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Relationship between anticoagulant medication and massive intraocular hemorrhage in age-related macular degeneration

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Abstract *Background:* A massive intraocular hemorrhage in the course of age-related macular degeneration (AMD) is a devastating event. We set out to determine the role of anticoagulant therapy prescribed for vascular or cardiac indications in the development of a massive hemorrhage. *Methods:* A retrospective case-controlled study was conducted of 50 cases of age-related macular degeneration complicated by massive subretinal and vitreous hemorrhage. The control group consisted of 50 cases of AMD with small subretinal hemorrhage. *Results:* There was a significant difference in the use of anticoagulant medication (warfarin sodium) between the groups. The difference in the use of antiplatelet medication (aspirin) between the groups was not significant. A patient with a massive intraocular hemorrhage and AMD is 11.6 times more likely to use anticoagulant medication. It appeared that more than 50% of the patients in the massive hemorrhage group were allowed to stop the anticoagulant medication.
Conclusion: Anticoagulant medication poses a significant risk in the development of a massive intraocular hemorrhage in patients with exudative AMD. Antiplatelet medication poses a less significant risk. Physicians prescribing anticoagulant medication should be informed about the macular status of the patient. the In case of neovascular AMD, anticoagulant medication should be prescribed only for absolute systemic indications.

Introduction

Age-related macular degeneration (AMD) occurs in 20% of individuals over 65 years of age, and the prevalence increases to 35% in subjects older than 74 years [2]. The majority of patients present with the "dry" or geographic form. The "serous" or neovascular form accounts for approximately 10%–20% of patients with AMD but makes up 80%–90% of patients who eventually become legally blind as a result of AMD [2, 6]. Eyes with a massive intraocular hemorrhage in the course of AMD end up much worse, often with light perception only [1, 4]. A massive hemorrhage is the result of rupture of vessels within an extrachoroidal neovascular membrane, leading to a dome-shaped subretinal coagulate often combined with a dense vitreous hemorrhage. As a result of the higher incidence of cardiovascular problems in elderly patients, anticoagulant medication is encountered more frequently in this age group than in the general population.

Anticoagulants appear to be a risk factor for hemorrhagic complications in patients with AMD [4]. We therefore examined the clinical data of 50 patients with AMD complicated by a massive subretinal hemorrhage and compared them with an age-matched group of 50 patients with AMD with a small subretinal hemorrhage (less than one disc diameter). We also reviewed the use of anticoagulant medication and the indications for all patients in both groups.

Patients and methods

We performed a retrospective study of the clinical records of 50 consecutive patients with a massive subretinal hemorrhage combined with a vitreous hemorrhage as a complication of AMD who had previously undergone diagnostic ultrasonography. The inclusion criterion for this study was a massive subretinal hemorrhage in combination with a vitreous hemorrhage dense enough to prevent funduscopy in patients known to have AMD. We compared these patients with a control group of 50 AMD patients with limited, less than one disc diameter, subretinal hemorrhages.

Diabetic patients and patients with myopia of more than 8 diopters were excluded from this study. All patients in both groups were diagnosed with neovascular AMD by their referring ophthalmologist before the onset of the hemorrhage.

Best corrected visual acuity was obtained using Snellen charts. Grading of size of the subretinal hemorrhage in the control group was based on the color fundus photographs. After information about the general medical condition was obtained for all patients in both groups, the use of anticoagulant medication and the indications were evaluated.

Statistical analysis was performed with the SAS statistical analysis software package (SAS Institute, Cary, N. C.).

Results

Of the 50 patients in the hemorrhage group, 19 (38%) were female and 31 (62%) were male; in the control group, 25 patients were female and 25 male. The mean age in the hemorrhage group was 77 years, range 63–90 years, SD 6 years; the mean age in the control group was 76 years, range 64–84 years, SD 4 years. There was no statistically significant difference in age between the groups (P=0.342, Wilcoxon rank sum test).

In the hemorrhage group 15 patients were using anticoagulant medication (warfarin sodium) and 8 patients were taking antiplatelet medication (aspirin). The patients taking anticoagulant medication all had an INR value between 3 and 4; the aspirin dosage varied between 80 and 100 mg per day. In the control group only two patients were on anticoagulant medication; six patients used antiplatelet medication. The use of anticoagulant medication was significantly higher in the group of patients with a massive hemorrhage (P=0.0001); there was no significant difference in the use of antiplatelet medication between the two groups.

The main indications for anticoagulant medication in the hemorrhage group were previous coronary bypass surgery (five patients), atrial fibrillation (three patients) and mechanical heart valve prosthesis (two patients). In the control group the indications were femoral bypass (one patient) graft and cardiac aneurysm (one patient). In the massive hemorrhage group the antiplatelet medication was mainly prescribed to prevent the recurrence of an embolic cerebral vascular accident (five patients). Three patients in the control group received antiplatelet medication because of atrial fibrillation, in two other patients this medication was prescribed because of their general vascular pathology (Table 1).

Ultrasonography demonstrated a dense vitreous hemorrhage and a dome or double dome shaped subretinal hemorrhage with irregular reflectivity in all patients in the hemorrhage group (Figs. 1, 2).

The thickness of the hemorrhage ranged from 1 to 6 mm; the diameter of the base of the lesion was variable. All the patients in the control group showed a small, less than one disc diameter, submacular hemorrhage on funduscopy (Figure 3).

The median visual acuity within 3 months before the hemorrhagic event was 0.1 in both groups. In the massive hemorrhage group the visual acuity ranged from 0.025 to 0.4, in the control group, from 0.05 to 0.4. There was no significant difference in visual acuity before the hemorrhagic event (P=0.784, Wilcoxon rank sum test). After the hemorrhagic event, visual acuity was significantly worse in the massive hemorrhage group as compared to the control group (mean follow-up 4 months, range 3–6 months). The median visual acuity in the massive hemorrhage group was 0.005 (range 0.001–0.05) versus a median visual acuity of 0.1 (range 0.025–0.3) in the control group (P=0.0001, Wilcoxon rank sum test).

Table 1 Indication for anticoagulant medication in the hemorrhage group (*H*, *n*=50) and the control group (*C*, *n*=50)

Indication	Warfarin				Aspirin			
	H		C		H		C	
	No.	%	No.	%	No.	%	No.	%
Coronary bypass	5	(10)	1	(2)	1	(2)	1	(2)
Aortic bifurcation prosthesis	1	(2)			1	(2)		
Mechanic heart valve prosthesis	2	(4)						
General vascular pathology					1	(2)	2	(4)
Cerebral vascular accident	1	(2)			5	(10)		
Atrial fibrillation	3	(6)	1	(2)			3	(6)
Cardiac aneurysm	1	(2)						
Femoral bypass graft	1	(2)						
Thrombosis in leg (>1year)	1	(2)						
	15	(30)	2	(4)	8	(16)	6	(12)

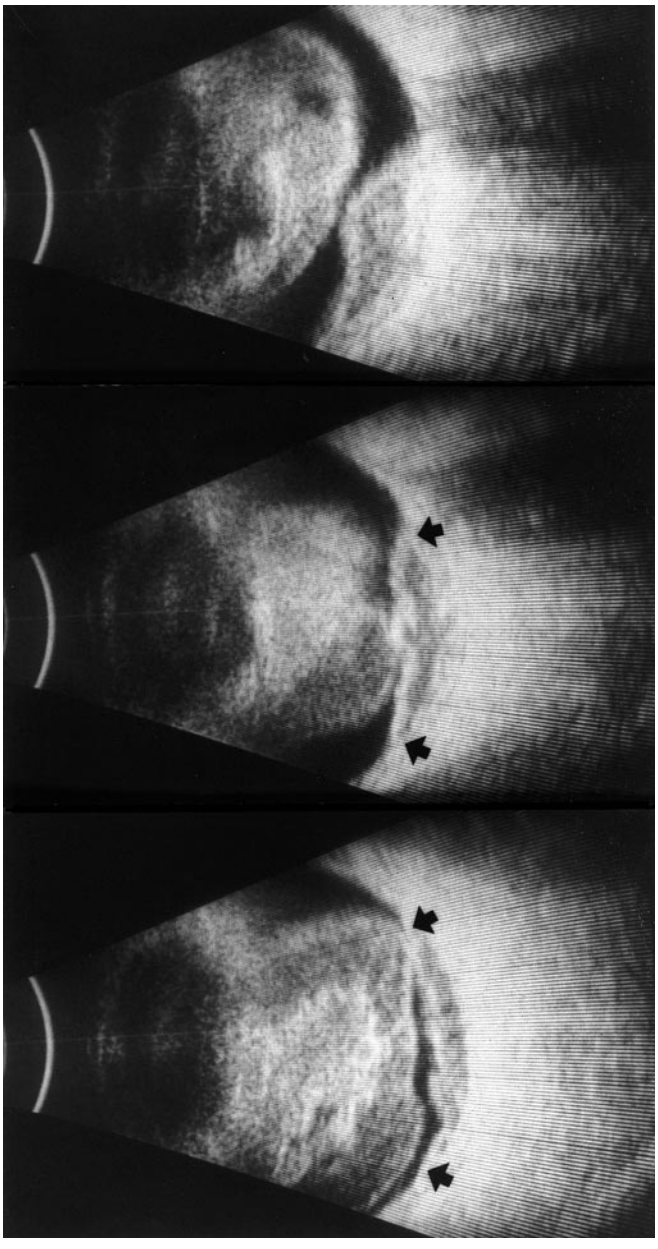

Fig. 1 Ultrasound photographs, from three angles, of a massive subretinal hemorrhage with a vitreous hemorrhage in a patient with age-related macular degeneration

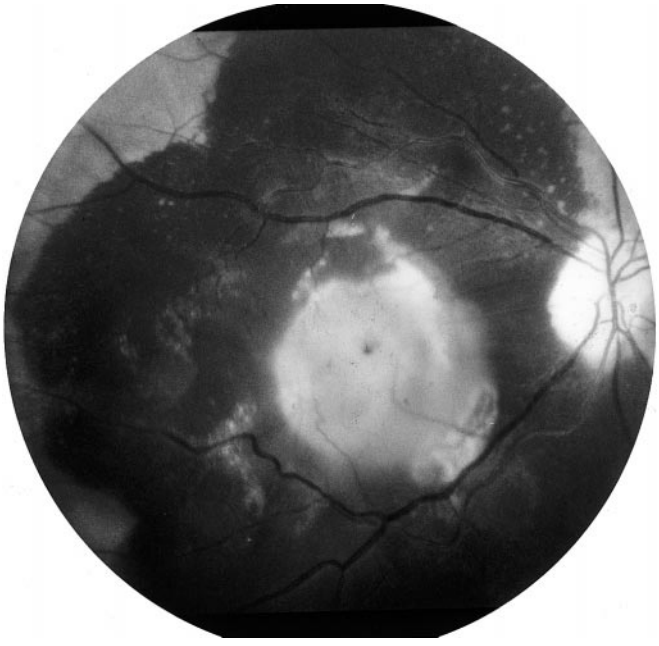

Fig. 2 Fundus aspect after massive subretinal hemorrhage; vitreous hemorrhage has cleared

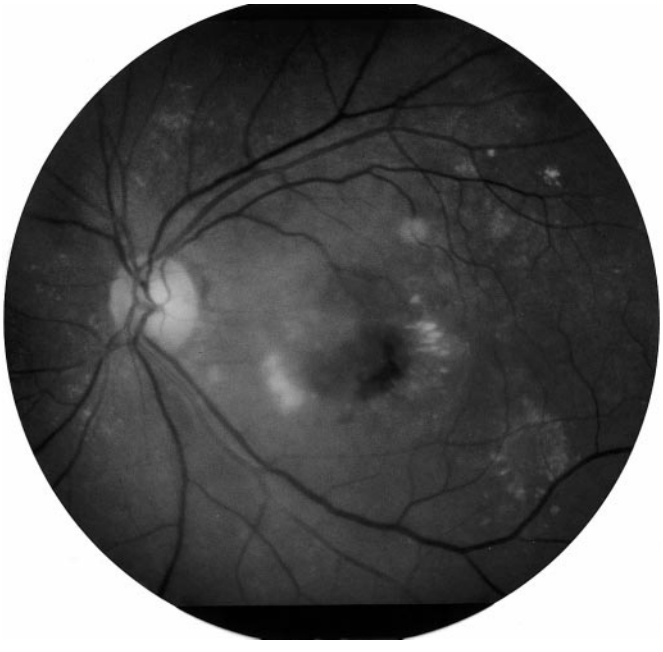

Fig. 3 'Small' subretinal hemorrhage in a patient with neovascular AMD

In the massive hemorrhage group three eyes eventually lost light perception and ten eyes ended up with a visual acuity of light perception only.

In our study the odds ratio of anticoagulant medication was 11.6 (95% confidence interval 3.1–44.3). This means that a patient with a massive hemorrhage is 11.6 times more likely to receive anticoagulant medication. The odds ratio of antiplatelet medication was 2.1 (95% confidence interval 0.7–6.6). In the latter case the value "1" is included in the confidence interval, indicating lesser significance of the odds of antiplatelet medication. On consulting the patient's own internist and/or cardiologist we learned that in 8 (53%) of 15 patients receiving anticoagulant medication the indications for this kind of therapy were relative and, if desired, the prescription could be stopped.

Discussion

Social blindness in AMD is mainly caused (90%) by choroidal neovascularization, the so-called "wet" or neovascular type. If the choroidal neovascularization is complicated by a massive hemorrhage the functional outcome is even worse, with patients often ending up with light perception only [2]. Not all contributing risk factors leading to a massive intraocular hemorrhage are known, but age of the patient and extent of the macular degeneration are among them. Furthermore, high blood pressure and cardiovascular diseases contribute to this risk. In a study by El Baba et al. [3], 19% of patients with AMD complicated by a massive hemorrhage were taking anticoagulant or antiplatelet medication and 40% had a positive history of systemic hypertension and cardiovascular disease. The risk of a hemorrhage in anticoagulated patients is related to the level of intensity and the duration of anticoagulant therapy. Increasing age is also a factor in increased responsiveness to anticoagulants [7]. Once a hemorrhage occurs, anticoagulant therapy probably intensifies the degree and extent of the bleeding [5, 7].

Since the consequences of a massive intraocular hemorrhage are severe, and since there are few effective therapeutic options once a hemorrhage has occurred, every risk factor should be eliminated if possible. The surgical removal of a massive subretinal hemorrhage has been described by several authors [8], but the visual outcome is poor due to delays between the onset of the hemorrhage and the actual vitrectomy, the amount of damage to the photoreceptors and the macular disciform degenerative process itself. In this study we described is a significant elevated risk for a massive intraocular hemorrhage in patients with exudative AMD who take anticoagulant medication. The actual INR value at the time of the massive hemorrhage was between 3 and 4 in the anticoagulant medication group. These values are near the upper border of the therapeutic index of anticoagulant medication, which may further increase the already substantial risk for a massive intraocular hemorrhage. For antiplatelet medication there also seems to be an elevated risk, albeit less significant than in the anticoagulant medication group.

A better estimate of the relative risk, however, can only be established in a cohort study.

In conclusion, this study confirms the idea that the use of anticoagulant medication is a major risk factor in patients with exudative AMD. We propose that in patients with exudative AMD anticoagulant therapy should be prescribed only for absolute indications such as mechanical heart valve prosthesis, when antiplatelet medication does not suffice. We advocate that physicians who prescribe anticoagulant medication always inform themselves about the ophthalmological status of elderly patients and, when in doubt, refer a patient to an ophthalmologist before initiating the medication.

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