AMBULATORY EYE SURGERY AND ANTITHROMBOTIC THERAPY – NEW APPROACHES

Tatjana Šimurina¹,²,³, Marija Danilović Luketić¹,⁴, Sandra Graf Župčić⁵,⁶ and Boris Mraović⁷

¹Department of Anesthesiology, Resuscitation, Intensive Medicine and Pain Management, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia;
²Department of Health Studies, University of Zadar, Zadar, Croatia;
³Department of Anesthesiology, Resuscitation and Intensive Care Medicine, Zadar General Hospital, Zadar, Croatia;
⁴Department of Anesthesiology, Resuscitation and Intensive Care Medicine, Požega General County Hospital, Požega, Croatia;
⁵School of Medicine, University of Rijeka, Rijeka, Croatia;
⁶Department of Neurology, Rijeka University Hospital Center, Rijeka, Croatia;
⁷Department of Anesthesiology and Perioperative Medicine, School of Medicine, University of Missouri, Columbia, USA

SUMMARY – One of the most common surgeries in elderly patients is eye surgery. An increasing number of patients undergoing ambulatory eye surgery are on antithrombotic therapy. These drugs may increase the risk of perioperative bleeding associated with ophthalmic needle blocks and/or eye surgery. Intraoperative bleeding and postoperative hemorrhagic complications may lead to the loss of vision or even eyes. On the other hand, stopping anticoagulants and antplatelets before the surgery may increase the risk of thrombotic events with potentially life-threatening complications. The aim of this narrative review is to provide a systematic review of the published evidence for the perioperative antithrombotic management of patients undergoing different types of eye surgery in ambulatory settings. A comprehensive review of the English-language medical literature search utilizing PubMed, Ovid Medline® and Google Scholar from January 2015 to December 2018 was performed. The database searches included studies providing evidence relevant to ambulatory eye surgery and perioperative antplatelet medications and anticoagulants. Updated recommendations will be given for continuation, discontinuation, and modification of antithrombotic agents in order to optimize the management of antithrombotic therapies in outpatients scheduled for eye surgery.

Key words: Surgical procedure, ophthalmologic; Ambulatory surgery; Anesthesia, regional; Anticoagulants; Agents, antiplatelet

Introduction

Eye surgery is increasingly performed as outpatient surgery over the last couple of decades. Phacoemulsification has contributed greatly to the transition from inpatient to outpatient ophthalmic surgery. Other factors are introduction of minimally invasive surgery, laser, ultrasound and robotic techniques, improved pain control, greater attention on patient outcomes, broader indications for regional anesthesia that has almost completely replaced general anesthesia, and clearly defined discharge criteria. Longer eye surgery procedures with a high risk of perioperative complications are not appropriate for ophthalmic ambulatory anesthesia.

Patients undergoing eye surgery are predominantly elderly with significant comorbidities and often take...
multiple medications including antithrombotic drugs. The use of antithrombotic drugs has significantly increased as the prevalence of cardiovascular diseases among aging people has increased. Surgical bleeding and hemorrhagic complications of ophthalmic needle blocks could be catastrophic for visual function. Discontinuation of antithrombotic agents, dose reduction, and/or low molecular weight heparin (LMWH) bridging may reduce the risk of bleeding related to eye surgery and needle based ophthalmic blocks, but at the expense of an increased risk of life-threatening thromboembolic events.

Guidelines have been published to address the issues of the use of antithrombotic drugs in the broader context of general and regional anesthesia, as well as specific recommendations for ophthalmic regional anesthesia. Recommendations for ophthalmic patients on antithrombotic therapy undergoing eye surgery are based on observational studies, retrospective and prospective cohort studies, case series, case reports, and expert reports. Prospective randomized trials are lacking because such studies would be considered unethical. There are a few factors that have recently emerged in deciding on discontinuation of antithrombotic drugs prior to eye surgery in order to minimize perioperative bleeding, i.e. an increasing number of patients on new-generation antithrombotic agents, advances in regional ophthalmic anesthesia and surgical techniques, changing demographic characteristics of ophthalmic patients, and increased awareness of patient outcomes. Moreover, there is sufficient evidence for the prothrombotic phenomenon, the so-called ‘rebound’ effect following antithrombotic withdrawal, that may be responsible for systemic adverse events. However, there is paucity of studies examining the balance between the risk of perioperative hemorrhage and the risk of thromboembolic complications in association with newer oral antithrombotic agents in outpatients undergoing eye surgery.

We hypothesized that current recommendations would need updating in accordance to newly published clinically relevant studies. The objective of this narrative review is to summarize current knowledge based on the recently published peer-reviewed medical articles with respect to continuation, discontinuation, and modification of antithrombotic agents in order to achieve an optimal approach for patients on antithrombotic treatment who are scheduled to undergo eye surgery in ambulatory settings.

Material and Methods

Two independent reviewers searched for medical literature written in English on PubMed, Ovid Medline® and Google Scholar. Peer-reviewed articles, systematic or narrative review articles, meta-analyses, prospective randomized studies, retrospective cohort studies, observational studies, case reports and case series were systematically searched for, through the time period from January 2015 to December 2018. Other types of publications such as editorials, letters to editors, animal experiments, studies in children, and data available only in abstracts were excluded. The search of databases included older and newer anticoagulants and antiplatelet drugs, the risk of intraoperative surgical bleeding during different types of elective same-day ophthalmic procedures, and hemorrhagic complications of ophthalmic regional anesthesia (topical anesthesia with intracameral local anesthetic, needle blocks [intraconal or extraconal] or cannula sub-Tenon’s [episcleral] blocks) in outpatients on antithrombotic agents. Further, we searched for thromboembolic events associated with cessation or modification of the antithrombotic treatment regimens. We searched the following Medical Subject Headings (MeSH) terms: Surgical Procedure, Ophthalmologic; Surgery, Outpatient; Ambulatory Surgery Procedures; Anesthesia, Regional; Anticoagulants; Agents, Antiplatelet; Aspirin; Warfarin; Clopidogrel; Heparin, Low-Molecular-Weight; Thrombin Inhibitors, Direct; Direct Factor Xa Inhibitors; Thrombosis and Embolism.

Results

We identified 20 articles (9 review articles, 2 systematic reviews with meta-analysis of randomized clinical trials [RCTs], 1 prospective randomized study, 3 retrospective analyses, 1 observational study, 2 case reports, and 2 case series) with relevant information on significant ocular hemorrhagic complications and thromboembolic adverse events in patients with anticoagulant (Acoag) and antiplatelet (Aplt) therapy. Out of 20 articles, 11 studies met the eligibility criteria (8 review articles, 1 retrospective analysis, 1 prospective randomized...
study, and 1 case report) and were selected to summarize updated information on intraoperative bleeding, postoperative hemorrhagic complications, and arterial or venous thromboembolic events. Critical appraisal was performed based on the selected studies and summarized updated recommendations are presented.

Discussion

We reviewed and analyzed new evidence from recently published literature and summarized optimal approaches to ophthalmic patients on antithrombotic treatment that are scheduled for eye surgery under local ophthalmic anesthesia in ambulatory settings.

Eye surgery is currently the most common procedure among elderly patients and is often performed as outpatient surgery in ambulatory surgical centers. The most common procedures are cataract extraction, strabismus repair, glaucoma surgery, simple vitrectomy, minimal plastic surgery, nasolacrimal duct probing, chalazion excision, and eye examinations such as tonometry, etc. The vast majority of ocular surgeries are procedures under topical anesthesia with intracameral application of local anesthetics and needle or cannula based ophthalmic blocks. When local application or regional blocks are not feasible, e.g., uncooperative or anxious patients, fast-track general anesthesia has been a safe choice even in frail elderly patients who are often polymedicated and usually on antithrombotic therapy. Often indications for antithrombotic drugs are stroke prevention in atrial fibrillation (AF), management and prevention of thromboembolism, in situ prosthetic heart valves, treatment of acute coronary syndrome, and secondary prevention of cardiovascular disease. More than 28% of ophthalmic patients take aspirin, 2% take clopidogrel, and around 5% take various anticoagulants. In general, eye surgery is considered a low-risk surgery with a cardiac risk less than 1%. However, many complications may occur in ophthalmic patients undergoing eye surgery who are on chronic antiplatelet and anticoagulant therapy. Surgical bleeding and hemorrhagic complications related to sharp needle (intracanal or extraconal) or cannula (episcleral) based blocks may have sight-threatening complications if antithrombotic therapy is continued. Even small intraoperative and postoperative bleeding may present a severe risk due to limited and not expandable space in the orbit and compartments of the eye globe.

Risk of sight-threatening bleeding in eye surgery

Predisposing factors to perioperative hemorrhage include increasing age, comorbidities (liver failure, renal failure, anemia, cardiac stent, uncontrolled hypertension), history of bleeding disorders or thromboembolic events, family history of bleeding and clotting disorders, medications used (antithrombotic drugs, steroids) and herbal treatments, eye characteristics (myopic eye with staphyloma), and type of eye surgery. Decision on cessation or continuation of antithrombotic drugs, or the use of bridging therapy with unfractionated heparin (UFH) or LMWH should be based on bleeding risk prediction and stratification of the risk of sight-threatening hemorrhagic complications.

Type of regional ophthalmic blocks

The type of regional ophthalmic blocks and patient-related risk factors are used to stratify the risk of sight-threatening bleeding to low, moderate and high risk if antithrombotic therapy is continued perioperatively (Table 1). According to the recommendation shown in Table 1, there are no significant bleeding risks in peribulbar and retrobulbar anesthesia for most ophthalmic patients on Aplt and/or Acoag treatment except for the case of mechanical heart valves or a combination of Aplt and Acoag therapy in a patient who has only one eye. Moreover, the risk of bleeding may be reduced by single shot inferonasal puncture into poor vascular tissue with a narrow and short needle through a small incision. Local anesthesia with peribulbar, retrobulbar or episcleral block can be performed safely not only in otherwise healthy ophthalmic patients without antithrombotic therapy but even in those with renal or liver failure or coagulopathy while antithrombotic treatment is maintained.

Hemorrhagic complications related to ophthalmic blocks are usually assessed on the 4-grade scale proposed by Kallio et al. as mild (grade 1 [spot ecchymosis] or grade 2 [lid ecchymosis involving half of the lid surface area or less]), moderate (grade 3 [lid ecchymosis all around the eye]), and severe (grade 4 [retrobulbar hemorrhage with increased intraocular pressure]). Three non-randomized controlled trials by Calenda et al. and two prospective cohorts by Kallio et al. and Katz et al. from a recent systematic review by...
Takaschima et al.\textsuperscript{17} did not find severe bleeding related to needle blocks in association with the use of antithrombotic drugs. There were no differences regarding mild to moderate hemorrhage (grades 1 to 3) between patients who underwent ophthalmic regional anesthesia and were still taking aspirin, clopidogrel or warfarin, and control group patients who did not take any antithrombotic drug. In a retrospective cohort study by Katz et al.\textsuperscript{16}, the incidence of retrobulbar hemorrhage was only 0.04% (95% confidence interval [CI]: 0.001-0.10) among 14,823 patients with peribulbar or retrobulbar blocks for cataract surgery.

**Type of ophthalmic procedures**

Antiplatelet medications can be continued for most of ophthalmic surgeries in ambulatory settings. Vigilance is needed regarding a new stronger Aptl, e.g., prasugrel or ticagrelor. A recently published article has reported a case of a 62-year-old female with proliferative diabetic retinopathy on dual Aptl therapy with aspirin and prasugrel for preventing coronary stent thrombosis. She presented for panretinal photocoagulation under retrobulbar block but she developed retrobulbar hemorrhage. Newer, more potent Aptl drugs might carry higher risks of severe bleeding complications in susceptible patients\textsuperscript{18}. Anesthesiologists and ophthalmologists should consider delay of the surgery until dual Aptl therapy is no longer needed, to hold prasugrel or avoid retrobulbar blocks and choose different regional ophthalmic blocks such as peribulbar block with the use of ultrasound.

In most ophthalmic outpatients, anticoagulants do not significantly increase the risk of severe ocular bleeding if anticoagulation markers are within the therapeutic range\textsuperscript{19}.

Table 1. Risk stratification for sight-threatening bleeding in ophthalmic needle and cannula blocks

| Risk   | Comorbidity, anticoagulant/antiplatelet therapy | Regional ophthalmic blocks |
|--------|-----------------------------------------------|-----------------------------|
| High   | ASA I, no therapy                             | Low                         |
|        | Liver/renal failure, coagulopathy             | Low                         |
| Moderate | Prophylaxis (single Aptl)                     | Low                         |
|        | Primary                                       | Low                         |
|        | Secondary                                     | Low                         |
| Low    | Dual Aptl                                     | Moderate                    |
|        | Stop one Aptl                                 | Low                         |
|        | Dual Aptl                                     | Low                         |
|        | Acoag (VKÅ: target INR 2.5)                   | Moderate                    |
|        | AF PE, DVT                                    | Low                         |
|        | Long-term for recurrent PE/DVT                | Low                         |
|        | /high risk of stroke                          | Low                         |
|        | Acoag +/- Aptl t (VKÅ: target INR 3.5)        | Moderate                    |
|        | MHV/Acoag+Aptl                                | Moderate                    |
|        | MHV/Acoag+Aptl + only one eye                 | High                        |
|        |                                                | Moderate                    |

ASA = American Society of Anesthesiologists; INR = international normalized ratio; Aptl = antiplatelet drugs; Acoag = anticoagulant drugs; VKÅ = vitamin K antagonist; AF = atrial fibrillation; PE = pulmonary embolism; DVT = deep vein thrombosis; MHV = mechanical heart valve (data in Table 1 are based on the results from reference 11).
in most patients. All antithrombotic drugs can be continued if the cataract surgery is performed under topical or sub-Tenon’s (episcleral) block\textsuperscript{30}. Even if local anesthesia is performed with sharp needles, Acoag and Acoag therapy can be continued provided that the international normalized ratio (INR) for vitamin K antagonists (VKA) is in the therapeutic range. Dual Acoag therapy should be avoided, the new P2Y12 inhibitors should be stopped but acetylsalicylic acid (ASA) could be continued. Direct oral anticoagulants (DOACs) at therapeutic doses should be stopped before and restarted after the cataract surgery under sharp needle blocks. A recent review by Grzybowski \textit{et al.}\textsuperscript{21} included case series by Barequet \textit{et al.}\textsuperscript{22,23}, Salam \textit{et al.}\textsuperscript{24} and Kobayashi\textsuperscript{25}, and Cataract National Dataset electronic multicenter audit by Benzimira \textit{et al.}\textsuperscript{10}, and showed that phacoemulsification of cataracts under local anesthesia is not associated with higher risks of severe intraoperative bleeding and postoperative hemorrhage in outpatients taking Acoag and Acoag agents. The risk of sight-threatening bleeding is intermediate in case of anticoagulation in patients with mechanical heart valves (MHV) who take VKA with INR target values of 3.5 undergoing cataract surgery, or who have both Acoag and Acoag therapy and have only one functional eye\textsuperscript{11}. For cataract surgery, DOACs should be continued.

Bridging therapy with UFH or LMWH is unnecessary for most ophthalmic procedures in ambulatory settings. A gradual decrease of the anticoagulation effect is predictable during short-term perioperative cessation of DOACs, but it is influenced by renal function\textsuperscript{19}. If resuming DOACs carries a risk of postoperative hemorrhage that outweighs the thromboembolic risk, then bridging therapy with reduced prophylactic doses of LMWH may be an option\textsuperscript{26}.

The risk of intraocular bleeding among new users of antithrombotic therapy was tested in a recent large retrospective cohort study with two parallel analyses of data from national insurance claim database by Uyhazi \textit{et al.}\textsuperscript{27}. They compared patients who were on dabigatan or rivaroxaban with those who were on warfarin, and patients with new use of prasugrel with those on clopidogrel. The main outcomes were hazard ratios (HR) of developing intraocular hemorrhage at 90 and 365 days. The novel oral antithrombotic drugs showed a significant decrease in hemorrhage compared with warfarin at 365 days (HR=0.75; 95% CI 0.58–0.97, p=0.03) but not at 90 days (HR=0.73; 95% CI 0.22–2.63, p=0.13). There were no differences between prasugrel and clopidogrel at 90 days (HR=0.75; 95% CI 0.29–1.92, p=0.55) or 365 days (HR=1.19; 95% CI 0.69–2.04, p=0.53). However, more evidence is needed for safety of novel oral anticoagulants in ophthalmic patients.

Trabeculectomy is the most common glaucoma surgery in ambulatory settings. Overall, glaucoma filtration surgery has an intermediate risk of bleeding. However, the risk is higher in patients on Acoag therapy for AF, pulmonary embolism (PE) or deep venous thrombosis (DVT), as well as in patients with MHV or on both Acoag and Acoag therapy. There is no unique approach to maintain or to hold Acoag and Acoag therapy prior to glaucoma surgery. The majority of eye surgeons do not stop therapy especially in cases with a high thromboembolic risk without increasing the risk of surgical complications. Current recommendations from the literature suggest that ASA should be stopped in cases where the Acoag is the only drug for primary prevention of cardiovascular disease, but they could be continued for secondary prevention. In patients on clopidogrel, it should be stopped, but ASA should be continued or introduced. New oral Acoag should be stopped before glaucoma surgery but ASA continued. Traditional anticoagulants and DOACs should be stopped before glaucoma surgery and bridging therapy should be considered according to patient thrombotic risk\textsuperscript{11,19,28}.

For strabismus repair surgery, the recommendations are similar to those for glaucoma surgery.

A growing number of vitreoretinal surgery (VRS) is performed as ambulatory surgery. The risk of ocular bleeding is higher in patients with liver failure, renal failure, diabetes and coagulopathy than in otherwise healthy patients\textsuperscript{29}. The risk of bleeding is classified as intermediate in case of dual Acoag therapy for coronary stent or Acoag therapy for AF, and anticoagulation with therapeutic range for recurrent PE or DVT, as well as in case of MHV or both Acoag and Acoag therapy. The perioperative risk of ocular bleeding is high in patients with MHV (for VKA, INR target value of 3.5) or those who have both Acoag and Acoag therapy, and in patients who have only one functional eye. Studies of VRS showed controversial results. In general, Acoag drugs could be continued in many patients undergoing VRS in ambulatory settings\textsuperscript{30}. Perioperative management is similar to glaucoma surgery except...
for the interruption of clopidogrel being required. Hemorrhagic complications such as retrobulbar, subretinal, suprachoroidal or vitreous cavity hemorrhage still can occur. Vigilance is needed in the presence of neovascular retinal diseases. Acoag therapy may be continued unless the surgeon requests discontinuation. DOACs at therapeutic doses should be stopped before VRS and the duration of withholding depends on renal function. A retrospective cohort study by Grand and Walia found a low risk of hemorrhagic complications or need for reoperation in patients undergoing VRS while maintaining therapy with rivaroxaban, dabigatran or prasugrel.

Oculoplastic surgery that is performed anterior to the orbital septum has a low risk. Minor oculoplastic surgeries with a low risk of hemorrhage such as chalazion, eyelid cyst removal and eyelid lesion removal could be performed in ambulatory settings, and Acoag and Aptl agents may be continued perioperatively. Patients scheduled for oculoplastic surgeries with a high risk of sight-threatening hemorrhage, such as deep orbital surgery, postseptal eyelid surgery and dacryocystorhinostomy should have antithrombotic drugs withheld providing that it is safe to do so. Acoag and Aptl therapy should be withheld in patients who have a low risk of thromboembolism (less than 5% annual risk). If patients are at a high risk of thromboembolism, they should have bridging therapy or continue the anticoagulation to avoid bleeding complications associated with bridging therapy.

For most ophthalmic day-surgeries, the risk of stopping antithrombotic therapy is higher than the risk of continuing antithrombotic drugs. If interruption of antithrombotic treatment is needed, a modification of therapy should be discussed with a cardiologist, hematologist, neurologist, ophthalmologist, and other specialists. The BRIDGE trial, a randomized, double-blind, placebo-controlled study by Douketis et al., included 1,884 patients with AF on warfarin therapy who underwent elective invasive gastrointestinal, cardiothoracic and orthopedic surgery. The results showed that in patients who had warfarin therapy interrupted before the surgery, no bridging therapy was inferior to bridging therapy with LMWH for prevention of perioperative arterial thromboembolism (G, No bridging group=4/918 (0.4%) vs. G , Bridging group=3/895 (0.3%)). Further, no bridging therapy was superior to bridging therapy with respect to major perioperative bleeding (G , No group=12/918 (1.3%) vs. G , 29/895 (3.2%), p<0.005) and minor bleeding preoperatively (G , No group=110/918 (12.0%) vs. G , 187/895 (20.9%), p<0.001). The bridging therapy increased the risk of bleeding but did not provide any benefit for stroke prevention (G , No group=2/918 (0.2%) vs. G , 3/895 (0.3%)).

Thrombotic risk

During the preoperative visit, anesthesiologists and ophthalmologists should identify the risk factors for ocular bleeding and the risk of thromboembolic events. The approach to antithrombotic therapy should be individualized for a particular patient scheduled for the specific type of eye surgery. It is important to be familiar with the indications for antithrombotic therapy, to know when it may be stopped without unnecessary risks. There is substantial evidence that cessation of anticoagulation even for a short perioperative period is associated with significant thrombotic events such as stroke, myocardial infarction, or even death. High-risk patients are those with advanced age, severe comorbidities, thrombophilia, cerebrovascular, coronary artery and peripheral vascular diseases, and those who have mitral prosthetic valves or more than one prosthetic valve. The risks and benefits of continuing or stopping antithrombotic drugs should be discussed with other specialists involved in patient management to make an optimal, individualized approach for perioperative antithrombotic therapy in ophthalmic surgery.

Conclusion

In this review, we discuss the balance between systemic thrombotic risks related to modification of antithrombotic therapy before ophthalmic day-surgery under regional anesthesia and the risk of intraoperative and postoperative bleeding associated with continuation of antithrombotic therapy. Ophthalmic patients require a slightly different approach than other surgical patients depending on the type of eye surgery and antithrombotic treatment. Ophthalmic surgeries are stratified according to the risk of hemorrhagic complications in the perioperative period. Many ophthalmic procedures can be safely performed as outpatient surgery while antithrombotic therapy is continued. For some ophthalmic outpatients, the risk of
stopping Aptl and Acoag medications may outweigh the risk of perioperative hemorrhage.

There is no unique approach to eye surgery and perioperative use of antithrombotic drugs. The best way is a tailored approach depending on the type of anesthesia and surgical technique and assessment of renal function. The ‘one size fits all’ approach is not acceptable and individualized approach is highly recommended. Local protocols for ambulatory centers may help minimize cessation of antithrombotic drugs and thrombotic complications while limiting the risk of perioperative hemorrhage and maximize patient satisfaction and safety. Economic pressures for more ambulatory surgeries, increased indications for surgery in elderly people, increased prevalence of antithrombotic therapy, and greater focus on patient outcomes determine the important role of anesthesiologists. Anesthesiologists have become team leaders with a responsibility for perioperative management of ophthalmic patients. Full communication between the patients and prescribing physicians is the key to ensure an optimal outcome for ophthalmic patients on antithrombotic treatment undergoing eye surgery under regional anesthesia in ambulatory settings.

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Sažetak

JEDNODNEVNA OČNA KIRURGIJA I ANTIKOAGULANTNA TERAPIJA – NOVIJI PRISTUPI

T. Šimurina, M. Danilović Luketić, S. Graf Župčić i B. Mraović

U populaciji bolesnika starije dobi očni kirurški zahvati su jedni od najčešćih kirurških zahvata. Sve više bolesnika kojima je potreban kirurški zahvat na očima su starije dobi i većinom su na kroničnoj terapiji lijekovima uključujući antitrombocitne lijekove. Ti lijekovi mogu povećati rizik od perioperacijskog krvarenja prilikom izvođenja regionalnih očnih blokova ili kirurškog zahvata. Krvarenje tijekom operacije oka i hemoragijske komplikacije poslije zahvata mogu dovesti do gubitka vidne funkcije ili čak samog oka. S druge strane, prekidanje uzimanja antitrombocitnih i antikoagulacijskih lijekova prije kirurškog zahvata dovodi do povećanog rizika za nastanak ozbiljnih i za život opasnih tromboembolijskih komplikacija. Cilj ovoga narativnog preglednog članka je sustavni pregled objavljenih dokaza o perioperacijskom antitrombotskom liječenju očnih bolesnika planiranih za različite zahvate u dnevnoj očnoj kirurgiji. Pretražene su baze medicinskih podataka pomoću PubMed, Ovid Medline® i Google Scholar za razdoblje od siječnja 2015. godine do prosinca 2018. godine. Obuhvaćene su studije relevantne za planirane očne operacije u jednodnevnoj kirurgiji i perioperacijsko liječenje antitrombocitnim i antikoagulacijskim lijekovima s naglaskom na sadašnje stavove u pogledu nastavka, prekida ili modifikacije antitrombotske terapije kako bi se pospješila priprema bolesnika za očne zahvate.

Ključne riječi: Kirurški zahvati, oftalmološki; Dnevna kirurgija; Anestezija, regionalna; Antikoagulacijski lijekovi; Antitrombocitni lijekovi