Anticoagulation and Trauma

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BACKGROUND

In 1933 Professor Karl-Paul Link of the University of Wisconsin first learned that coumarin, a component of clover hay, was leading to death in cattle from bleeding complications. He created a use for it as a rodenticide and called it warfarin. Warfarin first gained notoriety in 1955 when it was prescribed to President Eisenhower following a myocardial infarction. Physicians began to prescribe warfarin to patients with arrhythmias for stroke prevention, but this was mainly an empiric approach since we were decades away from establishing data on efficacy or safety.

Barritt and Jordan performed the first randomized trial with warfarin in patients with pulmonary emboli and showed improved outcomes in the Lancet in 1960.[1] An ongoing problem was the dosing of anticoagulation since lab testing of prothrombin time (PT) was variable among institutions due to difficulty in obtaining uniform thromboplastin reagents. Additionally, there was also little agreement as to what degree a patient should be anticoagulated. Since this original trial, there have been numerous investigations establishing the benefit of anticoagulation for deep venous thrombosis, pulmonary emboli, stroke prevention in patients with atrial fibrillation, and other cardiovascular disease processes.

Currently the use of anticoagulation agents is rapidly increasing as atrial arrhythmias, valvular diseases and other forms of cardiovascular disease are more prevalent in our growing elderly population. Warfarin is used in approximately 13% of patients over 65 but its use is decreasing as direct or "novel" anticoagulants become more popular.[2] The widespread use of anticoagulants is problematic in trauma since it increases bleeding risk and worsen outcomes in trauma patients, especially those with traumatic brain injury (TBI).[3] In light of Rhode Island's large population of older adults, a cohort which is projected to double within the next two decades, it is pertinent to review the use of these agents and their impact on trauma care. We will discuss indications for anticoagulant use, their impact on trauma, and their reversal in order to make better decisions about their long-term use.

INDICATIONS FOR ANTICOAGULATION USE

In the last 50 years the indications for anticoagulation use has been tailored through large, randomized, multi-institutional trials. In 1994 a pooled analysis of 5 of these trials revealed a stroke rate of 4.5% in untreated control patients with atrial fibrillation and a rate of 1.4% in those treated with warfarin.[4] A subsequent meta-analysis from JAMA in 2002 showed a 45% reduction in CVA and 29% reduction in cardiovascular events when warfarin was used in patients with non-valvular atrial fibrillation. These authors found a significant increase in rates of major bleeding with warfarin, stating that for every 1,000 patients with atrial fibrillation treated with warfarin, 23 ischemic CVAs would be prevented while 9 major bleeding events would occur.[5] It is accepted that anticoagulation is beneficial for prevention of CVA and other thromboembolic events but that there is no regimen that is both effective and limits bleeding risks. Other common indications for anticoagulation include pulmonary embolus, deep vein thrombosis, congestive heart failure, known atrial clot, and mechanical heart valves. There is less controversy about the indications, but discussions remain regarding duration and degree of anticoagulation.

$CHADS_2$ AND CHA_2DS_2-VASc

The most effective anticoagulation strategy minimizes complications, namely bleeding events and exacerbation of injuries, by optimizing patient selection. Most efforts have focused on identifying thromboembolic risk in patients while not assessing risk of trauma or bleeding. The $CHADS_2$ scoring system utilizes the following risk factors for ischemic CVA: congestive heart failure, hypertension, age greater than 75 years, diabetes, and history of prior CVA or transient ischemic attack (TIA). It was developed using a Medicare registry of over 2,000 patient-years of follow-up and was more accurate that two other prediction models. CVA rate was noted to increase by a factor of 1.5 for each one-point increase in $CHADS_2$ score.[6] In an attempt to refine this model, CHA_2DS_2-VASc system incorporated additional categories for vascular disease, age stratification, and sex. The American College of Cardiology, American Heart Association, and European Society of Cardiology recommend use of the CHA_2DS_2-VASc score to guide decision making. If the bleeding risk per year with anticoagulation is approximately 1–1.5% based on earlier literature, patients should only start an agent if their CVA risk is greater than 1–2% which corresponds to a CHA_2DS_2-VASc score of two or greater.

EXACERBATION OF INJURY WITH ANTICOAGULANTS

With millions of Americans and thousands of Rhode Islanders on anticoagulation, it is important to understand how anticoagulants affect outcome after injury. An early assessment of 212 patients with subdural hematomas found that 46 of these patients were on anticoagulation; thus anticoagulation appeared to be a risk factor for ICH.[7] Later, patients that suffered intraparenchymal brain hemorrhage and subdural hematoma were found to be at higher risk of death compared to patients who suffered similar injuries while not on anticoagulation.[8]

There remains a deficit in data regarding hemorrhagic complications and exacerbation of traumatic injury. The gap in data was filled in significantly in the 2000s with several retrospective reviews. A 5-year review of 3,000 injured patients showed those with INR>1.5 had a relative mortality risk of 3.3 compared to those with INR<1.5.[9] A meta-analysis suggests risk of death from blunt head trauma was doubled in patients on pre-injury warfarin in the 11 pooled studies.[10] Additionally, in our clinical experience at the Rhode Island Trauma Center (RITC), there are large numbers of advanced-age patients that present with low-energy mechanisms (e.g. falls from standing, minor contusions, etc.) that suffer significant morbidity from subcutaneous hematomas due to anticoagulation. These cases and types of injury are not well described in the literature despite requiring hospital admission, transfusions and occasionally operative intervention. It is likely that inclusion of these types of injuries in prior studies would have negated some of the benefits of anticoagulation.

AS THROMBOEMBOLIC RISK RISES SO DOES RISK OF FALLS, TRAUMA EXACERBATION

Those patients at highest risk of thromboembolic events are also at greatest risk of suffering falls and worse outcomes after trauma. This is also illustrated by reviewing components of the CHA_2DS_2-VASc score; patients of increased age with comorbidities such as CHF, diabetes, and vascular disease are more likely to benefit from thromboembolic prevention while also being more likely to suffer trauma such as falls. Also, these individuals have decreased physiologic reserve and are faced with a more difficult recovery after injury. Strategies of aiming for an INR goal of 1.5–2 have been attempted but there is not enough evidence to recommend the practice.[11]

NOVEL, DIRECT ANTICOAGULANTS

Direct thrombin and factor Xa inhibitors, also known as direct oral anticoagulants (DOACs), are increasingly popular since no monitoring is necessary, unlike with vitamin K antagonists. DOACs are unaffected by dietary changes and have fewer medication interactions. Dabigatran was approved in 2010 for patients with non-valvular atrial fibrillation and the landmark RE-LY trial found similar efficacy with lower bleeding rates with dabigatran compared to warfarin.[12] Other DOACs include melagatran, a thrombin inhibitor, and rivaroxaban and apixaban, both Factor Xa inhibitors. In a 5-year review that compared apixaban, rivaroxaban, and dabigatran to warfarin, patients on apixaban were found to have the lowest rates of CVA or systemic embolism. Apixaban and dabigatran were associated with lower bleeding risk than warfarin.[13] In the early stages of DOAC use, trauma surgeons and emergency medicine providers were concerned about the lack of reversal agents and it was assumed that trauma morbidity and mortality would be increased compared to warfarin. However, a recent retrospective review of injured elderly patients did not show differences in mortality, blood transfusion requirements, and length-of-stay when DOACs were compared to warfarin.[14] Conversely, patients with major blunt trauma, defined as injury severity scores above 15, were shown to have lower rates of mortality and need for transfusion when on pre-injury DOACs versus warfarin.

Head-injured patients are the most vulnerable to bleeding exacerbation from anticoagulation use. DOAC use has been associated with significantly lower mortality, and decreased rates of operative management and discharge to a skilled nursing facility compared to warfarin in cases of blunt TBI.[15] In patients over 65 years of age with ICH from low level falls, there was no difference in mortality, but lower rates of transfusion and shorter ICU length-of-stay with DOACs have been noted compared to warfarin.[16] The reason for these findings may be that, unlike with warfarin, patients do not become "supra-therapeutic" on DOACs due to their fixed dosing.

REVERSAL OF ANTICOAGULATION AFTER INJURY

For reversal of warfarin, most trauma centers including ours, have shifted from using fresh frozen plasma (FFP) and vitamin K to prothrombin complex concentrates (PCC) and vitamin K. PCCs are stored in a freeze-dried powder form and can be rapidly reconstituted without delay, unlike FFP, which requires thawing. The concentration of vitamin K dependent clotting factors of PCCs is much greater than that of FFP. We use 4-factor PCC containing factors II, VII, IX, and X preferentially instead of 3-factor versions of PCC. In the literature, the proportion of patients with INR less than 1.2, within 3 hours of administration, was shown to be 67% versus 9% in ICH patients that received PCC versus FFP. In fact, a 2016 randomized trial was suspended due to safety concerns regarding the low rate of patients' INRs correction with FFP.[17] Timeliness of INR correction is especially critical in closed non-expansile spaces such as the skull or vertebral column where the goal is to rapidly avoid hematoma expansion.

Patients on DOACs that present with injuries are more complicated. Dabigatran was on the market for more than 5 years before its reversal agent idarucizumab became available. Idarucizumab is a monoclonal antibody fragment that binds strongly to dabigatran and was approved in 2015. Prior to this, urgent hemodialysis was the only way to reduce drug levels of dabigatran, but this was cumbersome. Idarucizumab is used to reverse dabigatran similarly to how PCCs are used to reverse warfarin. In a trial of patients suffering serious bleeding consequences while taking dabigatran, idarucizumab was shown to normalize clotting times in minutes, with side effects and cost comparable to a dose of PCC.[18]

In patients with normal renal function, Factor Xa inhibitors apixaban and rivaroxaban, have a shorter half-life of 7–9 hours in comparison to dabigatran, whose half-life extends 14–17 hours. Recently, a reversal agent for these drugs, andexanet alfa, became available. While this agent fully reverses the action of apixaban and rivaroxaban in minutes, at present its therapeutic profile is narrow. Andexanet competitively inhibits the factor Xa at its active site, however there is limited evidence in the literature of the efficacy of this agent and there is no head-to-head data comparing it to PCC, while thrombotic events appear to be more frequent than with PCC.[19] Furthermore, andexanet is difficult to reconstitute and there is a delay of a half an hour or more in preparing it, and its cost is prohibitive. Until additional evidence is available, and changes are made to the formulation of this agent, its benefits as a reversal agent are more theoretical than real. Many trauma centers, including ours, have opted to use an "end-around" strategy by giving a higher dose of PCC to overcome anticoagulant effects of apixaban and rivaroxaban.

GOALS, FUTURE DIRECTIONS TO IMPROVE SAFETY, OUTCOMES

Until recently there has been no objective way to assess the risk of major bleeding in patients on anticoagulation agents. To overcome this obstacle, HAS-BLED, a scoring system that assesses the 1-year risk of major bleeding events in patients on anticoagulation for atrial fibrillation, was developed. The HAS-BLED tool incorporates comorbidities including hypertension, renal/liver dysfunction, prior CVA, history of bleeding, labile INR, age, and use of drugs or alcohol, to produce a score of 0-9 with some components overlapping with CHA_2DS_2-VASc. Scores of greater than 2 are considered higher risk. Increasing HAS-BLED scores have been associated with stepwise increases in rates of major bleeding events in a cohort of more than 7,000 patients.[20] We routinely tabulate HAS-BLED scores on patients admitted to the RITC to guide our conversations with primary prescribers about long-term anticoagulation plans.

While HAS-BLED and CHA_2DS_2-VASc provide important data points, our trauma group routinely discusses the indications and safety of anticoagulation in individual geriatric patients with the primary prescriber following admission. In 2015 we commenced a protocol, with support from an institutional grant, to study the results of our conversations with primary prescribers whether to restart anticoagulation at discharge, stop it indefinitely, or until follow-up evaluation with the prescriber. The most common result was for anticoagulation to be held until follow-up evaluation with the prescriber. Patients with disposition to home versus a facility and those under 75 years of age were more likely to resume anticoagulation at discharge while those that suffered a fall mechanism were less likely to resume anticoagulation. After the study period ended, this protocol was instituted as standard of care at our center. While it is hard to quantitate, we think this practice has improved patient safety and primary provider satisfaction. Future research will focus on frailty, a condition that is a potent indicator of susceptibility to complications and adverse events, rather than chronologic age and portends poor outcomes of many medical interventions.

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