ORAL ANTICOAGULATION AND THE RISK OF VITREOUS HEMORRHAGE AND RETINAL TEARS IN EYES WITH ACUTE POSTERIOR VITREOUS DETACHMENT

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Purpose: To determine if oral anticoagulation alters the association between vitreous hemorrhage (VH) and retinal tears in eyes with acute, posterior vitreous detachment (PVD).

Methods: In this retrospective chart review, the complete records of consecutive patients with spontaneous, symptomatic acute PVD from a single referral-based practice were reviewed. The use of oral anticoagulants, the presence of a VH, and the presence of a retinal tear or detachment were recorded.

Results: A total of 336 consecutive eligible patients (336 eyes) were included in the final analysis. Vitreous hemorrhage occurred in 118 (35%) eyes; in 43% of patients taking aspirin, clopidogrel, or warfarin versus 31% not taking these medications ($P = 0.03$). Retinal tears occurred in 46% of patients with VH versus 27% of patients without VH ($P = 0.0007$). Retinal tears occurred in 39% of patients with VH taking aspirin, clopidogrel, or warfarin compared with 52% of patients not taking these medications. ($P = 0.20$) A decreased proportion of patients with acute PVD taking one or more of the oral anticoagulant medications studied, regardless of the presence of VH, were diagnosed with a retinal tear ($P = 0.0017$) or retinal detachment ($P = 0.0001$).

Conclusion: Retinal tears are commonly found (46%) in the eyes of patients who present with symptoms and signs of acute PVD and VH. Patients taking aspirin, clopidogrel, or warfarin who develop an acute PVD are more likely to present with VH. No statistically significant association was demonstrated between the use of oral anticoagulants in patients with acute PVD and VH and the presence of retinal tears or retinal detachment.

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Posterior vitreous detachment (PVD), the separation of the posterior vitreous from the retina, usually occurs after age-related liquefaction of the vitreous and age-related weakening of the adhesion between the posterior vitreous cortex and the internal limiting membrane.[1] The posterior vitreous is most firmly attached to the retina in areas with a thin internal limiting membrane, including the edge of the optic disk, the fovea, and over retinal vessels.[1] During the separation of the posterior vitreous from the retinal surface, vitreous traction may induce a tear in the retina, a retinal blood vessel, or both.

Vitreous hemorrhage (VH) from a broken retinal blood vessel, with or without a retinal tear, occurs in 6% to 41% of patients with acute symptomatic PVD.[2–12] Retinal tears occur in 30% to 90% of patients with acute symptomatic PVD with VH[2–13] and in only 2% to 4% of patients with acute symptomatic PVD without VH.[7]

In the past few decades, after many of the above-referenced studies were published, the use of aspirin and warfarin has increased.[14–19] Because of the increasing use of oral anticoagulants, we decided to investigate the prevalence of retinal tears in patients with an acute PVD, with and without concomitant VH, and the impact of anticoagulant medication on the association between VH and retinal tears.

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Table 1. Participant Demographics

	N	Percent	Range
Total eyes	336	100.0	
Age, mean (years)	63	—	39–91
Females	196	58.3	
Left eyes	173	51.5	
Phakic	255	75.9	
Pseudophakic	81	24.1	
Average duration of symptoms (days)	7.7	—	1–30
Average length of follow-up (months)	10	—	2–60
Initial symptoms			
Flashes alone	15	4.5	
Shadow	40	11.9	
Flashes and floaters	134	39.9	
Floaters alone	147	43.8	

Methods

We retrospectively reviewed the charts of 565 consecutive patients (611 eyes) with symptomatic PVD examined by one of the authors (S.M.C.) between January 2005 and December 2009. This study was carried out with the approval from the Institutional Review Board of the University of South Florida. The study is in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations. The examining author is a retina specialist in a referral-based private practice. Symptomatic PVD was defined as the onset of unilateral flashes, floaters, or shadow in the previous 30 days with the presence of a complete PVD determined using slit-lamp biomicroscopy and indirect ophthalmoscopy with scleral depression. Retinal detachment was defined as a clinical diagnosis of retinal detachment and, according to the treating physician, necessitated treatment with 1 of 3 methods: pneumatic retinopexy, scleral buckle, or vitrectomy surgery.

The patient's age, sex, affected eye, lens status, description and duration of symptoms, presence of VH, and presence of a retinal tear or detachment upon presentation or upon subsequent visits, were recorded. Subsequent retinal tears or detachment were defined as retinal tears or detachment in eyes with no retinal tears upon presentation and that presented with retinal tears or detachment on any follow-up examinations. Vitreous hemorrhage was defined as the presence of any blood found during a thorough inspection of the vitreous cavity. The severity of VH was not evaluated in this study. The patient's medications at the time of retinal examination were reviewed and the use of anticoagulant medication was recorded. Specifically, the daily use of aspirin, clopidogrel, warfarin, vitamin E, fish oil supplement, a multivitamin, and eye vitamins for nonexudative macular degeneration were recorded.

Table 2. Anticoagulant Use

Oral Medication	N	% Total Eyes (N = 336)
Aspirin	116	34.5
Clopidogrel	7	2.1
Warfarin	13	3.9
Clopidogrel or warfarin	20	6.0
Aspirin, clopidogrel, or warfarin	127	37.8
Fish oil	40	11.9
Vitamin E	15	4.5
Multivitamin	131	39.0
Eye vitamin	8	2.4
Any of the above medications	215	64.0

Patients with any of the following factors were excluded from the final analyses: symptoms of acute PVD for >1 month, follow-up for <2 months, age <35 years, previous vitreoretinal surgery, recent cataract surgery (within 12 months) or laser posterior capsulotomy (within 3 months), previous ocular trauma, laser or cryotherapy for retinal tears or detachment, retinal vascular disease, choroidal neovascularization, ocular inflammation (uveitis), ocular ischemic syndrome, partial PVD, a choroidal mass, or macroaneurysm in the study eye; history of proliferative diabetic retinopathy in either eyes; history of blood dyscrasia, human immunodeficiency virus; or sickle cell anemia.

Statistical Analysis

A Fisher exact test was used to statistically analyze each outcome and a 2-tailed P value was calculated for each analysis. Regarding the determination of whether oral anticoagulant medication affects the frequency of VH in patients with acute PVD, only 9 subgroups were analyzed (Table 3). These included the use of 1) aspirin, 2) clopidogrel, 3) warfarin, 4) clopidogrel or warfarin, 5) aspirin, clopidogrel, or warfarin, 6) fish oil, 7) vitamin E, 8) a multivitamin, 9) and an "eye vitamin."

Similarly, only the same 9 subgroup analyses were performed to determine the effects of oral anticoagulants on the frequency of retinal tears or detachment in patients with acute PVD and VH (Tables 5 and 6).

Because of the fact that 9 subgroup analyses were performed to answer each question, a statistical adjustment was made, using the Bonferroni method, to define statistical significance as $P < (0.05/9)\ 0.0055$.

Results

Only one eye per patient was included in the final analysis. For patients who had isolated episodes of

Table 3. Anticoagulant Use and VH

Oral Medication	Number Taking Medication	Number Taking with VH	% Taking with VH	Number Not Taking Medication	% Not Taking with VH	*P**
Aspirin	116	49	42.2	220	31.4	**0.0546**
Clopidogrel	7	3	42.9	329	35.0	0.6998
Warfarin	13	6	46.2	323	34.7	0.3909
Clopidogrel or warfarin	20	9	45.0	316	34.5	0.3438
Aspirin, clopidogrel, or warfarin	127	54	42.5	209	30.6	**0.0337**
Fish oil	40	17	42.5	296	34.1	0.2961
Vitamin E	15	5	33.3	321	35.2	1
Multivitamin	131	46	35.1	205	35.1	1
Eye vitamin	8	2	25.0	328	35.4	0.7177
Any of the medications	215	80	37.2	121	31.4	0.341

*Evaluates prevalence of vitreous hemorrhage in those taking medication versus those not.

acute symptomatic PVD in both eyes during the study period, only the first eye with a diagnosis of "acute PVD" was included. After exclusions were made, 336 consecutive eligible patients (336 eyes) with an acute spontaneous PVD were included in the final analysis.

The average age of the patients in the study was 63 years; 58% of the patients were female. Table 1 lists the demographics of the patients included in the study, along with right or left eye, lens status, duration of symptoms, description of symptoms, and length of follow-up.

The use of anticoagulant medication by the patients included in the study is detailed in Table 2. The relationship between the use of anticoagulant medications and the presence of VH is displayed in Table 3. Vitreous hemorrhage occurred in 118 (35%) eyes; 42.2% (49 of 116) of patients taking aspirin had a VH as opposed to 31.4% (69 of 220) of patients not taking aspirin daily ($P = 0.05$); and 43% (54 of 127) of patients taking aspirin, clopidogrel, or warfarin had a VH versus (64 of 209) 31% of patients not taking these medications ($P = 0.034$).

The relationship between VH and the presence of retinal tears upon examination is displayed in Table 4. Of the 113 retinal tears diagnosed, 101 were diagnosed at presentation, whereas 12 were diagnosed on a subsequent visit. Retinal detachment was diagnosed in 48 of the 113 patients with retinal tears.

Retinal tears occurred in 45 of 118 patients (38%) with acute PVD and VH on presentation and 9 (8%) patients subsequently, for a total of 54 (46%) patients during follow-up. There were significantly more tears found in patients who presented with VH versus patients who did not present with VH ($P = 0.0007$).

There were also significantly more retinal tears found on subsequent retinal examinations in patients with acute PVD and VH than in patients without VH ($P = 0.005$). The relationship between the use of anticoagulant medication and the presence of VH and a retinal tear or detachment is displayed in Table 5. Retinal tears or detachment occurred in 18 of 49 patients (37%) with VH taking aspirin compared with 36 of 69 patients (52%) with VH not taking aspirin ($P = 0.13$). Retinal tears or detachment occurred in 21

Table 4. Vitreous Hemorrhage and Retinal Tears or Detachment

	N	% Total (N = 336)	
Retinal tears initially	101	30.1	
Subsequent tears (SRT)	12	3.6	
Retinal detachments	48	14.3	
	VH (118), n (%)	Non-VH (218), n (%)	*P*
Retinal tears initially	45 (38.1)	56 (25.7)	0.0245*
Subsequent tears	9 (7.6)	3 (1.4)	0.005†
Retinal detachments	4 (3.3)	44 (20.2)	0.0001‡
Total tears	54 (45.7)	59 (27.0)	0.0007§

*Evaluates prevalence of tear on initial examination of eyes with VH versus no VH.
†Evaluates prevalence of tear on subsequent examination of eyes with VH versus no VH.
‡Evaluates prevalence of retinal detachment of eyes with VH versus no VH.
§Evaluates prevalence of tear on any examination between eyes with VH versus no VH.

Table 5. Anticoagulant Use, VH, and Retinal Tears or Detachment

Oral Medication	Number with VH	% with VH with Tear*	% with VH + No Med with Tear*	P†
Aspirin	49	36.7	52.3	0.1334
Clopidogrel	3	100.0	44.3	0.0929
Warfarin	6	66.7	44.6	0.4104
Clopidogrel or warfarin	9	77.8	43.1	0.0778
Aspirin, clopidogrel, or warfarin	54	38.9	51.6	0.1966
Fish oil	17	35.3	47.5	0.4345
Vitamin E	5	60.0	45.1	0.6592
Multivitamin	46	39.1	50.0	0.2626
Eye vitamin	2	50.0	45.7	1
Any of the medications	80	41.3	55.3	0.1708

*Retinal tear includes retinal tear or detachment found on initial or subsequent examinations.
†Evaluates the prevalence of retinal tears or detachment in the eyes with VH of patients taking medication versus those not.

of 54 patients (39%) with VH taking aspirin, clopidogrel, or warfarin compared with 33 of 64 patients (52%) not taking these blood thinners ($P = 0.20$).

Data on the presence of clinical retinal detachment in patients taking anticoagulant medications are presented in Table 6. There were 48 retinal detachments (14.3%) diagnosed in this cohort. Patients taking aspirin or a multivitamin had a lower likelihood of retinal detachment ($P = 0.01$) compared with patients not taking these medications. (Table 6).

The proportion of patients with an acute PVD and VH who were diagnosed with a retinal detachment (4 of 118 patients (3.3%)) was less than the proportion of patients with an acute PVD without VH who were diagnosed with a retinal detachment (44 of 218 patients, 20.2%)) (P= 0.0001). Patients taking one or more of the 7 oral anticoagulant medications included in this study were less likely to present with a retinal tear (59 of 215 patients, 27.4%) versus those patients not taking at least one of these anticoagulant medications (54 of 121 patients, 44.6%) ($P = 0.0017$). Those taking at least one of the oral anticoagulation medications studied were also less likely to present with a retinal detachment (18 of 215 patients, 8.4%) versus patients not taking at least one of the oral anticoagulation medications (30 of 121 patients, 24.8%) ($P = 0.0001$; Table 6).

Discussion

The presence of a VH in an eye with signs and symptoms of acute PVD substantially increases the likelihood of a retinal tear.[2,10,20,21] The majority of previous studies have reported that between 50% and 75% of eyes with acute PVD and VH have a retinal tear.[2–8,10–13] Consequently, 25% to 50% of patients with an acute PVD and VH, in these studies, did not have a retinal tear. Our study had a higher percentage (54%) of patients with an acute PVD and VH and no retinal tear. This higher prevalence of VH in eyes without a retinal tear, when compared with previous

Table 6. Retinal Detachment and Anticoagulant Use

Retinal detachments (total)	48
Percent of total eyes (n = 336) with retinal detachment	14.3%

Oral Medication	Number Taking Medication	No. RDs	% Taking Medication with RD	P*
Aspirin	116	9	7.8	0.01
Clopidogrel	7	2	28.6	0.26
Warfarin	13	2	15.4	1.00
Clopidogrel or warfarin	20	4	20.0	0.51
Aspirin, clopidogrel, or warfarin	127	11	8.7	0.02
Fish oil	40	2	5.0	0.09
Vitamin E	15	2	13.3	1.00
Multivitamin	131	10	7.6	0.01
Eye vitamin	8	1	12.5	1.00
Any of the above medications	215	18	8.4	0.0001

*Evaluates the prevalence of retinal detachment in the eyes of patients taking medication versus not.

studies, may be related to the increasing use of oral anticoagulants in the patient population.[14–19]

Similar to other studies, we found that the prevalence of retinal tears discovered on subsequent examinations was elevated in eyes that presented with acute PVD and VH (7.6%). The high prevalence of initial and subsequent retinal tears in eyes with acute PVD and VH emphasizes the need for thorough peripheral retinal evaluation of these patients during the initial and frequent follow-up examinations.

The overall prevalence of retinal tears or detachment in eyes with acute symptomatic PVD included in this study was 34%. Because the patients included in this study were drawn from the practice of a retina specialist, this percentage is higher than the 14% prevalence of retinal tears in eyes with acute symptomatic PVD found in the meta-analysis by Hollands et al.[22]

Before a PVD, the vitreous is firmly attached to several structures in the posterior segment of the eye, including the retinal vessels.[1] When the force of an acute PVD severs this attachment, bleeding may occur. While the retinal blood vessels are located in the anterior retina, the force applied to the retina may be so large that it causes a retinal tear. Not all VHs, however, are associated with retinal tears. Oral anticoagulation may create an environment inside the eye whereby patients bleed into their vitreous more easily in the absence of a force necessary to produce a retinal tear.

This study found that the use of aspirin ($P = 0.05$) or aspirin, clopidogrel, or warfarin ($P = 0.03$) were both more likely to result in VH as a result of an acute PVD. Given the anticoagulant effects of these medications, this was not unexpected. The use of clopidogrel or warfarin alone, or in combination, may not have demonstrated statistical significance because of the small number of patients in this study taking these two medications. We believe that the force that occurs during the PVD is more likely to cause clinically significant bleeding in patients taking anticoagulants.

The prevalence of retinal tears in patients who were taking anticoagulant medication and experienced an acute PVD and VH was not significantly different from those not taking these medications. This was true regardless of which type of anticoagulation medication was analyzed. There was a trend, however, for those patients taking aspirin to have an increasing prevalence of VH without a retinal tear compared with those patients not taking aspirin. A recent report has found a significantly lower prevalence of retinal tears and detachment in patients with acute PVD and VH taking systemic anticoagulation medication.[23] This is not surprising given the results from our study demonstrating an increased risk of VH in patients with acute PVD taking anticoagulant medication. The authors of the recent report, however, did not present data of patients with acute PVD without VH.[23] Although we have demonstrated a trend toward a lower prevalence of tears in patients on systemic anticoagulation with acute PVD and VH, perhaps statistical significance was not reached in our study because of a smaller sample size.

The current report also analyzed data on clinical retinal detachments. The prevalence of retinal detachment in this cohort was high (14.3%). This was probably the result of referral bias to a retina specialist. An interesting aspect of this cohort was the significantly decreased number of clinical retinal detachments found in eyes with VH, despite the increased risk of retinal tears. One possible explanation for this phenomenon is the lead-time bias in patients with VH. The symptoms associated with a VH during an acute PVD are more likely to be noticed and cause a patient to report for examination before the evolution of a retinal tear into a detachment. Eyes with a VH had symptoms for an average of 5.4 days before examination by the retina specialist, whereas eyes without hemorrhage had symptoms for a mean of 9.0 days before seeing the retina specialist. Referral bias may also have affected this parameter because of the fact that general ophthalmologists are more likely to refer a patient to a retina specialist for examination if they observe VH regardless of the presence of a retinal tear or detachment.

The proportion of retinal tears and detachments was lower in patients taking oral anticoagulation versus patients not taking these medications. Although these correlations do not prove causation, they suggest that the use of these medications might be protective from retinal tears or retinal detachment. This could be despite the fact (or because of the fact) that some of these medications may predispose eyes with an acute PVD to present with VH and, thereby, cause referral to the retina specialist without retinal tears or detachment. Analysis of eyes with acute PVD and VH, who presented with retinal detachment, was limited in this report because of the low number of these patients (4 eyes).

The results of the current study demonstrate the complex relationship between the use of oral anticoagulation medication, the presence of VH, and the development of retinal tears or detachment in patients with acute PVD. The data suggest that during an acute PVD, there is a clear correlation between VH and the presence of a retinal tear or detachment, a probable increased frequency of VH with the use of oral anticoagulation, and a possible decreased probability of developing a retinal tear or detachment with the use of oral anticoagulation, regardless of the presence of a VH.

Further study could examine the effect of the dosage of anticoagulant medication and its serum level on the

presence of VH and retinal tears and detachment. In addition, analyzing the severity of VH in patients taking oral anticoagulant medication may also provide more insight into the precise effects of these medications during PVD.

Key words: anticoagulation, posterior vitreous detachment, retinal tear, retinal detachment, vitreous hemorrhage.

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