Direct Oral Anticoagulant Reversal Agents

Direct oral anticoagulant (DOAC)-associated intracranial hemorrhage (ICH) has high morbidity and mortality.

see Intracranial hemorrhage and anticoagulation.

Anticoagulation reversal

and treatment options in major bleeding include protamine, phytonadione (Vitamin K), hemodialysis, oral-activated charcoal, antifibrinolytic agents including tranexamic acid, desmopressin, blood products including packed red blood cells (PRBCs) and platelets, prothrombin complex concentrates (PCCs), and specific reversal agents.

With the increased use of oral anticoagulation with vitamin K antagonists, emergency physicians encounter a growing number of patients requiring a rapid reversal of anticoagulant effects in order to perform urgent surgical procedures. Initiation of these procedures can be delayed because the coagulation status has to be assessed through examination of blood samples in central laboratories (CL). This delay may lead to negative effects, especially in potentially life-threatening conditions such as intracranial haemorrhage.

Point-of-care (POC) devices for assessment of international normalized ratio (POC INR) have improved the management of anticoagulation therapy in the outpatient setting. The use of these devices may also have beneficial effects in the treatment of anticoagulated patients requiring urgent neurosurgical procedures.

The POC coagulometer CoaguChek XS(®) was used in 17 patients with a history of anticoagulant use and a condition requiring urgent anticoagulant reversal prior to neurosurgical procedures (burr-hole trepanation: n = 8, craniotomy: n = 7, laminectomy: n = 2).

No technical difficulties occurred and rapid assessment of INR was achieved in all cases within 2 min. POC INR values correlated well with CL INR assessment with a mean INR deviation of 0.036 ± 0.12. The mean gain of time through the use of the POC INR device compared with CL assessment of INR was 47 ± 6 min (range: 37-61 min).

The initial experiences with a POC INR device in anticoagulated patients undergoing urgent neurosurgical procedures demonstrate that its use may contribute to an improved management of these patients [1)].

Safety and outcome data

The safety and outcome data of Direct Oral Anticoagulant (DOAC) reversal agents in intracranial hemorrhage are limited.

Chaudhary et al. evaluated the safety and outcomes of DOAC reversal agents among patients with ICH.

Data sources: PubMed, MEDLINE, The Cochrane Library, Embase, EBSCO, Web of Science, and CINAHL databases were searched from inception through April 29, 2022.

Study selection: The eligibility criteria were (1) adult patients (age ≥18 years) with ICH receiving treatment with a DOAC, (2) reversal of DOAC, and (3) reported safety and anticoagulation reversal outcomes. All nonhuman studies and case reports, studies evaluating patients with ischemic stroke requiring anticoagulation reversal or different dosing regimens of DOAC reversal agents, and mixed study groups with DOAC and warfarin were excluded.

Data extraction and synthesis: Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used for abstracting data and assessing data quality and validity. Two reviewers independently selected the studies and abstracted data. Data were pooled using the random-effects model.

Main outcomes and measures: The primary outcome was proportion with anticoagulation reversed. The primary safety endpoints were all-cause mortality and thromboembolic events after the reversal agent.

Results: A total of 36 studies met the criteria for inclusion, with a total of 1832 patients (967 receiving 4-factor prothrombin complex concentrate [4F-PCC]; 525, Andexanet alfa [AA]; 340, idarucizumab). The mean age was 76 (range, 68-83) years, and 57% were men. For 4F-PCC, anticoagulation reversal was 77% (95% CI, 72%-82%; I2 = 55%); all-cause mortality, 26% (95% CI, 20%-32%; I2 = 68%), and thromboembolic events, 8% (95% CI, 5%-12%; I2 = 41%). For AA, anticoagulation reversal was 75% (95% CI, 67%-81%; I2 = 48%); all-cause mortality, 24% (95% CI, 16%-34%; I2 = 73%), and thromboembolic events, 14% (95% CI, 10%-19%; I2 = 16%). Idarucizumab for reversal of dabigatran had an anticoagulation reversal rate of 82% (95% CI, 55%-95%; I2 = 41%), all-cause mortality, 11% (95% CI, 8%-15%, I2 = 0%), and thromboembolic events, 5% (95% CI, 3%-8%; I2 = 0%). A direct retrospective comparison of 4F-PCC and AA showed no differences in anticoagulation reversal, proportional mortality, or thromboembolic events.

Conclusions and Relevance: In the absence of randomized clinical comparison trials, the overall anticoagulation reversal, mortality, and thromboembolic event rates in this systematic review and meta-analysis appeared similar among available DOAC reversal agents for managing ICH. Cost, institutional formulary status, and availability may restrict reversal agent choice, particularly in small community hospitals [2].

Direct oral anticoagulants (DOACs) have overtaken warfarin as the preferred anticoagulants for stroke prevention with atrial fibrillation and for treatment of venous thromboembolism. Despite the increased prevalence of DOACs, literature studying their impact on trauma patients with intracranial hemorrhage (ICH) remains limited. Most DOAC reversal agents have only been recently available, and concerns for worse outcomes with DOACs among this population remain.

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Beynon C, Jakobs M, Rizos T, Unterberg AW, Sakowitz OW. Rapid bedside coagulometry prior to urgent neurosurgical procedures in anticoagulated patients. Br J Neurosurg. 2014 Jan;28(1):29-33. doi: 10.3109/02688697.2013.869549. Epup 2013 Dec 9. PubMed PMID: 24313307.

2)
Chaudhary R, Singh A, Chaudhary R, Bashline M, Houghton DE, Rabinstein A, Adamski J, Arndt R, Ou NN, Rudis MI, Brown CS, Wieruszewski ED, Wanek M, Brinkman NJ, Linderbaum JA, Sorenson MA, Atkinson JL, Thompson KM, Aiyer AN, McBane RD 2nd. Evaluation of Direct Oral Anticoagulant Reversal Agents in Intracranial Hemorrhage: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022 Nov 1;5(11):e2240145. doi: 10.1001/jamanetworkopen.2022.40145. PMID: 36331504.