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REVIEW

Management of antithrombotic therapies in patients scheduled for eye surgery

A narrative review

Fanny Bonhomme, Farhad Hafezi, Françoise Boehlen and Walid Habre

The large majority of patients undergoing ophthalmic surgery are elderly and take systemic medications on a regular basis, including antiplatelet and anticoagulant treatments. It is current practice for many physicians to discontinue antithrombotic treatment prior to surgery to reduce bleeding complications that may lead to retrobulbar haemorrhage and, ultimately, to loss of vision. However, discontinuation of antithrombotic treatment in such patients may lead to thromboembolic events with serious consequences. The present narrative review highlights the risk of thrombosis when discontinuing antithrombotic drugs and the risk of bleeding when continuing them.

The published literature on this topic shows that discontinuation of antiplatelet or anticoagulant treatment leads to a substantially increased risk of arterial or venous thromboembolic events and related complications, especially in patients with atrial fibrillation, prosthetic heart valves or recent coronary stenting. This risk is distinctly higher than the risk of significant local haemorrhage. Ophthalmic bleeding events reported in the literature are usually minor, without serious consequences, even if antiplatelet or anticoagulant treatments are continued, provided that the anticoagulation level is within the therapeutic range. Thus, the current data are in favour of maintaining antiplatelet and anticoagulant drugs for most ophthalmic procedures, regardless of the anaesthetic techniques.

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Introduction

Eye surgery, including cataract surgery, is an increasingly performed surgery in European countries. The large majority of patients undergoing ophthalmic surgery are elderly and take regular systemic medications, including antiplatelet and anticoagulant treatments. More than 28% of these patients take aspirin, 2% take clopidogrel and more than 5% take an anticoagulant.[1] The anaesthetic techniques for ophthalmic surgical procedures vary, with an increasing tendency towards topical, local or regional anaesthesia.[2,3] Whereas in 1990, local or regional anaesthesia was used in 46% of ophthalmic surgical procedures, in 2003 the number had increased to more than 95%. General anaesthesia has become an exception, essentially used in paediatric population or for specific procedures (such as strabismus correction). The management of antiplatelet and anticoagulant drugs for the surgical procedure or for regional anaesthesia is an increasing problem for physicians. On one hand, intraoperative bleeding may have important functional consequences; on the other hand, arterial or venous thromboembolic events may lead to serious and potentially fatal complications. Although the perioperative management of antithrombotic treatment is well established for cataract surgery since bleeding risk has been studied,[4–6] recommendations concerning the other ophthalmic procedures are changing, based on studies published in recent years. The aim of this review is to assess the delicate balance between the thrombotic risk associated with disruption of antithrombotics and the bleeding risk associated with their continuation. In a first part, we will assess the risk of arterial and venous thromboembolic events related to discontinuation or modification of antithrombotic treatment. We will then focus on recent studies about bleeding risk in patients treated by antithrombotic agents, especially undergoing vitreoretinal procedures. On the basis of the published results, we will provide updated proposals for antiplatelet and anticoagulant management

From the Division of Anaesthesiology (FB, WH), Division of Ophthalmology (FH), the Haemostasis Unit (FrB), Geneva University Hospitals, Geneva, Switzerland

Correspondence to Dr Fanny Bonhomme, Division of Anaesthesiology, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland
Tel: +41 22 372 74 03; fax: +41 22 372 76 90; e-mail: Fanny.Bonhomme@hcuge.ch

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depending on the different ophthalmic and anaesthetic procedures.

Disruption of antiplatelet therapy and thrombotic risk

Antiplatelet drugs are a cornerstone of therapy for patients with atherosclerotic vascular disease, including coronary artery disease, cerebrovascular disease and peripheral arterial disease. Antiplatelet therapy is indicated for secondary prevention in cases of acute coronary syndrome, myocardial infarction, myocardial revascularisation, stroke (transient ischaemic attack and ischaemic stroke) or chronic peripheral arterial insufficiency.[7] For coronary artery disease, the choice, initiation and duration of antiplatelet therapy for myocardial revascularisation depend on the clinical setting. It often requires the combination of several antiplatelet drugs. The duration of dual antiplatelet therapy is usually 1 month after bare metal stent implantation in stable angina, and 12 months after drug-eluting stent implantation.[8] Some patients at high risk for thromboembolic events may benefit from prolonged dual antiplatelet therapy beyond 1 year.

Premature discontinuation of antiplatelet therapy may lead to major cardiovascular events, including stent thrombosis, myocardial infarction, nonfatal stroke and death. In a retrospective analysis, Rossini *et al.*[9] found that patients who had stopped antiplatelet therapy early after drug-eluting stent implantation, experienced a greater incidence of major adverse cardiac events (28.6%) and stent thrombosis (7.6%). Mortality (13.4%) and cardiovascular death (5%) were also significantly higher among patients with early discontinuation. The earlier the discontinuation, the greater the incidence of major adverse cardiac events, stent thrombosis and death (with highest rates when antiplatelet drugs are stopped within the first 30 days). Concerning thienopyridines, clopidogrel withdrawal (with aspirin alone continued) was associated with higher rates of major cardiac complications for 12 months; after 1 year, only a nonstatistically significant increase was observed. Recently, in a large prospective cohort study of patients with coronary stents, interruption of oral antiplatelet therapy more than 5 days prior to an invasive procedure was found to increase the incidence of major adverse cardiac and cerebrovascular events.[10] The relationship between antiplatelet discontinuation and adverse cardiac events might be partially explained by a rebound of platelet reactivity,[11,12] and also by the prothrombotic and proinflammatory effects of surgery. In a less consistent way, other factors may increase the risk of stent thrombosis: the extent of coronary disease; the number of stents and their length and positioning; diabetes; and smoking status.[13] Some case reports and a large cohort study[14] have reported that discontinuation of low-dose aspirin results in a 40% increase in the risk of stroke, with a longer delay between discontinuation and stroke than for cardiac events.

For these reasons, American and European guidelines[15,16] recommend continuing aspirin in the perioperative period, unless the risk of bleeding is clearly higher than the risk of cardiovascular events. When necessary, it is sufficient to stop aspirin 3 days before the invasive procedure. For other antiplatelet therapies, clopidogrel and ticagrelor should be stopped for 5 days, and prasugrel for 7 days.

Disruption of anticoagulant therapy and thrombotic risk

Long-term anticoagulation is warranted in three major clinical situations: atrial fibrillation in order to prevent stroke or systemic embolism; valvular heart disease (mechanical prosthetic heart valve replacement); and venous thromboembolism prophylaxis (in case of high risk of recurrence of thromboembolic events). Anticoagulant agents are also indicated for a shorter period to treat acute arterial or venous thromboembolic events. Interruption of antithrombotic therapy exposes patients to an increased risk for thromboembolic events that can have catastrophic consequences (stroke with major disability, valve thrombosis, pulmonary embolism and death, for example). The risk for perioperative arterial or venous thromboembolic events can be stratified into high (annual risk for thromboembolism >10%), moderate (annual risk for thromboembolism between 5 and 10%) and low risk (annual risk for thromboembolism <5%) for each clinical indication.[17] For mechanical heart valves, the highest risks are observed for mitral valve prosthesis, older aortic valve prosthesis and after recent stroke or transient ischaemic attacks. Recent venous thromboembolic events and patients with severe thrombophilia are at high risk of perioperative thromboembolic complications. Regarding atrial fibrillation, the $CHADS_2$ score[18] (congestive heart failure, hypertension, age $\geq$75 years, diabetes, and previous stroke or transient ischemic attack [doubled]) helps to quantify the risk of stroke and to choose the most appropriate antithrombotic therapy. The absolute risk of ischaemic stroke is around 4.5% per year in patients without vitamin K antagonist treatment, and decreases to 1.4% per year on vitamin K antagonist treatment. The recent recommendations for perioperative management are to continue oral anticoagulants for minor procedures, and to stop oral anticoagulants for other invasive procedures.[17] The choice of bridging anticoagulation therapy during interruption of oral anticoagulant therapy has to take into account the thrombotic risk based on patient-related and surgery-related factors. However, it must be kept in mind that bridging therapy does not totally prevent thrombotic complications[19]; in patients at high risk for thromboembolism receiving bridging therapy with a therapeutic dose of low molecular weight heparin, the incidence of arterial thromboembolic

events is around 1 to 2%, and when unfractionated heparin is used, the incidence of thromboembolic events varies between 0 and 5%. Thromboembolic events more often occur after discharge during the period of oral anticoagulant resumption.[20]

Bleeding and functional risks of ophthalmic surgery during continuation of antithrombotic treatment

The main fear concerning maintenance of antithrombotic therapy in case of ophthalmic surgery is the risk of haemorrhage secondary either to the anaesthesia technique or to the surgical procedure. When using retrobulbar anaesthesia (RBA) or peribulbar anaesthesia (PBA), the occurrence of a retrobulbar haemorrhage from an arterial puncture can have devastating consequences, leading to a compressive haematoma and retinal ischaemia and visual loss. In fact, the main risk factor for retrobulbar haemorrhage is arterial fragility (arterial hypertension, diabetes), rather than haemostatic disorders. The risk of arterial puncture can be minimised by using single injection techniques, by limiting the depth of needle insertion (not more than 25 mm), by using fine and short needle (<25G and <25 mm) and by injecting into poor vascular compartment tissue (avoiding superonasal puncture).[21] Venous puncture is less severe because it leads to noncompressive haematoma, and more often surgery can be performed.

Expulsive choroidal haemorrhage is a rare and dramatic complication of ocular surgery that usually leads to either loss of vision or loss of the eye. Most frequently, it is associated with cataract surgery, but it can occur also after glaucoma surgery, corneal transplantation, traumatic rupture of the globe, perforation of a corneal ulcer or retinal surgery. The incidence of suprachoroidal haemorrhage during cataract surgery ranges from 0.03% in phacoemulsions to 0.13% in extracapsular cataract extractions.[22] The main risk factors for expulsive haemorrhage are advanced age, arteriosclerosis, diabetes, arterial hypertension and local eye conditions (choroidal sclerosis, glaucoma, myopia, recent surgery).[23] Conjunctival or cutaneous haematomas are unsightly but have no serious consequences.

Cataract surgery

In most centres, phacoemulsification surgery is commonly performed with topical anaesthesia alone or topical and intracameral anaesthesia.[3] The potential drawbacks of topical anaesthesia are usually not serious (eye movements). With regard to haemorrhagic complications, topical anaesthesia is obviously safer than RBA, PBA or sub-Tenon's block. Maintenance of antiplatelet (aspirin or clopidogrel) or anticoagulant therapy during the perioperative period in patients scheduled for cataract surgery does not increase the risk of severe bleeding or ophthalmic complications,[4–6,24] as cataract extraction is an avascular procedure. In a meta-analysis of 11 studies, patients who continued oral anticoagulants (vitamin K antagonist) had an increased bleeding risk, but these haemorrhages were self-limiting and insignificant (hyphaemas, subconjunctival haematoma) without compromise to visual acuity.[25]

Vitreoretinal surgery

In the recent years, there have been a number of studies about the possibility of continuing antithrombotic therapy in patients undergoing vitreoretinal surgery. In a review of 57 vitreoretinal surgical procedures performed on patients treated with warfarin, Dayani and Grand[26] reported no anaesthesia-related or intraoperative haemorrhagic complications, and four postoperative haemorrhages [two in the subtherapeutic INR (international normalised ratio) group and two in the supratherapeutic INR group]. These haemorrhages resolved spontaneously without any sequelae. Fu *et al.*[27] reported 25 retinal surgeries with retrobulbar or peribulbar block, and reported only one intraoperative subretinal haemorrhage associated with scleral buckling and the external drainage of subretinal fluid. In an observational study of 822 patients,[28] five risk factors for bleeding were identified in multivariate analysis: male sex; smoking history; proliferative diabetic retinopathy; glaucoma and anticoagulant use. Anticoagulant drugs were associated with an increased risk of intraocular haemorrhage, but with no serious consequences, no re-operations and no surgery failure. Antiplatelet use, with or without withdrawal, before surgery was not a risk factor for bleeding.

In a recent case–control series of 60 patients receiving warfarin (INR between 0.94 and 4.6) and undergoing pars plana vitrectomy,[29] the authors did not observe any increase in complications among patients continuing warfarin. They concluded that the risks of stopping warfarin anticoagulation seem greater than the perceived benefits of reduced complications, and do not recommend that surgeons withhold warfarin treatment before vitrectomy.

A retrospective study reported that severe bleeding complications might be more frequent in patients receiving antiplatelet therapy.[30] In this study, the incidence of overall and mild postoperative haemorrhagic complications was similar between the controls, the patients receiving anticoagulation and the patients on antiplatelet therapy, whereas the incidence of potential sight-threatening haemorrhagic complications were more frequent in patients receiving antiplatelet drugs. The risk factors for bleeding were different between the groups; in the antiplatelet group, patients had more diabetes mellitus (43.2 vs. 19.4% in controls) and more hypertension (72.7 vs. 36.1%). When focusing on a population scheduled for diabetic vitrectomy, no difference in the incidence of postoperative vitreous haemorrhage or surgical re-operation was observed between the patients on antiplatelet

therapy (aspirin, or clopidogrel or both) and patients not taking antithrombotic drugs.[31]

Glaucoma surgery

Currently, there is no strong evidence available to guide the management of patients on antithrombotic treatment undergoing glaucoma surgery. In a retrospective study, Cobb *et al.*[32] reviewed 367 trabeculectomies. None of the 55 patients on aspirin experienced significant intraoperative or postoperative haemorrhage. Aspirin was associated with a significantly higher risk of hyphaema but did not significantly affect intraocular pressure at 2 years. Of the five patients on warfarin, all suffered haemorrhagic complications (two required re-operation for hyphaema evacuation) and four had trabeculectomy failure. These results were confirmed by another retrospective study.[33] Patients on anticoagulant therapy had a higher rate of haemorrhagic complications (31.8% if anticoagulation continued, 15.4% if anticoagulation stopped), than patients on antiplatelet therapy (haemorrhages in 8%) and controls (haemorrhages in 3.7%). No guidelines can be suggested because of the paucity of data, but a questionnaire survey in England showed that two-thirds of surgeons do not stop warfarin or antiplatelet therapy prior to glaucoma surgery.[34]

Oculoplastic surgery

Though low, the risk of bleeding among patients on antithrombotic therapy during cutaneous surgery is increased.[35] Two recent studies reported a higher incidence of haemorrhages during or after cutaneous surgery in patient on antithrombotic therapy, but without serious consequences.[36,37] For oculoplastic procedures, the incidence of severe haemorrhagic complications is low. In an American survey,[38] the incidence of orbital haemorrhage associated with cosmetic eyelid surgery was 0.055% (1 : 2000), and orbital haemorrhage with permanent visual loss was 0.0045% (1 : 10 000). In a prospective study, serious bleeding with potential to affect surgical outcome, occurred in 0.4% of oculoplastic surgeries.[39] The authors identified four risk factors for bleeding or bruising: age more than 60 years; male sex; heart disease; and arterial hypertension. Anticoagulants and antiplatelet drugs did not increase the risk of bleeding, but only a few patients were receiving these drugs. The authors suggested that selected procedure could be safely performed without stopping antithrombotic agents.

Proposals for management of antithrombotic therapy in patients undergoing eye surgery

For most ophthalmic procedures, the risk of stopping antithrombotic treatment (anticoagulants or antiplatelet drugs) is higher than that of maintaining these therapies. Indeed, the risk of arterial or venous thromboembolic events when discontinuing antithrombotic drugs may be high, with potential devastating consequences, while haemorrhages and bleeding complications among patients on antithrombotic therapy have often no serious consequences. Local anaesthesia (including sub-Tenon, retrobulbar and peribulbar techniques) and most ophthalmic procedures can be performed safely in patients while antithrombotic treatment is maintained. If an interruption of these treatments is needed, the modification of the treatment should be discussed with a cardiologist or a haematologist, the surgeon and the anaesthetist. Anaesthetists play a key role by providing preoperative assessment and guiding other physicians.

On the basis of the published evidence and clinical practice, we propose the following management of antithrombotic treatment, including unfractionated heparin, low molecular weight heparin, vitamin K antagonist, aspirin and clopidogrel (Table 1) and in particular, the following points:

(1) anticoagulant and antiplatelet therapies should be continued regardless of the anaesthetic technique
(2) for cataract surgery, antiplatelet and anticoagulant treatment should be continued
(3) for vitreoretinal procedures, antithrombotic treatment should be continued, except if interruption is considered essential by the surgeon
(4) for most anterior chamber and extraocular procedures (except strabismus surgery), antithrombotic treatment should be continued
(5) for glaucoma surgery, antithrombotic treatments can be safely continued, but occurrence of haemorrhage can lead to surgery failure; for this reason, anticoagulants may be stopped if thrombotic risk is low
(6) if vitamin K antagonist is continued, the anticoagulation level (INR) must be in the therapeutic range, and anticoagulation level must be checked prior to surgery
(7) if oral anticoagulant treatment is stopped, the need for bridging therapy must be evaluated according to thromboembolic risk.

These proposals are consistent with other guidelines or recommendations.[40,41]

With regard to the newer anticoagulants (rivaroxaban, dabigatran, apixaban) and newer antiplatelet drugs (prasugrel, ticagrelor), the data are insufficient to provide any recommendations. As these agents provide an important antithrombotic effect, the bleeding risk is probably higher than that induced by older agents. We recommend that these new agents should be stopped if possible, with use of bridging therapy provided by an older agent if necessary.[42]

Conclusion

Cessation of antithrombotic treatments may lead to serious and potentially life-threatening thromboembolic events that by far outweigh the reduced risk for local bleeding complications. Local anaesthesia (sub-Tenon,

Table 1 Perioperative management of antithrombotic therapy in patients undergoing ophthalmic surgery

Surgeries for which treatment can be continued (caution with direct oral anticoagulants and new antiplatelet therapies)									
Surgery	aspirin	clopidogrel	prasugrel ticagrelor	unfractionned heparin IV	LWMH	fondaparinux	VKA with short half life	VKA with long half life	Direct oral anticoagulants (rivaroxaban, dabigatran, apixaban…) at therapeutic dose
Cataract with topical	Continue								
Cataract (RBA) Chalazion, Eyelid cyst, Lacrimal probing, Dacryocysto-rhinostomy, Pterygium, Keratoplasty, Evisceration, Enucleation, Cerclage/indentation	Continue	Continue	After high thrombotic risk period Stop 7 d : prasugrel 5 d : ticagrelor (continue aspirin)	Continue	Continue	Continue	Continue (check that INR is within therapeutic range the day of surgery)	Continue (check that INR is within therapeutic range the day of surgery)	After high thrombotic risk period Stop 24h before, Restart 24h after
Posterior segment : retinal detachment, vitreoretinal surgery, vitrectomy	Continue	Continue unless surgeon special request		Continue unless surgeon special request					
Surgeries for which a stop/bridging is required									
Surgery	aspirin	clopidogrel	prasugrel ticagrelor	unfractionned heparin IV	LWMH	fondaparinux	VKA with short half life	VKA with long half life	Direct oral anticoagulants (rivaroxaban, dabigatran, apixaban…) at therapeutic dose
Glaucoma Eyelids : entropion, ectropion, Eyelid ptosis Orbital decompression	Stop 3 d if primary prevention Continue if secondary prevention	After high thrombotic risk period Stop 5 d (continue/ introduce aspirin)	After high thrombotic risk period Stop 7 d : prasugrel 5 d : ticagrelor (continue aspirin)	Stop 3h before	Last injection 12h before if prophylactic Last injection 24h before if therapeutic with 2 doses/d (36h if 1dose/d)	Last injection 24h before if prophylactic Last injection 36h before if therapeutic	Aim INR<1,5. Last intake 4 days before surgery ± Bridging by UFH or LWMH	Aim INR<1,5. Last intake 7 days before surgery or vitamin K supplement ± Bridging by UFH or LWMH	No laboratory assay Last intake 5 days before surgery ± Bridging by UFH or LWMH
Strabismus	Continue	Continue							

i.v., intravenously; LMWH, low molecular weight heparin; RBA, retrobulbar haemorrhage; UFH, unfractionated heparin; VKA, vitamin K antagonist.

retrobulbar, peribulbar) is safe in patients taking anticoagulant or antiplatelet therapy. For most ophthalmic procedures, anticoagulants (heparin and vitamin K antagonist) do not increase the risk of severe haemorrhages and serious complications, if anticoagulation levels are within the therapeutic range. Current data suggest that antiplatelet drugs (aspirin and clopidogrel) and anticoagulants like heparin and vitamin K antagonist should be continued in the perioperative period for most ophthalmic procedures. Precautions are recommended regarding the new powerful antithrombotic drugs.

We suggest that each centre performing ophthalmic surgery produce local protocols to minimise antithrombotic discontinuation and thromboembolic events, while limiting the risk of significant bleeding to maximise intraoperative and postoperative safety.

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