Perioperative Management of Direct Oral Anticoagulants in Intracranial Surgery

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Abstract: The use of direct oral anticoagulants is increasing rapidly, because of perceived benefits over older agents, such as predictable pharmacokinetics and a reduced risk of bleeding. Elderly patients, who are more likely to be prescribed these drugs, are also presenting for neurosurgical procedures more often. The combination of these factors will result in neurosurgeons and neuroanesthesiologists encountering patients prescribed direct oral anticoagulants on an increasingly frequent basis. This review provides a summary of the current evidence pertaining to the perioperative management of these drugs in the context of elective and emergency intracranial surgery. It highlights emerging therapies, including specific antidotes, as well as areas where the evidence base is likely to improve in the future.

Key Words: anticoagulant, DOAC, neurosurgery

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The use of direct oral anticoagulants (DOACs) is increasing rapidly.1 Their perceived benefits include predictable pharmacokinetics, fewer interactions, and a reduced risk of bleeding.2 They are commonly used for the prevention and treatment of venous thromboembolism (VTE) and for the prevention of cerebrovascular embolism in patients with atrial fibrillation (AF).3 Increasing numbers of elderly patients are presenting for treatment of neurosurgical disorders, such as intracranial tumors and traumatic brain injury (TBI).4,5 This demographic is more likely to be prescribed oral anticoagulants, such as DOACs.6–8 Neurosurgeons and neuroanesthesiologists will, therefore, encounter patients prescribed DOACs on an increasingly frequent basis. This narrative review presents current evidence of relevance to neurosurgical patients and suggests approaches to managing their anticoagulation.

ANTICOAGULANTS AND BLEEDING IN NEUROSURGERY

Clinicians’ knowledge of DOACs and the associated implications for surgical procedures is often poor, with local policies varying widely.9,10 A number of recent guidelines have been published to assist the perioperative use of anticoagulant therapy.11–13 These guidelines attempt to balance the thrombosis risk associated with interruption of therapy against patient-specific and procedure-specific bleeding risks. However, the evidence base supporting these guidelines often specifically excludes very high-risk groups such as neurosurgical patients and no clinical trials have been conducted to determine safe perioperative DOAC use in this patient cohort.14 Postoperative hemorrhage is one of the most feared complications of neurosurgery and the patients are more sensitive to deficits in hemostasis than in other surgical disciplines.15

DOAC MECHANISMS OF ACTION

The DOACs have been developed to selectively inhibit the enzymatic activity of thrombin and factor Xa (FXa). This direct, targeted inhibition results in a rapid and predictable anticoagulant effect. Although these agents share many similarities and have overlapping indications, they differ in several ways.

DIRECT THROMBIN INHIBITORS

Thrombin (factor IIa) is a serine protease that catalyzes the formation of fibrin from fibrinogen and potentiates platelet activation and aggregation.16,17 Dabigatran competitively inhibits thrombin in a concentration-dependent manner. It also inhibits tissue factor-induced thrombin generation and decreases endogenous thrombin generation.17 It is licensed for the prevention of VTE following orthopedic surgery, the prevention of embolic events in nonvalvular atrial fibrillation (NVAF) and in the treatment or secondary prophylaxis of VTE.18,19

DIRECT FXA INHIBITORS

Factor X is activated to form FXa, an important component of the prothrombinase complex. Prothrombinase cleaves prothrombin to form thrombin which results in the production of fibrin.10 Apixaban, rivaroxaban, and edoxaban inhibit free and bound FXa, thereby reducing thrombin generation.20 Apixaban and rivaroxaban are licensed for the prevention of VTE after orthopedic surgery, the prevention of embolic events in NVAF, and for the treatment or secondary prophylaxis of VTE.21,22 Rivaroxaban is additionally licensed for the prevention of atherothrombotic events in the context of...
Our approach to elective cases, as illustrated in Figure 1, most closely mirrors the timings recommended by the French Working Group but also takes into account the above publications.\(^{12,13,27,35,36}\) We believe a relatively cautious approach is justified by the risk of catastrophic harm associated with bleeding in neurosurgical patients, combined with the relatively low risk of peri procedural thromboembolism in most patients.\(^{27}\) It is also supported by emerging evidence of the increased risks associated with renal impairment and dabigatran use, specifically a pharmacokinetic profile that is less predictable than previously thought.\(^{37}\)

**BRIDGING THERAPY AND THROMBOSIS RISK**

When managing pauses in anticoagulation, it is also important to consider the thrombosis risk for the individual patient. For vitamin K antagonists (VKAs), the previous practice has been to risk stratify patients before a pause in therapy. This can be done either according to the underlying diagnosis or with a validated system such as CHADS\(^2\) or CHA\(_2\)DS\(_2\)-VASc, which are applicable to patients with AF. If indicated, bridging therapy with heparin can then be commenced.\(^{38}\) More recently, the BRIDGE study demonstrated that in patients with AF taking VKAs, forgoing bridging therapy was noninferior to bridging and was associated with a lower risk of major bleeding.\(^{14}\) Heparin bridging is currently only recommended for patients with a CHA\(_2\)DS\(_2\)-VASc score \(\geq 7\) or a CHADS\(_2\) score \(\geq 5.\)\(^{11}\) Because of the short onset and offset of the effect seen with DOACs, bridging therapy is not usually recommended when pausing these agents.\(^{11,39}\) Published protocols for managing DOACs without bridging seem to be safe and support this approach.\(^{40}\) However, most studies that have evaluated bridging have excluded those patients undergoing neurosurgery, as well as other procedures associated with a high risk of bleeding.\(^{32}\) Given the lack of data to guide optimal practice in neurosurgery, the best approach is to discuss those patients at high thromboembolic risk on a case-by-case basis, taking expected DOAC pharmacokinetics into account. Particularly high-risk factors include mechanical heart valves, recent stroke, and recent or recurrent VTE.\(^{12,41}\)

**RESTARTING ANTICOAGULATION**

Unlike warfarin, the short onset time of DOACs means that effective anticoagulation will be achieved rapidly after therapy is reinsti tuted.\(^{11}\) However, clinician awareness of this seems to be poor.\(^{10}\) It is therefore important to plan the postoperative prescription of DOACs carefully. Unfortunately, there is a lack of prospective evidence to guide reinstituting DOACs in general and for neurosurgical patients specifically. Most guidelines recommend holding full-dose DOACs for 48 to 72 hours postoperatively.\(^{12,13,33,36}\) Some authors advocate the use of risk stratification scores to balance the risk of thrombosis against the risk of bleeding in the postoperative phase.\(^{42}\) Although these systems may have some
discriminative value in the perioperative setting, they are not validated or endorsed for this purpose.\textsuperscript{27,43} Our approach is to reintroduce DOAC therapy at 72 hours in elective cases unless there are neurosurgical concerns. Patients considered at high thromboembolism risk and emergency neurosurgical cases should be discussed individually within the multidisciplinary team.

**MANAGEMENT OF PATIENTS REQUIRING EMERGENCY INTRACRANIAL SURGERY**

As the use of DOACs increases, clinicians can expect to encounter an increasing number of neurosurgical emergencies associated with their use. They will also be required to manage DOAC-anticoagulated patients presenting with other neurosurgical pathologies, such as intracranial tumors, subarachnoid hemorrhage, and TBI.\textsuperscript{44,45}

**TBI**

Globally, TBI remains a disease that primarily affects young adults, typically as a result of road traffic collisions. However, the picture is changing in high-income countries, where falls are now the leading cause of TBIs.\textsuperscript{46} Elderly patients are at increased risk of falls, are more likely to suffer a TBI when they do fall and are more likely to suffer a worse outcome following a TBI.\textsuperscript{47,48} The prevalence of comorbidities necessitating oral anticoagulation, such as AF, is also highest in this patient group.\textsuperscript{46} It is therefore increasingly likely that clinicians will treat TBI patients who have been prescribed DOACs, although their safety following TBI seems better than VKAs, with a 3-fold to 6-fold reduction in the risk of secondary hemorrhage.\textsuperscript{47,49}

**INTRACRANIAL HEMORRHAGES (ICHs)**

When compared with VKAs, DOACs are also associated with a reduced frequency of ICHs.\textsuperscript{49–53} ICHs linked to DOAC use also tend to be smaller than those associated with VKAs, with a reduced frequency of poor functional outcomes.\textsuperscript{54,55} DOAC-associated nontraumatic intracerebral hemorrhages are less likely to require surgery, with 5.3% needing evacuation as compared with 9.9% of those associated with VKAs.\textsuperscript{51} However, the overall impact of ICHs in the context of DOAC use remains significant, with a quarter of patients not surviving and 30% being left with some form of disability.\textsuperscript{56}

**MONITORING OF ANTICOAGULANT EFFECT**

Because of their rapid onset of action and greater pharmacokinetic predictability than VKAs, the anticoagulant effect of DOACs is not routinely measured in clinical practice.\textsuperscript{57} Indeed, this is considered a key advantage of these new agents over VKAs such as warfarin.\textsuperscript{58} However, there are certain clinical situations such as overdose, urgent surgery, liver failure, and drug interactions where monitoring of anticoagulant effect is needed.

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**FIGURE 1.** Algorithm summarising the preoperative management of direct oral anticoagulants in patients undergoing elective intracranial surgery.\textsuperscript{12,13,27,35,36} CrCl indicates creatinine clearance; DOAC, direct oral anticoagulant.
desirable. It is easy to foresee a patient admitted from a neurosurgical clinic for the urgent treatment of an intracranial tumor, whose chronic rivaroxaban therapy was found to be complicated by worsening renal impairment. A reliable screening test to exclude residual anticoagulant effect would be highly desirable in such a case.

Conventional coagulation assays have low, unpredictable sensitivity for detecting the action of DOACS and are not suitable for quantification. The international normalized ratio for instance, which is generated from the prothrombin time, can give falsely reassuring low values in the presence of therapeutic dabigatran concentrations but it has also been linked to spuriously high values. The PT may be useful for screening in the case of rivaroxaban but has not been shown to predict the risk of major bleeding. The activated partial thromboplastin time demonstrates a curvilinear relationship with dabigatran and may have value as a screening test, but is not suitable for quantification, especially at high drug concentrations. Viscoclastic hemostatic tests assays such as thromboelastography may also have utility for screening but demonstrate significant variability and further work is needed to define their role. Currently, the most accurate assays for assessing dabigatran activity are the diluted thrombin time, ecarin clotting time, and chromogenic anti-IIa assays. Specific, calibrated anti-FXa assays are required for FXa inhibitors.

A practical approach to assessing the effect of DOACs for patients requiring urgent (but not immediate) neurosurgery is to perform screening tests where possible, such as the activated partial thromboplastin time for dabigatran, but with a low threshold for quantifying plasma DOAC concentrations. Typical peak plasma levels vary by an agent but range between 157 and 249 ng/mL. Although the plasma level associated with an elevated bleeding risk is not fully established, if drug levels are <30 ng/mL, then the residual anticoagulant effect can be excluded. It is important to note that the cost-effectiveness of this approach is yet to be determined, with the cost of specific assays and antidotes likely to remain high. National guidelines also advise caution when interpreting the results of these tests in the emergency setting.

**NONSPECIFIC APPROACHES TO DOAC-ASSOCIATED NEUROSURGICAL EMERGENCIES**

There is marked heterogeneity in approaches relevant to the emergency neurosurgical patients prescribed DOACs. This is in part because of a lack of evidence supporting safe drug concentrations during surgery and partly because of the inaccuracy of conventional coagulation assays for assessing the effect of DOACs, as discussed above. Strategies such as delaying surgery, administering activated charcoal or instituting renal replacement therapy to remove circulating dabigatran, have been described. However, these are unlikely to be helpful for neurological emergencies because of their time-critical nature. The use of hemostatic agents such as prothrombin complex concentrate (PCC) is widely practiced but controversial, because of a lack of evidence for efficacy and potential for causing adverse thrombotic outcomes.
SPECIFIC DOAC ANTIDOTES

The management of emergency cases is evolving because of the availability of specific antidotes. Idarucizumab, launched in 2015, is a monoclonal antibody fragment that has high specificity and affinity for dabigatran, rapidly reversing its anticoagulant effects.67,68 It acts immediately and lasts for 24 hours but where there is a risk of ongoing bleeding, a second dose may be required. Andexanet alfa, a modified FXa decoy protein, has been shown to effectively reduce anti-FXa activity in the context of major bleeding and has been approved in the United States for all FXa inhibitors.69

Although highly effective,67,70 it is important to note that these antidotes should not be used routinely and are not indicated in all cases of bleeding associated with DOACs. It is still unclear whether full reversal should be sought in all cases of intracranial hemorrhage.65 The cost of these antidotes is high, idarucizumab costing around US$3050 (GBP£2400, €2680) per dose. Andexanet alfa is ~10 to 20 times this price and repeated doses may be required.37,50 Current protocols limit the use of idarucizumab to emergency surgery or life-threatening bleeding37; in reality, most neurosurgical emergencies will fulfill these criteria. Local protocols for managing major hemorrhage should be followed in the case of significant blood loss but in many neurosurgical cases, it is bleeding into a confined space that is the greater problem. A suggested algorithm illustrating our approach to emergency neurological patients receiving DOAC therapy, on the basis of published guidelines, is detailed in Figure 2.58,65,71

CONCLUSIONS

The use of new oral anticoagulants is expanding rapidly and clinicians caring for neurological patients will become increasingly familiar with this challenge. The evidence base guiding the management of this cohort is narrow and current guidelines are largely extrapolated from pharmacological data, as well as studies that have excluded neurological patients. Emerging therapies including specific antidotes have the potential to improve safety but will have significant cost implications. Until clinical experience of DOAC usage and complications in the neurological population grows, existing guidelines should be treated with caution. Safe perioperative care will be facilitated by close cooperation between neurosurgeons, neuroanesthesiologists, and hematologists, particularly where patients are at high risk of thromboembolic disease.

REFERENCES


