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## Aspirin interruption before neurosurgical interventions: A controversial problem

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### Abstract

Aspirin is widely used for primary or secondary prevention of ischemic events. At the same time, chronic aspirin consumption can affect 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 guidelines recommend aspirin interruption for at least 7 d before neurosurgical intervention, but this suggestion is not supported by clinical evidence. This narrative review presents evidence that challenges the necessity for aspirin interruption in neurosurgical patients, describes options for aspirin effect monitoring and the 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

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**Core Tip:** A decision on continuing or interrupting aspirin use before neurosurgical intervention should be made based on a 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 postponement.

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## 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 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 has consistently repeated in various guidelines, including 2022 European Society of Cardiology (ESC) 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 d"[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 associated with preoperative chronic aspirin therapy. Instead, there is a trend towards a beneficial effect of aspirin continuation concerning postoperative thromboembolic events[6,7].

This narrative review summarizes evidence that challenges the necessity for aspirin interruption in neurosurgical patients, describes options for aspirin effect monitoring and the 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

The antiplatelet effect of aspirin is mediated by inhibiting cyclooxygenase (COX) activity inside platelets followed by suppression of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) synthesis[8]. TXA<sub>2</sub> 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 the antiplatelet effect of aspirin are the increased effectiveness of low doses (75-325 mg/d), due to the 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 reversibly with the arachidonic acid substrate at the active site of COX, and therefore the duration of their antiplatelet effect corresponds to elimination time. The 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 the ability to generate TXA<sub>2</sub> after a single aspirin uptake.

However, aspirin is recognized as a rather weak antiplatelet agent because it produces only partial platelet inhibition, and other non-TXA<sub>2</sub>-dependent activators of platelet aggregation [*e.g.*, 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 to conventional aspirin therapy[11].

## ASPIRIN ANTIPLATELET EFFECT ASSESSMENT

The immediate clinical effect of aspirin uptake on primary hemostasis results in increased bleeding time[12]. Due to significant difficulties in standardizing this type of test, significant efforts in recent decades have been put into developing alternative and reliable measures of the antiplatelet effect of aspirin. Among the tested methods were light transmission aggregometry, serum thromboxane B<sub>2</sub> concentration, impedance aggregometry, thromboelastography platelet mapping system, VerifyNow<sup>®</sup> assay (Werfen, Barcelona, Spain), platelet function analyzer-100 (Siemens Healthineers, Erlangen, Germany), *etc*. Each of these proposed methods demonstrated significant variability in the assessment of aspirin effect and poor correlation to each other[13,14]. Even more importantly, there is still no reliable clinical evidence of predictive value of any of these tests and correlation with clinically significant outcomes[15].

From a practical point of view, it seems important that non-specific viscoelastic tests (thromboelastography, rotational thromboelastometry), which were designed for integral assessment of blood clot formation, cannot demonstrate aspirin-associated hypocoagulation. At the same time, this phenomenon can be interpreted as the 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 minimal. The largest seminal RCT (POISE-2), which included more than 10000 patients, revealed a higher frequency of major bleeding in the aspirin cohort with a hazard ratio 1.23 (95% CI: 1.01 to 1.49;  $P = 0.04$ )[2]. However, the design and conclusions of this trial were criticized due to the 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 patients is presented below and summarized in Table 1.

## RISK OF BLEEDING IN BRAIN TUMOR SURGERY

One of the initial concerns on the safety of perioperative aspirin consumption in brain tumor surgery was presented in a 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.

A similar conclusion was reached in a 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 d before intervention for intraaxial pathologies. Notably, the total perioperative discontinuation time in the AT group was markedly shorter (median of 4 d) compared to the historical AT group (16 d). 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.

The risk of postoperative bleeding in patients undergoing endoscopic endonasal surgery for pituitary adenomas with short-term discontinuation of low-dose aspirin was 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.

The 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 did not succeed in finding any clinical evidence of additional risk of such complications in patients on chronic aspirin therapy.

## RISK OF BLEEDING IN CEREBROVASCULAR SURGERY

Risk of hemorrhagic complication in 158 patients who underwent 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.

A 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

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

Ref.	No. of patients	Reported schemes	Key message
<b>Brain tumor surgery</b>			
Merriman <i>et al</i> [19], 1979	2	4-20 tablets of aspirin 325 mg/ d	Complications could be associated with preoperative aspirin consumption
Case report			
Hanalioglu <i>et al</i> [20], 2019	1291	3 groups:	ASA was not associated with increased bleeding risk
Retrospective single-center, cohort study		No ASA (1068 patients) Stopped ASA (at least 7 d before surgery - 104 patients) Continued ASA (119 patients)	
Rychen <i>et al</i> [21], 2023	312	ASA was continued perioperatively for extraaxial surgery, and discontinued 2 d 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
Prospective cohort study with retrospective control			
Enciu <i>et al</i> [22], 2023	304	2 groups:	Short-term (even < 2 d) discontinuation of low-dose aspirin was not associated with increased bleeding risk
Retrospective single-center, cohort study		Short-term ASA discontinuation (lower than 7 d) (45 patients) Standard-term ASA discontinuation (259 patients)	
Rychen <i>et al</i> [7], 2023	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
Systematic review			
<b>Cerebrovascular surgery</b>			
Schubert <i>et al</i> [23], 2014	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
Retrospective single-center, cohort study			
Nakamizo <i>et al</i> [24], 2017	401	2 groups:	Intracranial hemorrhage after aneurism clipping was more frequent in the antithrombotics group
Retrospective single-center, cohort study		Continued antithrombotics, including ASA (45 patients) No antithrombotics (259 patients)	
Rashidi <i>et al</i> [25], 2021	200	2 groups:	Continued ASA use was not associated with an increased risk of a postoperative hemorrhage
Retrospective single-center, cohort study		Continued ASA or short-term ASA discontinuation (lower than 7 d) (32 patients) No ASA (168 patients)	
Ebel <i>et al</i> [26], 2021	215	2 groups:	Short ( $\leq 5$ d) aspirin discontinuation time did not appear to have increased rates of postoperative bleeding
Retrospective single-center, cohort study		Patients were treated with antithrombotics (50 patients) No antithrombotics (165 patients)	
<b>Spinal surgery</b>			
Goes <i>et al</i> [6], 2017	370 (3 studies)	2 groups:	There is no difference in perioperative complications between aspirin continuation and discontinuation
Meta-analysis		ASA-continuing group (170 patients) ASA-discontinuing group (200 patients)	
Zhang <i>et al</i> [29], 2017	414 (4 studies)	2 groups:	Continued aspirin administration do not have an increased risk for bleeding
Meta-analysis		ASA-continuing group ASA-discontinuing group	
Cheng <i>et al</i> [30], 2018	1173 (7 studies)	3 groups:	No difference in intraoperative blood loss, operation time, and postoperative complications
Systematic review		No ASA therapy (587 patients) Stopped ASA (3-10 d before surgery - 416 patients)	

		Continued ASA (170 patients)	
Claydon <i>et al</i> [28], 2022	364	2 groups:	There was no association of low-dose ASA continuation with increased blood loss
Prospective, multi-center observational cohort study		ASA-continuing group (21 patients) No ASA group	
Tarukado <i>et al</i> [27], 2023	88	3 groups:	Continuing ASA did not affect perioperative complications or clinical outcomes
Retrospective single-center, cohort study		No antithrombotics (65 patients) Stopped ASA (9 patients) Continued ASA (14 patients)	

ASA: Aspirin.

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 ( $\leq 5$  d) aspirin discontinuation time did not appear to have increased rates of postoperative bleeding in another retrospective study, which included 215 cases[26].

## RISK OF BLEEDING IN SPINAL SURGERY

A relatively large amount of clinical evidence has accumulated to date regarding the safety of continued aspirin use in spinal neurosurgery. For instance, in a 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 focused on risk factors affecting blood loss during elective anterior lumbar surgery. Based on an analysis of 364 patients, the continuation of low-dose aspirin was not associated with increased blood loss[28].

Previous studies were systematized in a couple of 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.

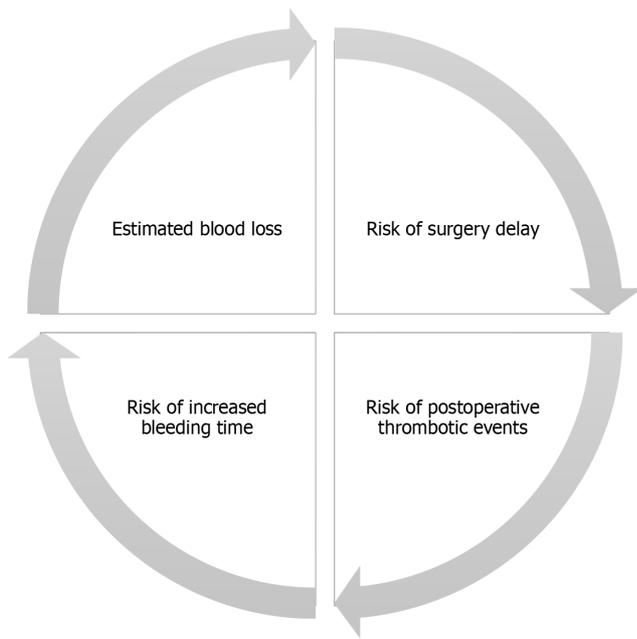
## BALANCING THE RISK

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

Moreover, even guidelines on this issue do not coincide with each other. For instance, European Society of Anaesthesiology and Intensive Care guidelines on perioperative bleeding management suggest 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 the intervention of 3 d. However, for invasive procedures at high risk of bleeding, a longer interruption (5 d) could be considered[18]. This period is much shorter in comparison with the vague statement of at least 7 d of discontinuation in ESC guidelines[1].

Of course, the decision on continuing or interrupting aspirin in particular cases should be made based on the discussion of specialists involved in perioperative management (neurosurgeon, anesthesiologist, cardiologist, *etc*), but a framework for such decision-making is not strictly defined. One of the potential approaches is presented in 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 postponement. 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 taken into account that high estimated blood loss can be aggravated by the antiplatelet effect of aspirin. This is particularly important in cases where surgical manipulation would be performed inside the tissues with the abnormal structure of the vascular wall, *i.e.* neoplasms. This risk is presumably lower for cerebrovascular and spinal



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

surgery. On the other hand, the risk of thrombotic complication can outweigh the 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 a 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 cause the underestimation of risks and harm of surgery delay.

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## CONCLUSION

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

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## FOOTNOTES

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