Dear Reviewer,
Thank you for your precious suggestions. Here after we have answered to all of your questions point-by-point and presented revised version of the manuscript with highlighted additional content:

Reviewer Comments:

This paper summarizes the pros and cons of interrupting aspirin administration before surgery in the neurological area, which is generally considered high-risk. Several issues seem to be raised.

#1 The paper reports the risks by type of surgery and disease. This may be an important factor because the bleeding time and risk of bleeding differ depending on the type of surgery and the disease. However, the paper seems to lack information on anemia, renal function, and conditions for which the patient is taking aspirin. I wonder if most guidelines would consider an assessment of individual bleeding and thrombotic risk after an assessment of the risk of the surgery itself and then postpone the surgery, etc. The authors should describe more about the evaluation of the individual patient.

Reply:

We fully agree with your opinion on individual patient-oriented bleeding and thrombotic risk assessment before any type of surgery, with special attention to preoperative physical status and systemic disorders, such as anemia, renal failure etc. Meanwhile, in this minireview we would like to focus mainly on the important role of specific type of neurosurgical intervention for decision making on continuing or discontinuing aspirin consumption, taking into account underlying cardiovascular risk.

In the revised version of our manuscript, we clarified your concerns in this way:

"Individual bleeding risk assessment should also include non-specific factors, such as preoperative anemia, renal dysfunction, chronic liver disease, metabolic disorders etc.[18] Such abnormalities should be corrected, if possible, before proceeding to surgery."

"On the other hand, risk of thrombotic complication can overweight bleeding risk in patients with high cardiac risk (history of myocardial infarction, coronary stenting, unstable angina etc., which are among the most common indications for chronic aspirin consumption). In such cases aspirin continuation can provide better outcome."

#2 The results reported here seem difficult to understand. The authors should summarize the individual reports in a table.

Reply:

Thanks for this rational suggestion! We summarized the data in the following Table in revised version of our manuscript:

Table 1. Characteristics of included studies on aspirin consumption before neurosurgical interventions.

Study	№ of patients	Reported schemes	Key message
Brain tumor surgery			
Merriman et al.[19], 1979 *case report*	2	4-20 tablets of aspirin 325 mg/day	Complications could be associated with preoperative aspirin consumption
Hanalioglu et al.[20], 2019, *retrospective single-center, cohort study*	1291	3 groups: 1) No ASA (1068 patients) 2) Stopped ASA (at least 7 days before surgery – 104 patients) 3) Continued ASA (119 patients	ASA was not associated with increased bleeding risk
Rychen et al.[21], 2023, *prospective cohort study with retrospective control*	312	ASA was continued perioperatively for extraaxial surgery, and discontinued 2 days before intraaxial surgery (83 patients). No ASA in prospective control (106 patients) and long-term ASA discontinuation in retrospective control group (123 patients).	Presented protocol of perioperative antithrombotics management was not associated with an increased hemorrhagic risk.
Enciu et al.[22], 2023, *retrospective single-center, cohort study*	304	2 groups: 1) Short-term ASA discontinuation (lower than 7 days) (45 patients) 2) Standart-term ASA discontinuation (259 patients)	Short-term (even <2 days) discontinuation of low-dose aspirin was not associated with increased bleeding risk
Rychen et al.[7], 2023, *systematic review*	646 (7 studies)	ASA was continued perioperatively in 61.8% and discontinued in 38.2% of the cases.	Perioperative ASA continuation in elective craniotomies was not associated with an increased hemorrhagic risk.
Cerebrovascular surgery			
Schubert et al.[23], 2014 *retrospective single-center, cohort study*	158	ASA was prescribed in 138 patients pre- or intraoperatively.	Antiplatelet therapy did not increase the risk of hemorrhage, but improved outcomes after revascularization procedures.
Nakamizo et al.[24], 2017	401	2 groups: 1) Continued antithrombotics, including ASA (45 patients)	Intracranial hemorrhage after aneurism clipping

retrospective single-center, cohort study		2) No antithrombotics (259 patients)	was more frequent in the antithrombotics group.
Rashidi et al.[25], 2021 *retrospective single-center, cohort study*	200	2 groups: 1) Continued ASA or short-term ASA discontinuation (lower than 7 days) (32 patients) 2) No ASA (168 patients)	Continued ASA use was not associated with an increased risk of a postoperative hemorrhage.
Ebel et al.[26], 2021 *retrospective single-center, cohort study*	215	2 groups: 1) Patients were treated with antithrombotics (50 patients) 2) No antithrombotics (165 patients)	Short (≤5 days) aspirin discontinuation time did not appear to have increased rates of postoperative bleeding.
Spinal surgery			
Goes et al.[6], 2017 *meta-analysis*	370 (3 studies)	2 groups: 1) ASA-continuing group (170 patients) 2) ASA-discontinuing group (200 patients)	There is no diference in perioperative complications between aspirin continuation and discontinuation.
Zhang et al.[29], 2017 *meta-analysis*	414 (4 studies)	2 groups: 1) ASA-continuing group 2) ASA-discontinuing group	Continued aspirin administration do not have an increased risk for bleeding.
Cheng et al.[30], 2018 *systematic review*	1173 (7 studies)	3 groups: 1) No ASA therapy (587 patients) 2) Stopped ASA (3-10 days before surgery – 416 patients) 3) Continued ASA (170 patients	No difference in intraoperative blood loss, operation time, and postoperative complications.
Claydon et al.[28], 2022 *prospective, multi-center observational cohort study*	364	2 groups: 1) ASA-continuing group (21 patients). 2) No ASA group.	There was no association of low-dose ASA continuation with increased bloodloss.
Tarukado et al.[27], 2023 *retrospective single-center, cohort study*	88	3 groups: 1) No antithrombotics (65 patients) 2) Stopped ASA (9 patients) 3) Continued ASA (14 patients)	Continuing ASA did not affect perioperative complications or clinical outcomes

*ASA – aspirin.

#3 Abbreviations such as ESC, RCT, ADP, ESAIC, etc., are mentioned from the beginning in the abstract and text; the authors should use them after the full spelling.

Reply:

Thanks for the comment, now we corrected these shortcomings in updated version of manuscript.

#4 It seems that English is difficult to understand; a native English checker should review the manuscript.

Reply:

Thanks for the comment. This version of the manuscript was double checked by Professor Federico Bilotta, who has a huge experience in scientific writing in English, worked as a Full Professor at Albert Einstein College of Medicine in New York, USA and who are currently National Anaesthesiologists Societies Committee (NASC) Chairperson at European Society of Anaesthesiology and Intensive Care (ESAIC). So we believe that he can be reported as “english-native equivalent” specialist.

Aspirin interruption before neurosurgical interventions: a controversial problem.

Minireview

Alexander Kulikov, MD, PhD, Anton Konovalov, MD, PhD,** Pier Paolo Pugnaloni***, Federico Bilotta, MD, PhD****

* Department of Anesthesiology, Burdenko National Medical Research Center of Neurosurgery, Moscow, Russia; ** Department of Vascular Neurosurgery, Burdenko National Medical Research Center of Neurosurgery, Moscow, Russia; *** Department of Anesthesiology, Critical Care and Pain Medicine, Sapienza University of Rome, Italy

Correspondence to Federico Bilotta, MD, PhD

Department of Anesthesiology, Critical Care and Pain Medicine, Sapienza University of Rome, Italy

e-mail: bilotta@tiscali.it

Abstract

Aspirin is widely used for primary or secondary prevention of ischemic events. At the same time, chronic aspirin consumption can affect the blood clot formation during surgical intervention and increase intraoperative blood loss**.** This is especially important for high-risk surgery, including neurosurgery. Current European Society of Cardiology (ESC) guidelines recommends aspirin interruption for at least 7 days before neurosurgical intervention, but this suggestion does not support by clinical evidence. This narrative review summarizes evidence that challenge the necessity for aspirin interruption in neurosurgical patients, describes options of aspirin effect monitoring and clinical implication of these methods, and summarizes current clinical data on bleeding risk associated with chronic aspirin therapy in neurosurgical patients, including brain tumor surgery, cerebrovascular procedures, and spinal surgery.

Key words: aspirin, neurosurgery, postoperative complications, bleeding risk, brain tumor surgery, cerebrovascular surgery, spinal surgery.

Core tip: Decision on continuing or interruption of aspirin before neurosurgical intervention should be made based on discussion of specialists involved in perioperative management (neurosurgeon, anesthesiologist, cardiologist etc.), taking into account estimated blood loss; risk of complications, associated with increased bleeding time; risk of postoperative ischemic complication associated with aspirin interruption; and risk of surgery postponing.

Introduction

Aspirin (acetylsalicylic acid – ASA) is a well-known inhibitor of platelet aggregation and due to this effect it is widely used for primary or secondary prevention of ischemic events[1]. At the same time, chronic aspirin consumption can affect the blood clot formation during surgical intervention and increase intraoperative blood loss[2]. This is especially important for high-risk surgery, including neurosurgery, where even mild hemostatic disorders can provoke severe postoperative complications, such as acute intracranial hemorrhage[3].

Historically, the indication to interrupt aspirin therapy before neurosurgical procedures is based not on the clinical evidence, but on an expert's consensus[4]. Over the years, this suggestion consistently repeated in various guidelines, including 2022 ESC (European Society of Cardiology) Guidelines, which state that "in patients with high peri-operative bleeding risk (e.g. undergoing spinal surgery or certain neurosurgical operations) aspirin should be discontinued for at least 7 days"[5]. However, clinical data, accumulated from observational studies in patients undergone spinal and intracranial surgery, do not prove a possible additional risk of postoperative hemorrhage referable to preoperative chronic aspirin therapy. Instead, there is a trend towards a beneficial effect of aspirin continuation concerning of postoperative thromboembolic events[6,7].

This narrative review summarizes evidence that challenge the necessity for aspirin interruption in neurosurgical patients, describes options of aspirin effect monitoring and clinical implication of these methods, and summarizes current clinical data on bleeding risk associated with chronic aspirin therapy in neurosurgical patients, including brain tumor surgery, cerebrovascular procedures, and spinal surgery.

Antiplatelet effect of aspirin

Antiplatelet effect of aspirin is mediated by inhibiting cyclooxygenase (COX) activity inside platelets followed by suppression of thromboxane A_2 (TXA_2) synthesis[8]. TXA_2 plays an important role in the amplification of platelet aggregation and aspirin effectively depresses this mechanism of platelet activation[9].

Among the clinically important aspects of antiplatelet effect of aspirin are increased effectiveness of low doses (75-325 mg/day), due to absence of concomitant inhibition of prostacyclin in endothelial cells, and irreversible COX inhibition, in contrast to other nonsteroidal anti-inflammatory drugs (NSAIDs). Ibuprofen, ketorolac etc. compete in a reversible manner with the arachidonic acid substrate at the active site of COX, and therefore duration of their antiplatelet effect corresponds to elimination time. Antiplatelet effect of aspirin lasts for several days after a single administration due to irreversible acetylation of platelet COX[10]. Only newly synthesized platelets, which are renewed approximately by 10% every day, can restore ability to generate TXA_2 after single aspirin uptake.

However, aspirin is recognized as rather weak antiplatelet agent, because it produces only partial platelet inhibition and other non-TXA_2–dependent activators of platelet aggregation (eg, thrombin, ADP (adenosine diphosphate), and collagen) can bypass the aspirin-dependent mechanism and result in effective coagulation[8]. Moreover, up to 25% of patients can be resistant for conventional aspirin therapy[11].

Aspirin antiplatelet effect assessment

The immediate clinical effect of aspirin uptake on primary hemostasis results in increase of bleeding time[12]. Due to significant difficulties in standardizing this type of test, a lot of efforts in recent decades were put to develop alternative and reliable measures of antiplatelet effect of aspirin. Among the tested methods were: light transmission aggregometry (LTA), serum thromboxane B_2 concentration, impedance aggregometry, thromboelastography platelet mapping system, VerifyNow® assay, PFA (platelet function analyzer) –100, etc. Each of these proposed methods demonstrated significant variability in assessment of aspirin effect and poor

correlation to each other[13,14]. Even more important that there are still no reliable clinical evidence of predictive value any of these test and correlation with clinically significant outcomes[15].

From a practical point of view, it seems important that non-specific viscoelastic tests (TEG (thromboelastography), ROTEM (rotational thromboelastometry)), which were designed for integral assessment of blood clot formation, can not demonstrate aspirin-associated hypocoagulation. At the same time this phenomenon can be interpret as principal possibility of dense clot formation in the presence of aspirin[16].

Impact of aspirin on bleeding risk in non-neurosurgical patients

Clinical evidence on aspirin continuation or discontinuation in general surgery is very limited. The largest seminal RCT (POISE-2), which included more then 10 000 patients, revealed higher frequency of major bleeding in aspirin cohort with hazard ratio 1.23 (95% CI 1.01 to 1.49; P=0.04)[2]. However design and conclusions of this trial were criticized, thereafter, due to potential interaction of aspirin with perioperative anticoagulants and NSAIDs[17]. As a result, current guidelines on perioperative bleeding suggest that “aspirin should not be withdrawn peri-operatively unless the risk of bleeding exceeds the thrombotic risk from withholding the drug”[18]. But, as mentioned above, neurosurgical patients should be treated in a special way. Data on bleeding risk in different sub-cohorts of neurosurgical patient is presented below and summarized in Table 1.

Table 1. Characteristics of included studies on aspirin consumption before neurosurgical interventions.

Study	№ of patients	Reported schemes	Key message
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Merriman et al.[19], 1979 *case report*	2	4-20 tablets of aspirin 325 mg/day	Complications could be associated with preoperative aspirin consumption
Hanalioglu et al.[20], 2019, *retrospective single-center, cohort study*	1291	3 groups: 4) No ASA (1068 patients) 5) Stopped ASA (at least 7 days before surgery – 104 patients) 6) Continued ASA (119 patients	ASA was not associated with increased bleeding risk
Rychen et al.[21], 2023, *prospective cohort study with retrospective control*	312	ASA was continued perioperatively for extraaxial surgery, and discontinued 2 days before intraaxial surgery (83 patients). No ASA in prospective control (106 patients) and long-term ASA discontinuation in retrospective control group (123 patients).	Presented protocol of perioperative antithrombotics management was not associated with an increased hemorrhagic risk.
Enciu et al.[22], 2023, *retrospective single-center, cohort study*	304	2 groups: 3) Short-term ASA discontinuation (lower than 7 days) (45 patients) 4) Standart-term ASA discontinuation (259 patients)	Short-term (even <2 days) discontinuation of low-dose aspirin was not associated with increased bleeding risk
Rychen et al.[7], 2023, *systematic review*	646 (7 studies)	ASA was continued perioperatively in 61.8% and discontinued in 38.2% of the cases.	Perioperative ASA continuation in elective craniotomies was not associated with an increased hemorrhagic risk.
Cerebrovascular surgery			
Schubert et al.[23], 2014	158	ASA was prescribed in 138 patients pre- or intraoperatively.	Antiplatelet therapy did not increase the risk of hemorrhage, but improved

retrospective single-center, cohort study			outcomes after revascularization procedures.
Nakamizo et al.[24], 2017 *retrospective single-center, cohort study*	401	2 groups: 3) Continued antithrombotics, including ASA (45 patients) 4) No antithrombotics (259 patients)	Intracranial hemorrhage after aneurism clipping was more frequent in the antithrombotics group.
Rashidi et al.[25], 2021 *retrospective single-center, cohort study*	200	3 groups: 3) Continued ASA or short-term ASA discontinuation (lower than 7 days) (32 patients) 4) No ASA (168 patients)	Continued ASA use was not associated with an increased risk of a postoperative hemorrhage.
Ebel et al.[26], 2021 *retrospective single-center, cohort study*	215	2 groups: 3) Patients were treated with antithrombotics (50 patients) 4) No antithrombotics (165 patients)	Short (≤5 days) aspirin discontinuation time did not appear to have increased rates of postoperative bleeding.
Spinal surgery			
Goes et al.[6], 2017 *meta-analysis*	370 (3 studies)	2 groups: 3) ASA-continuing group (170 patients) 4) ASA-discontinuing group (200 patients)	There is no diference in perioperative complications between aspirin continuation and discontinuation.
Zhang et al.[29], 2017 *meta-analysis*	414 (4 studies)	2 groups: 3) ASA-continuing group 4) ASA-discontinuing group	Continued aspirin administration do not have an increased risk for bleeding.
Cheng et al.[30], 2018 *systematic review*	1173 (7 studies)	3 groups: 4) No ASA therapy (587 patients) 5) Stopped ASA (3-10 days before surgery – 416 patients) 6) Continued ASA (170 patients	No difference in intraoperative blood loss, operation time, and postoperative complications.
Claydon et al.[28], 2022	364	2 groups: 3) ASA-continuing group (21 patients).	There was no association of low-dose ASA

prospective, multi-center observational cohort study		4) No ASA group.	continuation with increased bloodloss.
Tarukado et al.[27], 2023 *retrospective single-center, cohort study*	88	3 groups: 4) No antithrombotics (65 patients) 5) Stopped ASA (9 patients) 6) Continued ASA (14 patients)	Continuing ASA did not affect perioperative complications or clinical outcomes

*ASA – aspirin.

Risk of bleeding in brain tumor surgery

One of the initial concerns on safety of perioperative aspirin consumption in brain tumor surgery was presented in small case series[19]. This study was based on two cases where postoperative hematomas were seemingly caused by a platelet defect due to aspirin use. This defect, not detectable by standard bleeding and clotting tests, could arise from both massive and small doses of aspirin. Highlighting the serious implications for neurosurgery, the study pointed out that such a defect can be effectively treated with platelet transfusions.

Data from a more recent retrospective study examining 1291 patients who underwent elective intracranial tumor surgery is much more reasonable[20]. The patients were divided based on their aspirin usage into three groups: no aspirin, stopped aspirin, and continued aspirin. The stopped-aspirin group included 104 patients (108 operations), and the continued-aspirin group had 119 patients (126 operations). The study highlighted that operative blood loss and complication rates were not significantly different between the groups, suggesting that perioperative aspirin use does not elevate hemorrhagic risk.

Similar conclusion was reached in prospective cohort study, focused on the perioperative management of antithrombotics (AT) in elective intracranial procedures[21]. This analysis involved 312 patients divided into three groups: 83 patients (27%) continued AT, 106 (34%) did not use AT, and 123 (39%) were historical AT users. The study's approach was to continue aspirin for extraaxial or shunt surgeries, and stop aspirin 2 days before intervention for intraaxial

pathologies. Notably, the total perioperative discontinuation time in the AT group was markedly shorter (median of 4 days) compared to the historical AT group (16 days). Hemorrhagic complications occurred in 4% of the AT group, 6% in the control group, and 7% in the historical AT group, indicating no significant increase in hemorrhagic risk with this protocol.

Risk of postoperative bleeding in patients undergoing endoscopic endonasal surgery for pituitary adenomas with short-term discontinuation of low-dose aspirin was in the focus of another retrospective study[22]. It included 304 patients, and 45 of them (14.8%) had short-term perioperative aspirin discontinuation. This study found no increased rate of postoperative bleeding in patients who discontinued aspirin for a short period.

Risk of postoperative hematoma formation in patients undergoing stereotactic brain biopsies is a critical concern in clinical practice, because in these clinical settings there is no direct visual control of potential vascular injury. Unfortunately, we were not succeed in finding any clinical evidence of additional risk of such complication in patients on chronic aspirin therapy.

Risk of bleeding in cerebrovascular surgery

Risk of hemorrhagic complication in 158 patients undergone revascularization surgery for moyamoya disease or cerebrovascular atherosclerotic disease was assessed in a retrospective observational study[23]. The study had a low complication rate with a high patency rate of 97%, and no mortality. Early morbidity was 10.7%, and ischemia was seen in 6.9% of patients. It was found that neither the type of treated pathology nor the surgical technique significantly influenced outcomes. Notably, antiplatelet therapy did not increase the risk of hemorrhage, but improved outcomes.

Patients who underwent craniotomy for unruptured intracranial aneurysm were included in another retrospective study[24]. Data on 401 cases were analyzed. Patients were divided into two groups: those who received perioperative antithrombotic treatment (45 patients) and those who did not (356 patients). The study found no significant difference in mortality, morbidity, or symptomatic brain infarction between the groups. However, intracranial hemorrhage was more frequent in the antithrombotic group. Posterior aneurysm location and surgical procedure were

associated with severe morbidity, and intracranial hemorrhage was associated with antithrombotic treatment.

More recent retrospective study did not find additional bleeding risk in patients on continued aspirin treatment undergoing cerebral aneurysm surgery[25]. 200 consecutive clipping procedures were analyzed and found that postoperative hemorrhage occurred in 3.1% of patients with aspirin and 3.0% of patients without aspirin. The difference was not statistically significant. However, cardiopulmonary complications were more frequent in the aspirin group. The study suggests that aspirin use may be relatively safe in patients with increased cardiovascular risk and emergency cerebrovascular surgery. Patients undergoing craniotomy for the treatment of neurovascular lesions with short (≤5 days) aspirin discontinuation time did not appear to have increased rates of postoperative bleeding also in another retrospective study, which included 215 cases[26].

Risk of bleeding in spinal surgery

Relatively large amount of clinical evidence has accumulated to date regarding the safety of continued aspirin use in spinal neurosurgery. For instance, in retrospective cohort study, which included 88 patients, the safety of continuing low-dose aspirin during microendoscopic laminectomy was investigated[27]. The patients were categorized into three groups based on their anticoagulation therapy status. There was no statistically significant difference between the three groups in operation time. The study concluded that continuing aspirin in these clinical settings did not affect perioperative complications or clinical outcomes. Another prospective multi-center observational cohort study was focused on risk factors affecting blood loss during elective anterior lumbar surgery. Based on analysis of 364 patients the continuation of low-dose aspirin was not associated with an increase in blood loss[28].

Previous studies were systematized in a couple of systematic reviews[29,30]. They assessed the impact of aspirin on bleeding and cardiovascular events in the perioperative period and concluded that continuation of aspirin does not increase the risk of blood loss, operative time, or postoperative blood transfusion during spinal surgery. However, both reviews

acknowledged the need for more research to understand the relationship between aspirin use and cardiovascular risks, emphasizing the importance of considering individual patient risks when managing aspirin therapy in spinal surgeries.

Balancing the risk

Presented clinical data reflects the paucity of reliable evidence on clinical decision making for continuing or interrupting aspirin uptake in perioperative period in patients scheduled for elective neurosurgical procedures. Potential disturbance in intraoperative blood clot formation stimulates defensive approach, but impact on outcome of aspirin uptake in these specific clinical settings remains uncertain. Inconsistence in clinical data provokes variability in clinical practice[31,32].

Moreover, even guidelines on this issue does not coincide to each other. For instance European Society of Anaesthesiology and Intensive Care(ESAIC) guidelines on perioperative bleeding management suggests that "intracranial surgery can be safely performed in the presence of low-dose aspirin", but in cases where aspirin withdrawal before surgery is considered, time from last drug intake to intervention of 3 days, although for invasive procedures at high risk of bleeding, a longer interruption (5 days) could be considered[18]. This period is much shorter in comparison with vague statement of at least 7 days discontinuation in European Society of Cardiology (ESC) guidelines[1].

Of course, decision on continuing or interruption of aspirin in particular case should be made based on discussion of specialists involved in perioperative management (neurosurgeon, anesthesiologist, cardiologist etc.), but framework for such decision making is not strictly defined. One of potential approach is presented on Figure 1. It can contain estimated blood loss; risk of complications, associated with increased bleeding time; risk of postoperative ischemic complication associated with aspirin interruption; and risk of surgery postponing. Individual bleeding risk assessment should also include non-specific factors, such as

preoperative anemia, renal dysfunction, chronic liver disease, metabolic disorders etc.[18] Such abnormalities should be corrected, if possible, before proceeding to surgery.

It should be taking into account that high estimated blood loss can be aggravated by antiplatelet effect of aspirin. This is particularly important in cases, where surgical manipulation would be performed inside the tissues with abnormal structure of vascular wall, i.e. neoplasms. This risk is presumably lower for cerebrovascular and spinal surgery. On the other hand, risk of thrombotic complication can overweight bleeding risk in patients with high cardiac risk (history of myocardial infarction, coronary stenting, unstable angina etc., which are among the most common indications for chronic aspirin consumption). In such cases aspirin continuation can provide better outcome.

Furthermore, in neurosurgical practice, it is frequently necessary to treat patients who can have serious consequences due to the delay in surgical intervention (e.g. intracranial bleeding of a brain lesion, progressive neurologic deficit due to mass effect, occurrence of seizures in patients with intracranial mass, etc.). Risk-benefit balance of aspirin interruption in such cases remains uncertain, but ESC recommendation for aspirin discontinuation might induce the underestimation of risks and harm of surgery delay.

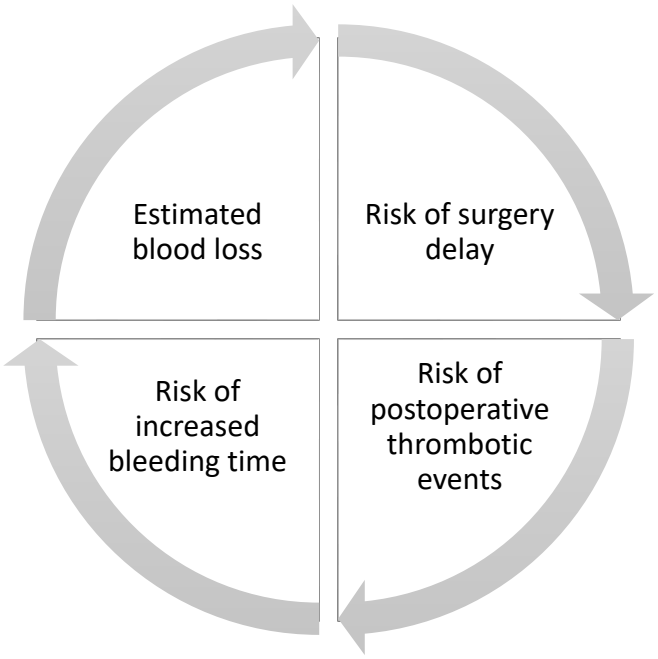

Figure 1. Framework for decision making on aspirin interruption before neurosurgical procedures.

Conclusion

Aspirin interruption before neurosurgical interventions remains a controversial clinical issue. Neurosurgical patients are very heterogeneous and might present different risk of perioperative bleeding. But current form of recommendation of aspirin discontinuation makes all clinical situations equal and motivate physicians to take same clinical decisions in any cases. Future studies should be designed for rational and evidence-based clinical decision making.

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