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Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients

A review

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Intracranial hemorrhage (ICH) is a common problem encountered by neurosurgeons. Patient outcomes are influenced by hematoma size, growth, location, and the timing of evacuation, when indicated. Patients may have abnormal coagulation due to pharmacological anticoagulation or coagulopathy due to underlying systemic disease or blood transfusions. Strategies to reestablish the integrity of the clotting cascade and platelet function assume a familiarity with these processes. As patients are increasingly treated with anticoagulants and antiplatelet agents, it is essential that the physicians who care for patients with ICH understand these pathways and recognize how they can be manipulated to restore hemostasis. *(DOI: 10.3171/2009.7.JNS0982)*

Key Words • coagulopathy • anticoagulant • antiplatelet agent • intracranial hemorrhage

Intracranial hemorrhage is a common problem encountered by neurosurgeons. Patient outcomes are influenced by hematoma size, growth, location, and the timing of evacuation, when indicated. Patients may have abnormal coagulation due to pharmacological anticoagulation or coagulopathy due to underlying systemic disease or blood transfusions. Strategies to reestablish the integrity of the clotting cascade and platelet function assume familiarity with these processes. As patients are increasingly treated with anticoagulants and antiplatelet agents, it is essential that the physicians who care for patients with ICH understand these pathways and recognize how they can be manipulated to restore hemostasis.

Abbreviations used in this paper: ADP = adenosine diphosphate; DDAVP = deamino-D-arginine-vasopressin; DTI = direct thrombin inhibitors; FFP = fresh frozen plasma; FV, . . . FXII = factor V, . . . factor XII; ICH = intracranial hemorrhage; INR = International Normalized Ratio; ISI = International Sensitivity Index; LMWH = low-molecular-weight heparin; OAC = oral anticoagulation; PFA = platelet function analyzer; PT = prothrombin time; PTT = partial thromboplastin time; QALY = quality-adjusted life year; rFVIIa = recombinant activated FVII; TF = tissue factor; TXA2 = thromboxane A2; UFH = unfractionated heparin; VKDF = vitamin K–dependent factor.

Normal Coagulation

Hemostasis, the process of blood clot formation, involves a coordinated series of complex interactions between platelets, endothelial cells, blood flow and shear stress, the clotting cascade, and fibrinolysis. It is classically divided into 2 basic reactions. Primary hemostasis involves platelet adhesion via von Willebrand factor and aggregation via fibrinogen at the site of endothelial injury, providing an immediate seal. Secondary hemostasis involves sequential activation of a series of proenzymes (nonactivated coagulation factors) to enzymes (activated coagulation factors), ultimately generating fibrin, which reinforces the initial platelet aggregate and provides the framework for further clot formation. These 2 processes are intimately related and regulated.

Platelets are crucial for the maintenance of vascular endothelial integrity. They are continuously involved in hemostasis, sealing microscopic gaps in capillary endothelium and providing a surface for coagulation factors to adhere. Severe thrombocytopenia ($< 20 \times 10^9$/L) can result in multiple petechial hemorrhages or spontaneous ICH. The blood flow in intact blood vessels is laminar with red cells in the center, white blood cells adjacent to red cells followed by platelets, which are separated by plasma from the endothelial cells. Normally, platelets cir-

culate in the blood in discoid (inactive) form; in response to various stimuli, however, they become activated and change to a spherical shape due to the formation of pseudopodia. Disruption of the vascular endothelium provides the initial stimulus for platelet deposition and activation by exposure of the underlying collagen that is normally concealed from circulating platelets. Platelets adhere to subendothelial collagen through specific platelet surface glycoprotein receptors (GPIb-V-IX) and von Willebrand factor. Soon after adhesion, platelets release ADP, histamine, serotonin, TXA2, platelet-derived growth factor, and other platelet granule constituents. The vasospastic response that accompanies vascular injury is augmented by TXA2 and serotonin, which are potent vasoconstrictors. After secretion, platelet aggregation occurs where the binding of fibrinogen to platelet membrane via GPIIb/IIIa results in platelet-platelet bridging, which forms the backbone of the initial hemostatic plug and provides the surface on which further coagulation reactions take place (Fig. 1).

After platelets adhere and aggregate, they help to initiate coagulation by binding TF–containing vesicles released by damaged tissue in the plasma, exposing negatively charged phospholipids on their surface, releasing coagulation factors stored in the granules, and generating procoagulant microparticles. The coagulation cascade involves a series of sequential enzymatic reactions that are progressively amplified to generate thrombin, a powerful enzyme that catalyzes the conversion of fibrinogen to fibrin. The coagulation cascade is traditionally divided into extrinsic (evaluated by PT) and intrinsic pathways (evaluated by PTT), which converge to a common pathway (both PT and PTT) based on reactions studied in vitro. In vivo, however, the coagulation system is a cell-based model that involves 3 phases: 1) initiation phase, includes the TF pathway where TF exposed on the cell surface (for example, damaged endothelium, brain, macrophages, cancer cells, and so forth) interacts with preformed FVIIa; 2) amplification phase, which involves FV and FVIII; and 3) propagation phase, which involves the so-called intrinsic pathway involving FXI, XII, and VIII. Although FXII, prekallikrein, and high-molecular-weight kininogen (known as contact factors) affect the PTT, they do not participate in coagulation in vivo (Fig. 2).

The coagulation system constantly produces thrombin at very low levels, which is regulated by natural anticoagulants (antithrombin, protein C and S, and TF pathway inhibitor [TFPI]). Plasmin, a fibrinolytic enzyme produced from plasminogen by the action of tissue plasminogen activator, dissolves cross-linked fibrin thrombi.

Laboratory Evaluation of Hemostasis

There are many available laboratory tests to assess the integrity of the clotting cascade and platelet function. A good understanding of these tests and their significance is important in deciding on various treatment options.

Platelet Count

The initial laboratory evaluation of platelets includes a platelet count. This measurement is a routine component of the complete blood count (CBC). Clinically significant thrombocytopenia is usually defined as a platelet count < 100×10^9/L. Note that a normal platelet count does not rule out platelet function abnormalities that can have a significant impact on bleeding. In general, sponta-

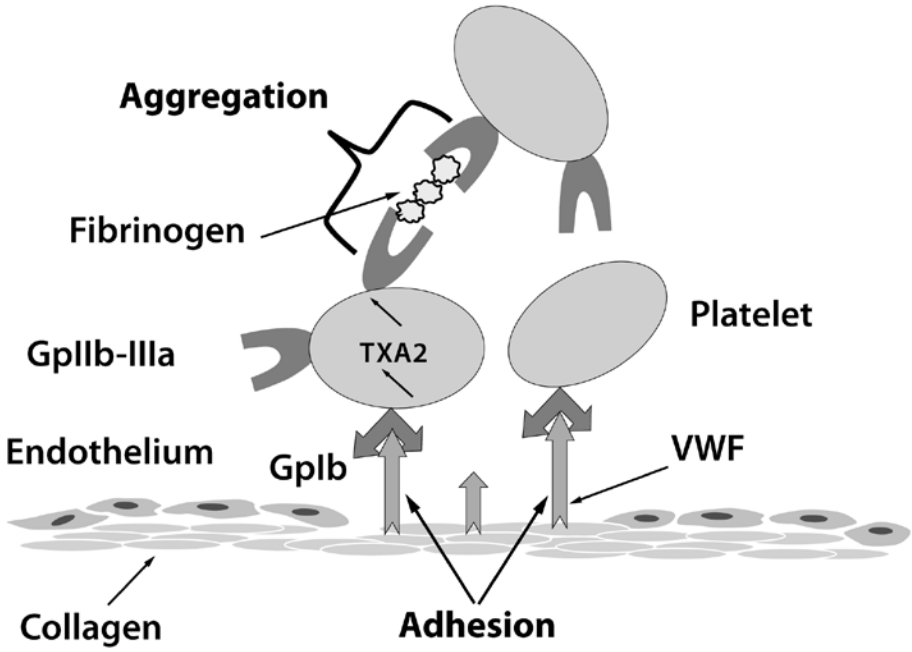

Fig. 1. Schematic showing primary hemostasis. On endothelial damage, platelets adhere to subendothelial collagen via von Willebrand factor (VWF) interacting at glycoprotein Ib (GPIb). This sequence is followed by the secretion phase where TXA2 and ADP/adenosine triphosphate are released to recruit more platelets at the site of injury. This sequence is followed by a conformational change in GPIIb/IIa, thus allowing the aggregation of platelets via fibrinogen.

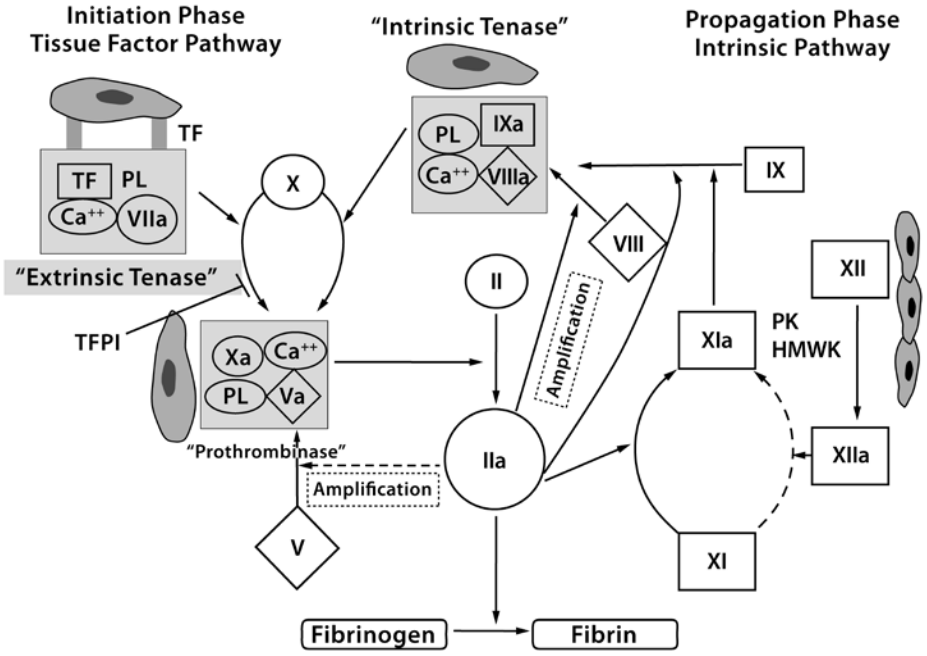

Fig. 2. Schematic showing secondary hemostasis: a cell-based model in which TF expressed on damaged cells initiates the "TF pathway." Tissue factor along with FVIIa and Ca^{++} on phospholipid (PL) cell surface forms the "extrinsic tenase," which converts FX to FXa. Factor Xa along with FVa forms "prothrombinase complex" to convert prothrombin to thrombin. At this stage, TF pathway inhibitor (TFPI) is activated, inhibiting the TF pathway. Thrombin generated at this stage begins the propagation phase by activating FIX and FXI and the amplification phase by activating FVIII and FV. Factors IXa and VIIIa along with PL and Ca^{++} form the "intrinsic tenase" to convert FX to FXa, thus generating more thrombin through prothrombinase complex, which converts fibrinogen to fibrin clot. Factor XII, high-molecular-weight kininogen (HMWK) and prekallikrein (PK) can also activate the intrinsic pathway in vitro as seen in PTT; however, they have no role in vivo.

neous bleeding does not occur with platelet counts > 20 × 10^9/L. Counts between 20 and 50 × 10^9/L may be associated with bleeding due to surgery or trauma.

The differential diagnosis for thrombocytopenia is broad. An unexpected low platelet count should prompt a repeat evaluation to rule out pseudothrombocytopenia, which is an artifactual phenomenon that occurs when platelets clump in vitro when EDTA is used as an anticoagulant (purple top Vacutainer tube). The presence of platelet clumps on a peripheral smear and the normalization of counts when the sample is collected in a citrated tube (blue top Vacutainer tube) confirm this diagnosis.

Screening Tests for Platelet Function

Historically, bleeding time has been considered a reliable screening test for abnormalities of primary hemostasis. The test is performed by making a standardized incision on the volar aspect of the forearm. A sphygmomanometer is placed around the upper arm and inflated to 40 mm Hg. The time required for bleeding to stop—determined by blotting the blood with a filter paper—is the bleeding time. This test is now considered obsolete because of several technical drawbacks, its nonreproducibility, and lack of controls. The PFA (PFA-100, Siemens Healthcare Diagnostics, Inc.) is currently used as a screening test for platelet function. This test mimics ex vivo bleeding time by using whole blood collected in citrate anticoagulant. There are 2 collagen-coated cartridges—one stimulates platelets with ADP, and the other with epinephrine. The aperture in the cartridge is closed by the interaction of von Willebrand factor with collagen, which in turn adheres and then aggregates platelets. Interpretations of epinephrine and ADP closure times are given in Table 1.

Prothrombin Time/INR

The prothrombin time evaluates the integrity of the TF pathway and the final common pathway. The PT test is performed by adding a suspension of tissue thromboplastin (TF + phospholipids) and calcium chloride to platelet-poor plasma. The time to the formation of a fibrin clot is the PT. The most common use for this test is in monitoring anticoagulation therapy with warfarin. Because different sensitivities of tissue thromboplastin reagents account for variability in PT, the INR was introduced to monitor warfarin therapy. The INR is a calculated value derived using the following formula: $(\text{patient PT/mean normal PT})^{ISI}$, where ISI is the International Sensitivity Index, a value assigned to the PT reagent when compared with a WHO reference standard with an ISI of 1.0.[75] The INR was standardized using plasma from patients on chronic warfarin therapy that affects only VKDFs II, VII, IX, and X. Therefore, the use of INR is inappropriate in other medical conditions in which clotting factors other than VKDF are also affected.

Partial Thromboplastin Time

Also known as activated PTT, the PTT test was so

TABLE 1: Interpretation of PFA-100 results*

Epinephrine	ADP	Interpretation
>200	normal	aspirin effect
<200 to normal	normal	aspirin resistant
abnormal	abnormal	von Willebrand Disease
>300	>300	GPIIb/IIIa inhibitors

* Results are valid if the hematocrit is > 30% and platelet count is > 100 × 10^9/L.

named because the coagulation of plasma is induced by the activation of FXII with a surface-activating agent such as silica or kaolin in the presence of a phospholipid extract of brain lacking TF—that is, a partial thromboplastin. It tests the integrity of the intrinsic pathway including contact factors (FXII, high-molecular-weight kininogen, and prekallikrein), FXI, FIX, and FVIII. Partial thromboplastin time is used to monitor heparin and direct thrombin inhibitor therapy.

Pharmacological Anticoagulation

Oral anticoagulants and antiplatelet agents are used with increasing frequency in patients for the primary or secondary prevention of ischemic stroke or myocardial infarction or for peripheral vascular disease. Anticoagulation therapy increases the risk of ICH.[4,12,25,27,30,67,73] The reported incidence of ICH in patients receiving oral anticoagulants is 7- to 10-fold greater than in patients who are not.[10,21,69] Anticoagulant-related ICHs tend to be larger and grow more often than hemorrhages in patients with spontaneous hematomas.[21,44] Anticoagulant use and the increased intensity of anticoagulation are independent predictors of the 3-month mortality rate.[26] The following section details the various anticoagulant and antiplatelet agents and strategies for reversal.

Coumadin Therapy

The coumarin compounds were first described by Link[49] and Campbell following an investigation of a hemorrhagic disorder in cattle that had ingested spoiled sweet clover. The hemorrhagic agent was found to be dicoumarol. In 1948 a more potent synthetic form of this compound was introduced as a rodenticide. The compound was named "Warfarin" as an acronym derived from the name of the patent holder, the Wisconsin Alumni Research Foundation. The first reported use in humans occurred in a failed suicide attempt by an army inductee in 1952.[37] Today, Coumadin (Bristol-Myers Squibb) is widely used as an oral anticoagulant for a variety of medical conditions. It acts by antagonizing VKDFs (coagulation FII, VII, IX, and X and the anticoagulant proteins C and S). Of the VKDFs, FVII has the shortest half-life (4–6 hours) and therefore is the most depleted with Coumadin therapy. This short half-life explains the observed increase in the PT/INR without a significant increase in the PTT during therapeutic anticoagulation with Coumadin. Coumadin overdose with supratherapeutic INR can be associated with prolonged PTT. Strategies for Coumadin reversal are aimed at increasing the levels of depleted coagulation factors by direct replacement and/or improved regeneration through vitamin K supplementation.

Vitamin K. Vitamin K supplementation in the setting of warfarin-associated ICH is aimed at regenerating VKDFs. This process is slow and must be coupled with factor supplementation for immediate effect. Transfused factors have a relatively short half-life but provide a bridge until the full effect of vitamin K takes place.

Vitamin K can be administered orally, intravenously, or subcutaneously. Oral supplementation has no role in the emergency reversal of anticoagulation in the bleeding patient because of the slow onset of action, unpredictable response, and variation between different formulations.[80] Intravenous administration results in the most rapid correction of INR. A reduction of INR begins within 2 hours of administration, and full correction can be achieved in many instances within 24 hours if hepatic function is normal.[53] Intravenous doses of 5–10 mg are generally recommended.[5,6] Intravenous vitamin K is associated with a small risk of anaphylactic or anaphylactoid reactions. Although the true incidence is unknown, it is thought to occur in 3 per 10,000 cases. It is more likely to occur in patients who rapidly receive large doses. It is also more likely to occur if formulations containing polyethoxylated castor oil are used to maintain the vitamin K in solution. Most modern formulations do not use this carrier and therefore may have a lower risk of allergic reaction.[68] To minimize this risk, vitamin K should be diluted and administered at a rate of 0.5–1 mg/minute. A dose of 5–10 mg may be repeated every 12 hours up to a total dose of 25 mg. Subcutaneous administration is slower and less reliable[61,66] and thus not recommended by the American College of Chest Physicians guidelines.[6] Vitamin K should not be administered intramuscularly because of unreliable absorption rates and the risk of causing an intramuscular hematoma. The risk of hematoma formation is higher in patients who have a supertherapeutic INR.

Fresh Frozen Plasma. Plasma is the most widely used coagulation factor replacement product in most hospitals. In FFP, plasma separated from whole blood donation is frozen within 8 hours (fresh) at –18°C. To facilitate emergency plasma transfusion at our institution (Parkland Health and Hospital System), thawed plasma is used. It is FFP that has been thawed and kept at 1–6°C for up to 5 days, as per FDA guidelines. Except for differences in FVIII levels, thawed plasma and FFP are considered equivalent in terms of factor concentrations.[17]

Although FFP can be effective, it requires the transfusion of several units (10–15 ml/kg). Moreover, with FFP transfusion there may be an attendant delay of up to several hours in the therapeutic effect (time to obtain ABO blood type, thaw and transfuse several hundred milliliters of plasma). It has been shown that time to treatment is the most important determinant of complete INR reversal at 24 hours.[23] There is also the associated risks of volume overload (especially in elderly patients with cardiac disease), allergic reaction, exposure to multiple donors, and the possibility of transfusion-related acute lung injury, which represents the most common cause of death in the US due to the transfusion of plasma-containing products.[74]

Prothrombin Complex Concentrate. Prothrombin complex concentrates (also known as FIX concentrate) are commercial products that contain selectively purified high levels of VKDF. These factors are purified from plasma using ion-exchange chromatography or calcium precipitate adsorption. A variety of commercial products are available and the levels of the various factors (especially FVII) differ by manufacturer.[2,33,34]

There is growing evidence to suggest the superiority of PCC to plasma. Normal hemostasis is achieved more rapidly and reliably with PCC than plasma. In many instances the full reversal of anticoagulation is documented in as little as 10 minutes after PCC infusion.[52,83] The volume infused is also much smaller since the factors are concentrated in solution. It has been estimated that 10 ml of PCC has equivalent coagulation factors as 600 ml of plasma.[55] Prothrombin complex concentrates are virally inactivated and devoid of immunoglobulins and thus unlikely to cause viral transmission or transfusion-related acute lung injury as compared with plasma therapy. In one study the reversal of OAC with PCC resulted in a trend toward improved outcomes when compared with plasma.[22] In another study PCC led to the decreased incidence and extent of hematoma growth when compared with FFP. This effect is likely caused by the rapid action of PCC since this difference was no longer significant when only the patients who had achieved full and rapid correction of INR were considered.[39] The elimination half-life of the various factors in PCC is relatively short. Therefore, repeat administration may be necessary especially if vitamin K has not been administered.[83]

The optimum dose of PCC for oral anticoagulant reversal is not clearly established and varies widely in the literature, which is due to a lack of standardized dosing and the significant variability of factor levels in different preparations. Moreover, PCC is available as a "3-factor" (adequate FII, IX, and X and very low FVII) or a "4-factor" (adequate FII, VII, IX, and X) preparation. In most studies the administered dose is between 20–50 IU/kg. Smaller doses have also been reported effective in the literature.[84] In one study, the authors used a 3-factor PCC plus rFVIIa or a combined 4-factor preparation. They did not comment on any difference between the 2 groups. The importance of FVII in OAC reversal is not clearly established. The level of FVII necessary for hemostasis has been estimated to be as low as 15% of normal. Most patients on long-term OAC maintain levels greater than this.[48] Because INR is sensitive to FVII levels, patients who receive a 3-factor PCC may have continued mild elevation of INR after treatment despite having factor levels potentially within the hemostatic range. Whether this mild elevation is clinically significant is not clear. At our institution, we administer a 3-factor PCC (Profilnine, Grifols) with a small dose of rFVIIa (Novoseven, Novo Nordisk Pharmaceuticals, Inc.) for warfarin-related ICH (Fig. 3).

A concern surrounding the use of PCC is the potential induction of a hypercoagulable state and the thromboembolic complications that may ensue. It should be clarified that there are 2 types of PCCs used in clinical practice. Nonactivated PCC is used for treating hemophilia B and as a factor replacement in the setting of OAC reversal.

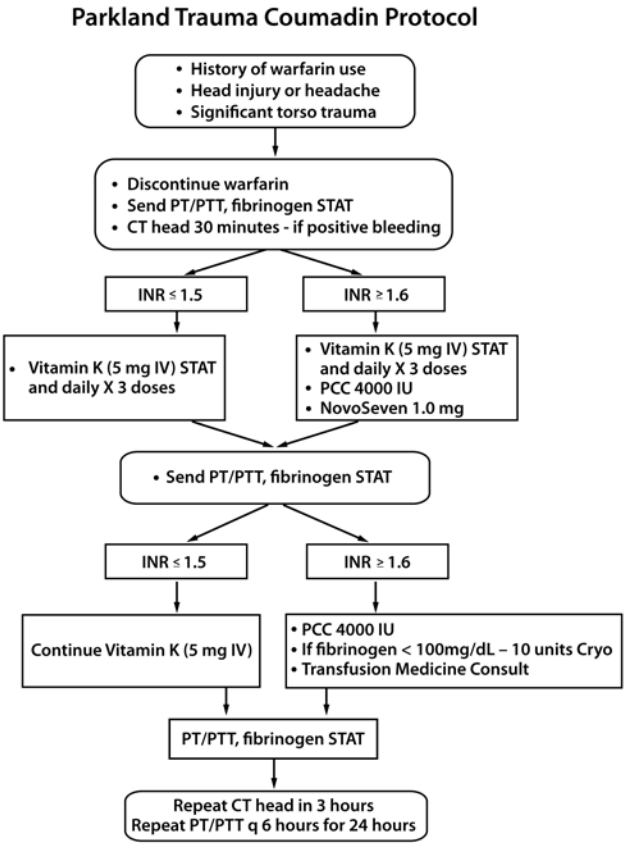

Fig. 3. Diagram of the Parkland Hospital trauma coumadin protocol. Cryo = cryoprecipitate; IV = intravenous; q = every; STAT = urgent or rush.

Activated PCC is used for treating hemophilia A or B with an inhibitor to FVIII or FIX. Activated PCC (for example, FEIBA [FVIII inhibitor bypassing activity]) contains activated clotting factors especially FVIIa and FXa. Because of the presence of activated factors in aPCC, they are associated with thrombotic complications especially in hemophiliacs with chronic liver disease. This hypercoagulable state is thought to be due to the relative deficiency of antithrombin in these patients.[34] Similarly, thrombotic complications were seen when nonactivated PCC was used for an extended duration (7–10 days) to treat patients with hemophilia B due to the cumulative effect of FII and X (levels excess of 200–300%) because of their longer half-lives as compared with FIX. Other contraindications to PCC administration include disseminated intravascular coagulation and hyperfibrinolysis. Since PCC is generally given only as a single dose for warfarin reversal, the thromboembolic risks are lower. There is a suggestion of lower thromboembolic risks when smaller doses are used in OAC reversal.[84] The overall risk is difficult to quantify because of the large variation in dosage, preparations, and patient populations in the literature. Most of the reports in the literature suggest that oral anticoagulant reversal with PCC is safe, and reports of complications are limited to case reports.[2,65]

Recombinant Activated FVII. Purified FVIIa was

first used in the early 1980s to treat patients with hemophilia A (deficiency of FVIII) or B (deficiency of FIX) in whom antibodies to FVIII or IX developed because of repeated transfusions. In this situation, FVIIa was used as a "bypass" agent to the deficient factors to reach thrombin generation and clot formation.[31,32] Because preparing FVII from plasma was a long and tedious process, human rFVIIa was developed by Novo Nordisk. The factor is activated in the manufacturing process. In the US it is FDA approved for the treatment of bleeding episodes or for surgical prophylaxis in patients with hemophilia A or B with an inhibitor to FVIII or IX or in those with a congenital FVII deficiency.

Despite the limited spectrum of indications, the use of rFVIIa has increased rapidly and the off-label indications are continuously expanding as clinicians use rFVIIa as a universal prohemostatic agent to treat more bleeding disorders.[62] In one retrospective multicenter chart review (701 patients) 92% of use was off label.[54] Recombinant FVIIa acts locally at the site of tissue injury by binding to exposed TF. This complex is able to generate small amounts of thrombin through FIX and X. The small amount of thrombin generated is sufficient to locally activate platelets. The activated platelet surface serves as a template on which FX can be activated. Factor Xa interacts with FVa to produce a large amount of thrombin at a high rate (thrombin burst). At higher doses, rFVIIa binds to locally activated platelets and directly activates FX producing a thrombin burst independent of FVIII or IX. This mechanism is thought to be the mechanism by which FVIIa can mediate thrombosis in patients with hemophilia lacking FVIII or IX.[47]

Recombinant FVIIa has been used to treat many coagulation disorders including coagulopathy due to warfarin use, liver failure, trauma, or platelet dysfunction. The first described use in neurosurgery was published in 2002 in a case in which a single dose of 120 μg/kg was used to normalize INR in a patient with an acute subdural hematoma.[77] Since then, there have been many reports of rFVIIa use to reverse warfarin-related coagulopathy. In many instances, it was used after other agents to reverse coagulopathy had failed or as an adjunct agent. Consistently, rFVIIa is able to rapidly improve INR, frequently in minutes, and there is adequate intraoperative hemostasis.[29] The optimum dose of rFVIIa is not clearly established. Generally, a dose less than that for hemophilia patients with bleeding (90–120 μg/kg every 2–3 hours until bleeding ceases) is needed. In the literature there is wide variation in dosing given the lack of standardized protocols and the different indications for this agent. Doses as low as 5 μg/kg have been said to prevent rebleeding after subarachnoid hemorrhage.[64] Sorensen et al.[72] have used doses ranging from 10–40 μg/kg (in addition to FFP and vitamin K) to successfully reverse coagulopathy in 7 patients with warfarin-related ICH. International Normalized Ratio values ranging from 1.7–6.6 decreased to 1.5 or less minutes after rFVIIa infusion. In the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial, 841 patients with normal coagulation parameters and nontraumatic ICH were randomly assigned to receive placebo or 20 or 80 μg/kg of rFVIIa within 4 hours of symptom onset. In this Phase III study, 80 μg/kg of rFVIIa significantly reduced intracerebral hematoma expansion (11 vs 26%).[58] This result is in contrast to findings in an earlier Phase IIb study in which rFVIIa did not improve survival or functional outcome.[59] It is unclear how these data may be translated to the patient with a warfarin-related coagulopathy. Although there is no clear consensus, doses of 20–60 μg/kg are generally effective in these patients.

In judging the efficacy of rFVIIa, one must realize that normalization of PT/INR does not always mean the full correction of coagulopathy. Prothrombin time is exquisitely sensitive to FVIIa activity, and the effect of rFVIIa on PT may be an ex vivo one rather than a true correction of hemostatic defects in vivo. Recombinant FVIIa does not replenish the deficiencies of FII, IX, and X associated with chronic warfarin use. Although it can induce hemostasis by a mechanism that essentially bypasses some of the deficient factors, it does not truly reverse the warfarin effect. In an experimental animal model in which the PT was elevated to 51 times normal by using a coumarin compound, rFVIIa was successful at substantially reducing PT but had no effect on bleeding time or total blood loss as compared with PCC.[15] It is unclear how this translates to human use since most surgeons who have used rFVIIa note a substantial improvement in bleeding when this agent is administered intraoperatively in patients with OAC-related ICH. In reviewing the literature on the use of rFVIIa in anticoagulated patients, it is probably wiser to look at bleeding end points (hematoma growth, total blood loss, and so forth) than PT/INR. These end points have been used in many instances with positive results. Thromboelastography may be a more accurate test of clotting in these patients.

In general, rFVIIa is safe with few complications. One concern about this agent is the induction of thromboembolism. In one review, rFVIIa resulted in an estimated 1.4–1.9% incidence of thromboembolism when used in patients without hemophilia. Diringer et al.[16] have examined the incidence of thromboembolic complications in all patients with acute ICH and intact coagulation systems who received rFVIIa in 3 controlled trials. Although the risk of disabling or fatal adverse events was no higher in the rFVIIa-treated patients compared with placebo, the administration of higher doses (120–160 μg/kg) was associated with an increased risk of arterial thromboembolic events. These episodes consisted of myocardial and cerebral ischemia. Of note, there was no increased incidence of venous thromboembolic events. The true incidence of thromboembolism in patients receiving rFVIIa for warfarin-related ICH is difficult to estimate for multiple reasons. The dose administered and the indication are highly varied in the literature. Many reports include patients who also received other prohemostatic agents or whose thromboembolic events occurred several days after rFVIIa infusion (half-life 2–3 hours).[46] Furthermore, patients on warfarin therapy typically undergo anticoagulation therapy for an underlying condition that predisposes them to thrombosis. Perhaps many of the patients who suffered from thromboembolism after rFVIIa treatment would have developed the same complications if their condition were reversed using any other agent. A

well-designed prospective trial is needed to fully estimate the incidence of thromboembolism when rFVIIa is used to treat warfarin coagulopathy.

Although shown to reduce hematoma expansion in neurosurgical patients, the high cost of treatment with rFVIIa has prevented its use in some medical centers. A recent study was focused on the cost-effectiveness of early treatment with rFVIIa for ICH in the US. A decision-analysis model was developed to estimate the lifetime costs and outcomes associated with rFVIIa treatment at doses of 40, 80, and 160 μg/kg compared with the current standard of care in treating ICH, from a US third-party payer perspective. The cost of rFVIIa for an 80 μg/kg dose in an 80-kg patient is ~ $6408. Outcomes included the incremental cost per life-year saved and the incremental cost per QALY gained. Compared with standard care, treatment with 40 and 160 μg/kg of rFVIIa resulted in total lifetime cost-effectiveness ratios of $6308/QALY and $3152/QALY, respectively. Treatment with 80 μg/kg of rFVIIa was found to be cost saving, and a gain of 1.67 QALYs can be achieved over a patient's lifetime. The treatment of non–warfarin-related ICH with rFVIIa appears to be cost-effective.[18] We are unaware of any studies focused on cost-effectiveness in patients who have warfarin-related ICH.

Our Protocol. At our institution, we have implemented a simple protocol (Fig. 3) to rapidly reverse warfarin coagulopathy in patients with ICH. Initial agents include fixed doses of 3-factor PCC (4000 IU) that mainly provide FII, IX, and X. Low-dose rFVIIa (1-mg vial) is used to supplement FVII and intravenous vitamin K (5 mg). Vitamin K is essential for the hepatic production of the depleted factors to avoid rebound effect since all transfused factors have a relatively short half-life.

Heparins

Unfractionated Heparin. Unfractionated heparin is the most widely used anticoagulant in the inpatient setting. It is a mixture of sulfated glycosaminoglycans of animal origin and of varying molecular weights. It exerts its anticoagulant effect by binding to antithrombin, inducing a conformational change that converts this circulating cofactor from a slow to a rapid inactivator of thrombin (FIIa), FXa, and, to a much lesser extent, FXIa and IXa. Although thrombin (FIIa) and FXa have the greatest sensitivity to the heparin-antithrombin complex, only heparin molecules > 18 polysaccharide units are able to inhibit thrombin. Molecules smaller than these, that is, LMWH, are unable to simultaneously bind thrombin and antithrombin but retain their ability to inhibit FXa. Most preparations of UFH inhibit FIIa more than FXa in a 2–3:1 ratio. Low-molecular-weight heparin predominantly inhibits FXa.

Although there is much experience and clinician comfort with UFH, the patient response is not always very reliable. It is estimated that only one-third of heparin molecules will possess the necessary pentasaccharide sequence to bind antithrombin. Moreover, as discussed above, the anticoagulant profile of each molecule is determined by its length. Finally, to further complicate the issue, larger molecules bind to activated endothelial cells, platelets, macrophages, and large macromolecules in plasma such as fibrinogen or von Willebrand factor, and thus are cleared from the circulation faster than smaller ones. This necessitates frequent PTT measurements to ensure therapeutic activity without over- or under-anticoagulation. Of note, PTT only estimates UFH's activity against thrombin but not its inhibition of FXa—which also explains why PTT is not affected by LMWH, which predominantly inhibits FXa.

Because of the short half-life of UFH (~ 1–2 hours), a constant infusion is needed to achieve therapeutic anticoagulation. It is this property that causes the rapid reversal of its effect simply by discontinuing the infusion. In situations of CNS hemorrhage, however, more rapid reversal is frequently needed.[1]

Protamine sulfate is the most widely used reversal agent for UFH. It is a mixture of arginine-rich, highly cationic, and basic peptides derived from fish sperm nuclei. Protamine complexes with heparin to form a stable salt, which is inactive and cleared from the circulation. Protamine is slowly administered intravenously (not to exceed 5 mg per minute) to avoid the risk of histamine release and resultant bronchoconstriction and hypotension. Protamine itself possesses anticoagulant properties when given in the absence of heparin. An "overdose" can result in more bleeding. The dose must be calculated carefully, taking into account the relatively short half-life of UFH. It is generally advised to err on the side of smaller doses and to repeat if needed. One milligram of protamine sulfate is able to neutralize 90 U of US Pharmacopeia (USP) bovine-origin heparin and 115 USP units of porcine origin. Most clinicians use a 1-mg to 100-U algorithm for bleeding immediately following a bolus infusion of heparin. If 30 minutes to 1 hour has elapsed since the intravenous injection of heparin, 0.5 mg of protamine sulfate should be given for every 100 U of heparin, and if 2 hours or more have elapsed since the intravenous injection of heparin, 0.25–0.375 mg of protamine sulfate should be given for every 100 U of heparin administered.[71] For patients who experience bleeding while receiving a continuous infusion, enough protamine is needed to neutralize all the heparin received within the last hour plus one-half the dose of the preceding hour plus one-quarter of the dose received the hour before that. A patient who has been on a stable infusion of heparin at 1000 U/hour and experiences bleeding would need to reverse 1000 U + 500 U + 250 U = 1750 U of heparin. This patient would need ~ 17.5 mg of protamine for reversal.[35]

Fresh frozen plasma should not be used to reverse the UFH effect because it provides additional antithrombin, which may further potentiate the anticoagulant effect of UFH and worsen the bleeding.

Low-Molecular-Weight Heparins. Low-molecular-weight heparins are derived from standard commercial-grade UFH by a process of enzymatic or chemical depolymerization to yield smaller fragments. On average, these molecules are one-third the size of an average heparin molecule. This smaller size leads to several changes in the characteristics of the compound. The most notable

is the anticoagulant profile. Because of their smaller size, most of these fragments cannot catalyze the inactivation of thrombin; that is, they cannot simultaneously bind thrombin and antithrombin. However, they do retain anti-FXa activity, which is the basis of their anticoagulant effect. Therefore, PTT (which is sensitive to thrombin activity but not FXa) cannot be used to monitor anticoagulant effect. When necessary, FXa activity can be measured. Low-molecular-weight heparin molecules also have less binding affinity to plasma proteins and endothelial cells, which improves their bioavailability and may account for the reliable dose-response that this class of anticoagulants possesses. Low-molecular-weight heparins have a much longer half-life than UFH and is further increased in patients with renal failure since these compounds are primarily cleared by the kidney.[1,35] The average half-life is ~ 4 hours, but anti-FXa activity may persist longer.[7]

Protamine may be used to reverse some of the anticoagulant effects of LMWH. On average, the reversal of 40–50% of the anti-FXa activity may be achieved.[1] The recommended dose is 1 mg of protamine for every 1 mg of LMWH administered in the previous 4 hours.[79]

Newer reports in the literature have suggested the utility of rFVIIa in the management of intractable bleeding due to LMWH therapy. One report describes the cessation of bleeding (rectus hematoma) after rFVIIa administration in a patient in whom treatment with FFP and protamine had failed. In this report the patient received 4.8 mg (50 μg/kg) followed by surgery to evacuate the hematoma. He was given 2 additional "prophylactic" doses after surgery.[38] In an ex vivo study, rFVIIa (at an equivalent dose to 90–270 μg/kg) reversed the effect of LMWH (enoxaparin) as assessed by thromboelastography.[85] Activated PCC may also be considered.

Direct Thrombin Inhibitors

Unfractionated heparin and, to a lesser extent, LMWH are indirect thrombin inhibitors. They rely on interaction with antithrombin for their function. In contrast, DTIs bind to thrombin directly without a mediator. Hirudin, the original DTI prototype, was first isolated from leach saliva. Subsequent studies led to the development of hirudin-like peptides called "hirugens" or "hirullins."[28,57] Common DTIs available today are lepirudin (Refludan, Bayer Pharmaceuticals), Argatroban (GlaxoSmithKline Pharmaceuticals), and bivalirudin (Angiomax, The Medicines Company). These agents have relatively short half-lives ranging from 24–45 minutes for bivalirudin to 1.3 hours (higher with renal failure) for lepirudin.[43] Direct thrombin inhibitors are typically more challenging to reverse given the lack of a specific antidote.

Multiple agents have been reported in the literature with mixed success. In one report, a patient with heparin-induced thrombocytopenia underwent cardiac surgery with anticoagulation using Argatroban rather than heparin. On completion of the procedure, the patient required the reversal of anticoagulation. Two doses of rFVIIa at 90 μg/kg failed to achieve hemostasis and did not have a large effect on the activated clotting time (394–329 seconds). The patient received blood product transfusion including FFP and platelets and ultimately (after ~ 2 hours) achieved adequate hemostasis.[56] In another report, the authors describe successful hemostasis in a patient with intractable bleeding who had received lepirudin using a single 35-μg/kg dose of rFVIIa. In this case, however, the patient had received numerous other agents including 15 U of FFP, 5 U of platelets, and aminocaproic acid.[63] Finally, in a study with melagatran, a single dose of rFVIIa at 90 μg/kg did not have a significant effect on most coagulation parameters in healthy volunteers.[82] In an animal study using melagatran, activated PCC was more effective than high-dose rFVIIa in reducing blood loss and reversing prolonged bleeding time.[19] A case study of a patient who had received hirudin and experienced gastrointestinal bleeding also showed a response to activated PCC.[41]

In an experimental model, DDAVP was able to reduce prolonged PTT induced by hirudin.[40] Bleeding time was shortened in rabbits pretreated with hirudin when DDAVP was administered.[9] In a similar study in rats infused with hirudin, DDAVP and rFVIII were successful at returning the bleeding time to the control range, whereas rFVIIa and the antifibrinolytic agent aminocaproic acid were unsuccessful.[11] Although the mechanism by which DDAVP reverses the effects of DTIs is not entirely clear, it is likely related to the elevation in FVIII and von Willebrand factor levels that results from DDAVP infusion. Deamino-D-arginine-vasopressin can increase the levels of these factors by 2- to 6-fold via endogenous release. In so-called mild hemophilia A and Type 1 von Willebrand disease, the recommended dose of DDAVP is 0.3 μg/kg intravenously.[45] Although DDAVP is largely safe, there are always concerns about the induction of hyponatremia with a resultant elevation in intracranial pressure or seizures. Cryoprecipitate infusion may be able to accomplish elevation in the levels of FVIII and von Willebrand factor without these risks.

Pentasaccharide Agents

The pentasaccharide agents are compounds that only inhibit FXa by binding to a specific site on antithrombin. As opposed to UFH and, to a certain extent, LMWH, pentasaccharides do not inhibit thrombin. These agents have a long half-life that is further increased by renal insufficiency. Fondaparinux (Arixtra, GlaxoSmithKline) has a half-life of ~ 14 hours, and idraparinux (investigational drug) has a much longer half-life permitting once weekly injections.[14] These agents do not have a specific antidote in case of a bleeding emergency or overdose. However, in case reports and experimental studies, rFVIIa was successful at correcting coagulation parameters and stopping bleeding associated with these agents. There are 2 studies utilizing healthy volunteers in the literature. In the first trial fondaparinux was used, whereas in the second idraparinux was tested. Both studies demonstrated improvement or normalization in the coagulation parameters with rFVIIa at 90 μg/kg.[8,50] Recombinant FVIIa at 30 μg/kg was successful at stopping bleeding in a patient after lung lobectomy. This patient had been taking idraparinux but stopped before surgery. Although he had stopped 4 weeks prior to surgery, his idraparinux-induced anti-Xa level was still in the therapeutic range.[13]

TABLE 2: Summary of anticoagulants/antiplatelet agents and their emergency reversal*

Anticoagulant/Antiplatelet Agent	Reversal	Lab Test	Comments
warfarin	1. vitamin K, 5-10 mg IV 2. 3-factor PCC, 4000 IU 3. low-dose rFVIIa, 1.0 mg†	PT/INR	1. FFP, 10–15 ml/kg, if PCC not available 2. slow administration of IV vitamin K, 0.5–1 mg/minute 3. monitor INR after administration of reversal & every 6 hrs for 24 hrs to check for rebound
UFH	1. stop infusion 2. protamine sulfate, 1 mg for each 100 U of active heparin	PTT	1. FFP contraindicated 2. slow administration (<5 mg/minute) to avoid protamine-induced bronchoconstriction or hypotension
LMWH	1. protamine sulfate, 1 mg for each 1 mg of LMWH 2. consider activated PCC (FEIBA) 3. consider rFVIIa	anti-Xa assay	1. protamine offers only partial reversal
DTI	1. no specific antidote 2. DDAVP, 0.3 μg/kg 3. consider cryoprecipitate 4. consider rVIIa (w/ extreme caution in HIT)	PTT	1. caution hyponatremia, seizures, & elevated ICP w/ DDAVP.
pentasaccharide	1. rFVIIa, 30–90 μg/kg	anti-Xa assay	
aspirin	1. 1 U platelet transfusion 2. consider DDAVP, 0.3 μg/kg 3. consider rFVIIa, 30–90 μg /kg	consider PFA-100	1. caution hyponatremia, seizures, & elevated ICP w/ DDAVP
clopidogrel or ticlopidine	1. 2 U platelet transfusion 2. consider DDAVP, 0.3 μg/kg 3. consider rFVIIa, 30–90 μg/kg	consider platelet aggregometry	1. caution hyponatremia, seizures, & elevated ICP w/ DDAVP

* FEIBA = FVIII inhibitor bypassing activity; HIT = heparin-induced thrombocytopenia; IV = intravenous.
† Refer to protocol in Fig. 3.

Antiplatelet Agents

Aspirin

The history of aspirin dates back several thousand years when plant preparations containing salicylates were used to treat various ailments including fever and pain. Aspirin was synthesized in 1899 by a German chemist named Felix Hoffmann, who worked for Bayer. He had produced the compound to give to his father who suffered from "rheumatism," with good results.[76] Aspirin was patented by Bayer on February 27, 1900.

Today, aspirin is widely used as an antiplatelet agent in patients with atherosclerotic vascular disease. It is absorbed within minutes of ingestion. Within the portal circulation, it irreversibly binds to cyclooxygenase-1 enzyme (COX-1) and inhibits TXA2 production in all platelets exposed to aspirin. It is rapidly metabolized within minutes, and its metabolite is ineffective. Thus, newly produced platelets have normal function. Ten percent of platelets are produced every day; therefore, in a patient with a platelet count of 200 × 10^9/L, 20,000 would be produced daily. If the patient had ingested aspirin 3 days earlier, then he would have at least 60,000 normally functional platelets. As such, aspirin induces only mild to moderate platelet dysfunction because all platelet glycoprotein receptors and other biochemical pathways are still intact. The aspirin effect can be easily detected by the PFA-100 test (Table 1).

Although aspirin use leads to a decreased mortality rate in certain groups of patients, regular aspirin use prior to ICH resulted in a 2.5 relative risk of death in one study.[70] Although there is no specific antidote, the aspirin effect can be reversed by 1 dose of platelet transfusion (1 single donor or 5 pooled concentrates), and this process remains the mainstay of reversal today. In experimental studies, rFVIIa has been shown to reverse the in vitro inhibition of thrombin generation caused by aspirin.[3] In case reports researchers have successfully used DDAVP to reverse the aspirin effect.[20,24] Deamino-D-arginine-vasopressin use may be a valuable option for rapid intraoperative control of bleeding.

Clopidogrel

Clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi Pharmaceuticals) is a thienopyridine compound that inhibits the ADP-dependent pathway for platelet activation and in numerous trials has been shown to be effective in a wide variety of patients with cardiovascular and cerebrovascular disease. It is widely studied in patients who have undergone coronary stent implantation or who present with acute coronary syndromes. Clopidogrel is inactive in vitro and is metabolized extensively by hepatic cytochrome P450 to produce an active metabolite. This metabolite irreversibly binds to the platelet ($P2Y_{12}$ receptor) inhibiting ADP-induced activation of the GPIIb/IIIa complexes, thrombin receptor agonist peptide (TRAP)-

induced fibrinogen binding, and P-selectin expression on the platelet membrane surfaces.[42] In most patients, platelet function returns to normal 5–7 days after discontinuing the medication.[81] Clopidogrel effect can be assessed by the platelet aggregation test but not the PFA-100 test. Like aspirin, clopidogrel lacks a specific antidote. In an ex vivo study in which healthy volunteers were given aspirin and clopidogrel, platelet transfusion successfully restored platelet reactivity.[78] In another study, also involving healthy volunteers given aspirin plus clopidogrel, ex vivo rFVIIa reversed the inhibitory platelet effect of these agents.[3] In a letter to the editor, Loertzer et al.[51] have described the prophylactic use of rFVIIa in 5 patients undergoing renal transplantation who were on aspirin or clopidogrel. These authors reported improvement in the coagulation parameters without thrombotic complications. The dose of administered rFVIIa was not mentioned in their report. Deamino-D-arginine-vasopressin was also used along with a nasal tamponade in the case of life-threatening epistaxis in a patient taking clopidogrel. The patient was given 20 μg and, according to the report, had successful control of bleeding. Hyponatremia developed to 123 mEq/L, but the patient suffered no complication.[60] Platelet dysfunction due to clopidogrel is more severe than that with aspirin; thus, for neurosurgical bleeding, generally 2 doses of platelets (2 single donor or 10 pooled concentrates) should be transfused. Each dose of platelets generally provides 50,000 functional platelets.

Ticlopidine

Ticlopidine (Ticlid, Roche) belongs to the thienopyridine group of antiplatelet drugs that also inhibit the $P2Y_{12}$ ADP receptor. Because of its serious side effect of thrombotic thrombocytopenia purpura and the potential to cause myelosuppression, it is used only when the patient is resistant to clopidogrel. Ticlopidine has a bleeding profile similar to clopidogrel, and similar strategies are used to reverse its effect.

Although there is a lack of published data regarding platelet transfusion and surgical outcome in neurosurgery, there is evidence that early transfusion of platelets in massively transfused trauma patients results in improved survival.[36]

Conclusions

The use of anticoagulants and antiplatelet agents is on the rise. Intracranial hemorrhage associated with these agents must be quickly reversed to improve the likelihood of recovery (Table 2). As new agents are being used, neurosurgeons must be aware of the effective strategies to reverse coagulopathy.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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