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EDITORIAL

Balancing bleeding, thrombosis and myocardial injury: A call for balance and precision medicine for aspirin in neurosurgery

Subhrashis Guha Niyogi, Akash Batta, Bishav Mohan

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Abstract

Perioperative management of antiplatelet therapy involves a delicate balancing of the risk of periprocedural blood loss with the cardiovascular and thrombotic risk to the patient. Due to the unique nature of neurosurgery, perioperative bleeding may have devastating consequences and cause major morbidity and mortality. The recommendation to discontinue aspirin prior to major neurosurgical procedures rests upon conventional practice, expert consensus with priority given to avoidance of any major bleed. On the contrary recent prospective data do not support the existence of additional bleeding risk in patients continuing aspirin compared to those who stop aspirin prior to procedure. Patients with cardiovascular and metabolic comorbidities are increasingly encountered in the operation theatre these days. In these patients, prevention of myocardial injury after non-cardiac surgery (MINS) is an important focus for perioperative risk reduction. Prolonged (≥ 7 days) cessation of antiplatelets is one of the most important predictors of MINS. This complicated milieu of risks and benefits highlights the difficulty of practicing evidence-based medicine and minimizing harm in patients on aspirin needing neurosurgery.

Key Words: Neurosurgery; Aspirin; Myocardial injury after non-cardiac surgery; Thrombotic risk; Haemorrhagic complications; Platelet function assessment

Core Tip: The decision to continue or discontinue aspirin during the perioperative period is nuanced and must be tailored to each patient. The procedure-related bleeding risks of neurosurgery must be weighed against the potential patient-specific risks of thromboembolism, major adverse cardiac events as well as subclinical myocardial injury after non-cardiac surgery (MINS). MINS increases the risk of both early and late postoperative morbidity and mortality and can be triggered by prolonged (≥ 7 days) cessation of antiplatelets. Practice guidelines incorporating the latest evidence and point-of-care tests of platelet function are possible aids in this complicated scenario.

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INTRODUCTION

Aspirin is currently one of the mainstays in primary as well as secondary prevention of thromboembolic events[1]. It selectively and irreversibly acetylates cyclooxygenase-1 in platelets and megakaryocytes, rendering them unable to synthesize thromboxane A_2 (TxA_2) for their lifetime. This inhibits platelet aggregation and prolongs the bleeding time. However, since it inhibits only the TxA_2 mediated pathway of platelet aggregation, not the major adenosine diphosphate-purinergic receptor P2y ($ADP\text{-}P2Y_{12}$) pathway, even in presence of chronic aspirin ingestion, ADP, collagen, thrombin can trigger effective platelet aggregation and cause haemostasis. While specialized methods can demonstrate aspirin effect, most point-of-care coagulation assays in clinical use do not reveal the change from the use of aspirin[2,3]. Work is on-going towards developing appropriate platelet function tests to quantify this effect[4,5].

ASPIRIN AND PREPROCEDURAL CONSIDERATIONS

The "partial inhibition" of platelet aggregation by Aspirin has led to a controversy around the perioperative use of Aspirin. It is important to balance the risk of potential periprocedural blood loss against the cardiovascular and thrombotic risk to the patient while managing antiplatelet therapy perioperatively.

Perioperative blood management guidelines by the American Society of Anesthesiology in 2015 and 2005 had recommended continuation of aspirin on "a case-to-case basis" as opposed to discontinuation of non-aspirin antiplatelet drugs like clopidogrel, ticagrelor, or prasugrel if clinically feasible. This was based on two randomized controlled trials in noncardiac surgeries, demonstrating comparable bleeding in patients receiving aspirin or placebo[6,7].

The more recent European guidelines provide a class I recommendation to withhold aspirin in surgeries with high bleeding risk, namely intracerebral and spinal neurosurgery in addition to vitreoretinal surgery[8]. Kulikov *et al*[9] explore the evidence base and the controversy surrounding this recommendation in a narrative review in the April 2024 issue of the journal. They have meticulously described the retrospective and prospective evidence base and highlighted the significant number of articles describing the safe conduction of neurosurgery with the continuation of aspirin, with no haemorrhagic complications. As they describe, the recommendation to discontinue aspirin rests largely upon the perceived risk of bleeding, exemplified by anecdotal case reports of major bleed and expert opinion. Extant practice here is to err on the side of caution and first to cause no harm. Taking an evidence-based call here is difficult, as randomized prospective data is sparse.

A recent systematic review has attempted to quantitatively synthesize the incidence of bleeding and thrombotic complications after elective craniotomies, capturing 646 unique patients across 7 studies. Though haemorrhagic complications were similar in patients with and without continuation of aspirin [haemorrhagic complication rate 3%, 95% confidence interval (95%CI): 0.01-0.05 *vs* 3%, 95%CI: 0.01-0.09 respectively; $P = 0.90$], it is worth noting that only 28.6% of these patients reflect prospective data[10].

Myocardial infarction, heart failure, ventricular arrhythmias and cardiac death are the classical major adverse cardiac events observed after non-cardiac surgery. While current standards of management have made these rare, many more patients have been found to suffer peri-operative myocardial injury but not fulfil the criteria for myocardial infarction. This injury, revealed by an asymptomatic rise in cardiac troponins, leads to late postoperative morbidity and mortality. Timely secondary prophylaxis achieves significant harm reduction in these cases. Hence, prevention of myocardial injury after non-cardiac surgery (MINS) is an important focus for perioperative risk reduction.

Saka *et al*[11] have prospectively investigated this in the elective neurosurgical context. 64 (20.5%) of 312 patients undergoing major or minor neurosurgery with comorbidities like coronary and peripheral artery disease, valvular heart disease, heart failure, atrial fibrillation, pulmonary embolism, cerebrovascular disease and age ≥ 65 years had MINS in their cohort. Prolonged (≥ 7 days) cessation of anticoagulants and antiplatelets was the most important predictor of MINS with an odds ratio of 4.9 (95%CI: 2.1-9.4) With the current lifestyle, dietary, environmental, medical, and socio-economic risk factors, and improvements in medical care, more and more patients live with multisystemic comorbidities these days. A similar trend has been observed in patients coming for neurosurgery and neurocritical care[12]. Hence, if a patient coming for neurosurgery is on aspirin for primary or secondary prevention of MACE, it is conceivable that they'll have a

high comorbidity burden, and continuation of platelet inhibitors would lead to significant harm reduction in them.

Likewise, neurosurgical patients are at a high risk of perioperative venous thromboembolism due to prolonged immobility, release of brain tissue thromboplastin, osmotic diuresis and intravascular fluid shifts, and benefit from continued thromboprophylaxis[13].

Of course, the promise of long-term harm reduction must be balanced with avoidance of short-term risks. Due to the unique nature of neurosurgery, perioperative bleeding may have devastating consequences and cause major morbidity and mortality. While intraoperative bleeding may be direct and cause hemodynamic compromise, poor perfusion and end-organ damage including secondary neurological injury, post-operative bleeding in intracerebral or neuraxial enclosed spaces may cause direct compressive or ischemic neurological injury and neuro-deficit. High vigilance, serial neurological examination and neuroimaging are necessary to pick up such complications early.

Bleeding during neurosurgery is affected by many factors - some of them related to the disease, some to the patient and his/her comorbidities, and some specific to the surgical procedure. While continuation of aspirin may be feasible in the majority of patients undergoing neurosurgical procedures, certain scenarios may pose unique challenges which make the continuation of aspirin tricky. A tumour with high vascularity may lead to higher perioperative blood loss and also a poor operative field causing suboptimal resection especially in those continuing aspirin. A patient with preexisting coagulopathy, for example, due to comorbid hepatic or renal disease, sepsis, trauma, or drugs like non-steroidal anti-inflammatory drugs, carbamazepine, thiazides or selective-serotonin-reuptake inhibitors may have synergistic action with the continued aspirin with resultant excess bleeding. Control of unexpected bleeding may be difficult in minimally invasive neurosurgical procedures with restricted visualization of the surgical field, leading to a poor outcome. All these situations in particular may tilt the balance in favour of aspirin cessation to limit short-term bleeding risk.

There is also significant variability in the clinical response to aspirin which needs to be considered during perioperative anticoagulation management and platelet therapy. Development and use of point-of-care tests like the VerifyNow Aspirin Assay® or Platelet Function Analyzer® now allow us to characterize that[14]. The VerifyNow Aspirin Assay® has already been used to identify hyper-responders to aspirin therapy, who have more perioperative bleeding and transfusion during cardiac surgery with ongoing aspirin[15]. Similar investigations in neurosurgical patients can also help identify those at an increased risk of bleeding on aspirin, and the drug interrupted accordingly.

CONCLUSION

Perioperative medicine has been moving to precision medicine with individualization, calibration and targeting of therapeutic choices. Further generation of high-quality evidence in large prospective cohorts can lead to the adoption of an evidence-based precision approach to the management of aspirin in neurosurgery. While major evidence gaps exist, individualized perioperative decision-making and point-of-care testing can help avoid unnecessary anti-platelet therapy interruption. Precision medicine to balance the risks of bleeding and thrombosis will lead to optimum harm reduction and the best possible outcomes in neurosurgical patients.

FOOTNOTES

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