not PDR is worsened by HIT.

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Statement of Ethics

This study was approved by the Ethics Committee of Osaka Medical College, Takatsuki City, Osaka, Japan.

Disclosure Statement

The authors have no conflicts of interest to report.

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Fig. 1. Preoperative fundus findings of the patient’s left eye. a Fundus image showing that the proliferative fibrovascular membranes are present superiorly along the vascular arcade. b Optical coherence tomography image showing that macular traction is present superiorly, with formation of a macular hole.
Fig. 2. Postoperative fundus findings of the patient’s left eye. 

**a** Fundus image showing that the proliferative fibrovascular membranes are removed and that the retina is reattached. 

**b** Optical coherence tomography image showing that residual subretinal fluid had gradually decreased and that the macular hole was closed.
Fig. 3. Graph illustrating the treatment course of the patient from hospitalization to discharge. APTT = Activated partial thromboplastin time; PT = prothrombin time.