Percutaneous Interventions in the Coagulopathic Patient

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ABSTRACT

Interventional procedures in patients with coagulopathies carry a perceived risk of increased bleeding and complications. Acquired and inherited deficiencies of blood-clotting factors, thrombocytopenia and platelet dysfunction, and effect of anticoagulation are common problems encountered by practicing clinical interventional radiologists. In this article we review common coagulopathies, available data on percutaneous procedures in coagulopathic patients, and recommendations for periprocedure treatment.

KEYWORDS: Interventional radiology, coagulopathy, complications, thrombocytopenia, review

Objectives: Upon completion of this article, the reader will understand common coagulopathies, available data on percutaneous procedures in coagulopathic patients, and recommendations for peri-procedure treatment.

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COAGULATION TESTING IN SCREENING FOR BLEEDING RISK

The tests ordered for screening for coagulation disorders include the prothrombin time (PT) usually measured as the international normalized ratio (INR), activated partial thromboplastin time (aPTT), and platelet count. Bleeding disorders associated with abnormalities of the

PT and aPTT are shown in Tables 1–3. The bleeding time has not been found to be useful in predicting surgical bleeding, nor have newer tests of platelet function, such as the Platelet Function Analyzer (PFA-100),^{1,2} and thus none of these tests currently have a defined role in preprocedure assessments. In patients who are not acutely ill with confounding coagulopathies, a history of bleeding is the most sensitive predictor of bleeding with surgical procedures. Screening tools to use in assessing bleeding history have been developed.³ Because abnormal screening laboratory tests do not necessarily correlate with bleeding, it is important to assess the bleeding history together with the coagulation screening tests, requesting further testing, as needed, to define a potential inherited or acquired bleeding diathesis.

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Table 1 Patient with Bleeding: Prolonged aPTT, Prolonged PT

Inherited
Deficiencies of factor I (fibrinogen)*, II, V, or XI [†]
Dysfibrinogenemia*
Acquired
Specific inhibitors of factor V, II, or X
Disseminated intravascular coagulation* ^{†,‡}
Factor deficiencies related to liver disease [†]
Factor deficiencies related to vitamin K deficiency [†]
Dysfibrinogenemia related to liver disease* [†]
Paraproteinemia [†]
Amyloidosis
Heparin therapy [§]

*Thrombin clotting time and reptilase time prolonged.

[†]Affects PT more than aPTT.

[‡]Often with thrombocytopenia.

[§]Affects aPTT more than PT.

In patients with personal or family histories of bleeding, a defined diagnosis should be obtained prior to a procedure. Patients with mild hemophilia (factor VIII or IX levels > 5%) bleed only with trauma or procedures and may go undiagnosed into adulthood. Because of a high spontaneous mutation rate, a family history of hemophilia may not be present. Female carriers of hemophilia may have similarly low levels consistent with the diagnosis of mild hemophilia. Other inherited factor deficiencies, particularly factor XI (FXI) deficiency and von Willebrand disease (VWD), may present with variable personal and family histories of bleeding. In type 1 VWD the FVIII level is often not low enough to prolong the aPTT, and thus the aPTT is not an adequate screening test for this disorder.

Several acquired disorders may be associated with an increased risk of bleeding. Those most commonly encountered in hospitalized patients are liver disease, disseminated intravascular coagulation (DIC), and thrombocytopenia. An uncommon but important acquired disorder to recognize is an acquired inhibitor to a coagulation factor, most notably FVIII, because of attendant significant bleeding risks.

Patients with advanced liver disease are usually coagulopathic, although the extent of the defects varies

among patients. The coagulopathy is due to decreased synthesis of clotting factors, decreased platelets related to hypersplenism and decreased synthesis of thrombopoietin, and increased fibrinolysis, primarily because of lack of clearance of fibrinolytic enzymes. There is significant variability in how these factors are affected, and true bleeding risk can be difficult to assess.

DIC is caused by an ongoing stimulus to coagulation that is not controlled by usual mechanisms, leading to ongoing thrombin generation (usually with microvascular thrombosis), consumption of coagulation factors and platelets (with an attendant risk of bleeding), and stimulation of fibrinolysis. Although there are many causes of DIC, in hospitalized patients sepsis is the most common and is usually associated with microvascular thrombosis with end-organ damage and bleeding. Chronic DIC with thrombosis is more commonly seen in the setting of cancer. End-stage liver disease is associated with low-grade DIC.

Thrombocytopenia is due to decreased production, sequestration (usually related to splenomegaly), or increased destruction. Thrombocytopenia is often seen in combination with other coagulopathies or hematologic disorders, such as DIC and liver disease. Immune-mediated thrombocytopenia, notably idiopathic thrombocytopenic purpura (ITP), is usually associated with less bleeding than in primary bone marrow disorders. In patients with bone marrow disorders, coexistent anemia may also enhance a bleeding tendency. Isolated thrombocytopenias are usually due to peripheral destruction. In general, the bleeding risk with thrombocytopenia is less than realized in the past. Early studies were confounded by coadministration of platelet inhibitory drugs. Spontaneous bleeding rarely occurs in stable, noninfected patients with a platelet count greater than 10,000/ μ L.

Patients with normal platelet counts or thrombocytopenic patients may also have platelet dysfunction. Platelet dysfunction may be acquired because of uremia, medications, herbal supplements, or paraproteinemias and after cardiopulmonary bypass.⁴ Less commonly, patients can inherit disorders of platelet function. In that setting, there is usually a personal and family history of mucosal bleeding and the platelet count is usually normal.

Table 2 Patient with Bleeding: Prolonged aPTT, Normal PT

Inherited
Deficiencies of factor VIII, IX, or XI
Von Willebrand disease*
Acquired
Specific inhibitors of factor VIII, IX, or XI [†]
Heparin therapy [†]

*Due to low factor VIII.

[†]Factor VIII inhibitors are much more common than the others.

[‡]Thrombin clotting time prolonged, reptilase time normal.

CORRECTION OF COAGULOPATHIES FOR PROCEDURES

In assessing the need for and planning for correction of a coagulopathy prior to a procedure, defining the underlying coagulopathy and the presence or absence of confounding medications or medical conditions is important. Patients with an isolated elevated aPTT may have a specific coagulation factor deficiency, such as FVIII or FIX deficiency (see Table 2), in which

Table 3 Patient with Bleeding: Normal aPTT, Prolonged PT

Inherited
Factor VII deficiency*
Dysfibrinogenemia ^{†,‡}
Acquired
Warfarin therapy
Factor deficiencies related to liver disease [§]
Factor deficiencies related to vitamin K deficiency [§]
Dysfibrinogenemia related to liver disease ^{†,§}
Disseminated intravascular coagulation ^{§,¶}
Paraproteinemia [†]
Specific inhibitor to FVII

*Bleeding variable and associated with levels < 15%.

[†]Prolonged thrombin clotting time and reptilase time.

[‡]Bleeding uncommon, when present usually mild.

[§]aPTT usually also prolonged when bleeding present.

[¶]Often with thrombocytopenia.

specific high-purity factor replacement products should be used for treatment. Other disorders, such as lupus anticoagulants and FXII deficiency, are not associated with bleeding risks and require no treatment. Acquired

factor inhibitors, notably FVIII inhibitors, are not corrected with plasma infusions and may be associated with significant bleeding. Available hemostatic agents are summarized in Table 4 and a discussion of their use follows.

Fresh Frozen Plasma

Although fresh frozen plasma (FFP) is routinely given prophylactically to patients with an elevated international normalized ratio (INR) to prevent bleeding, clinical studies have not documented its effectiveness in this setting. Stanworth et al published a systematic review of randomized controlled trials on the clinical effectiveness of FFP infusions.⁵ They noted that most clinical uses of FFP, currently recommended by practice guidelines, are not supported by evidence from randomized trials. In particular, there is little evidence for the effectiveness of the prophylactic use of FFP. Because many of the trials enrolled small numbers of patients, true differences would be difficult to detect. Reported experiences with larger numbers of patients are retrospective reviews of clinical outcomes. However, these

Table 4 Hemostatic Agents

Hemostatic Agent	Clinical Uses	Dose
Fresh frozen plasma (FFP)	Coagulopathy of liver disease or reversal of warfarin in patients with bleeding or need for immediate procedure; replacement of congenital deficiencies of factor II, V, VII, X, XI	15–30 mL/kg, or as needed to obtain hemostatic levels
Cryoprecipitate	Deficiencies of fibrinogen, factor XIII*	10 bags increase fibrinogen by ~75 mg/dL in a 70-kg patient
Platelets	Thrombocytopenia, acquired or inherited platelet dysfunction [†]	4–6 random donor or 1 single donor unit increases count ~25,000/ μ L [‡]
Desmopressin (DDAVP)	Von Willebrand disease (known to be responsive) and inherited and acquired platelet dysfunction	0.3 μ g/kg
Fibrin sealants	Local hemostasis, usually with surgery or procedures	Product applied usually with two-syringe technique as directed by manufacturer
High-purity factor VIII	Hemophilia A (factor VIII deficiency)	Varies by baseline level and indication [§]
High-purity factor IX	Hemophilia B (factor IX deficiency)	Varies by baseline level and indication [§]
VWF/FVIII concentrates	Von Willebrand disease for which DDAVP is not effective	Varies by baseline level and indication [§]
aPCC/PCC	Patients with hemophilia with inhibitors to FVIII or acquired inhibitors to FVIII, reports of use in severe nonhemophilic bleeding, PCCs used in congenital deficiencies of FII, VII, X	Varies by baseline level and indication [§]
rFVIIa	Hemophilia with inhibitors to FVIII or FIX, acquired inhibitors to coagulation factors, congenital factor VII deficiency, numerous reports in severe nonhemophilic bleeding	For hemophilia with inhibitors 90 μ g/kg every 2–3 hours (studies of larger doses given less frequently under way); dosing in nonhemophilic bleeding 20–120 μ g/kg

*Investigational concentrate available.

[†]If treatment is required for this indication, may be able to use DDAVP instead of transfusion.

[‡]Response varies greatly depending on clinical situation.

[§]Treat in collaboration with hemophilia treatment center or hematologist experienced in the care of hemophiliacs.

aPCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate; VWF, von Willebrand factor.

also show that FFP infusions in patients with mild to moderate elevations of the INR do not affect bleeding risks. This has been studied most in liver procedures, where patients frequently have underlying liver disease and a resultant coagulopathy. Hepatic procedures involving malignancies are associated with an increased risk of bleeding.⁶ This risk does not appear to be decreased by pretreatment with FFP infusions, although it has not been studied in a prospective manner. Although the experience is smaller, there are similar data for the lack of correlation between FFP infusion and bleeding complications from central line placement, paracentesis, and thoracentesis.^{5,7,8} In part this is due to the fact that the overall complication rate from many of these procedures is low in many patients with coagulopathies.

Chowdhury et al evaluated the effect of FFP infusion on correction of coagulopathies in critically ill patients who were bleeding or about to undergo procedures, comparing a standard 10–15 mL/kg with 30 mL/kg in achieving hemostatic levels (factor levels > 30 IU/dL; fibrinogen > 1 g/L).⁹ They found that the PT and aPTT did not accurately predict factor deficiencies and that commonly prescribed doses of FFP infrequently achieve what are considered to be hemostatic levels in this population of patients. These results extend findings reported by Youssef et al that, in patients with chronic liver disease, an infusion of 2–4 units of FFP did not adequately correct the PT in 90% of patients.¹⁰

Although transmission of human immunodeficiency virus, hepatitis B, and hepatitis C through transfusion is now rare, each occurring with approximately 1 per 2,000,000 units transfused, other emerging infections, allergic reactions (1–3%), and transfusion-related acute lung injury (0.02–0.0005%) continue to be ongoing risks.¹¹ In addition, volume overload from transfusion of FFP is an issue for many patients. The use of FFP in the United States continues to increase, and meeting that demand is dependent on blood donations. These factors further support the need for prospective randomized trials of prophylactic FFP infusions and the development of treatment protocols on the basis of clinical outcome data.

Platelet Transfusions

Thrombocytopenia is associated with an increased risk of bleeding with procedures. The “hemostatic” count needed for procedures depends on many factors including the cause of the thrombocytopenia, coexisting coagulopathies, and the type of procedure to be performed. In the noninfected stable patient not undergoing procedures, a platelet count of 10,000 is sufficient to maintain hemostasis¹²; an even lower count is probably safe for patients with ITP. A count of > 50,000/ μ L is safe for most surgical procedures, although a count lower than that should be sufficient for many procedures. Bone

marrow aspiration and biopsies from the posterior iliac crest are routinely performed in severely thrombocytopenic patients without complications. Bleeding from this procedure can be seen in coagulopathic patients such as those receiving heparin therapy, those with DIC, and those with inherited or acquired coagulation factor deficiencies.

Transjugular liver biopsies (TJLBs) are frequently performed in ill patients. Wallace et al reported their experience of TJLB in 50 thrombocytopenic patients with hematologic malignancies.¹³ Although patients received platelet transfusions before the procedure, the post-transfusion counts ranged from 5000 to 105,000/ μ L and in 24 procedures were less than 30,000/ μ L. No hemorrhage-related complications were encountered. They concluded that the threshold platelet count for safe TJLB is less than 30,000/ μ L.

Concerning lumbar puncture in thrombocytopenic patients, Vavricka et al reviewed records of 66 patients with acute leukemia who received 195 lumbar punctures.¹⁴ Although serious hemorrhagic complications did not occur, those with lower platelet counts were more likely to have red blood cells in the spinal fluid. They recommended a platelet count $\geq$ 20,000/ μ L, on the basis of their findings.

Ray and Shenoy prospectively evaluated radiologic placement of central venous access devices in 105 patients (87 catheters, 10 arm ports, and 8 chest ports).¹⁵ Patients with platelet counts < 50,000/ μ L had no greater bleeding complications than those with platelet counts of 50,000–100,000/ μ L or those with platelet counts of 100,000–150,000/ μ L. Five other studies have evaluated central line placement in coagulopathic patients, generally with both an elevated INR and decreased platelet count.¹⁶ Overall, the bleeding rate was extremely low (1 to 2%) with no reports of fatal bleeding.

Approximately one third of the platelet mass in the body is sequestered in the spleen.¹⁷ This sequestration increases as the spleen size increases, although in patients with splenomegaly and platelet counts < 40,000/ μ L, additional causes of thrombocytopenia should be sought. If platelet transfusions are given to patients with splenomegaly, they should be infused immediately before or even during the procedure, as their circulation time is significantly decreased.

Other Hemostatics

Desmopressin (1-deamino-cys-8-D-arginine vasopressin or DDAVP) is a synthetic analogue of the natural hormone vasopressin. Infusion of DDAVP results in almost immediate release of von Willebrand factor (VWF), FVIII, and tissue plasminogen activator.¹⁸ An intranasal high-concentration formulation of DDAVP (1.5 mg/mL) is also effective in increasing levels, but

with a peak effect at 2 hours versus 30 minutes for an intravenous infusion. DDAVP also results in increased platelet adhesiveness through unclear mechanisms, although it is probably due to the increase in VWF release and possibly a direct effect on platelet adhesiveness. DDAVP improves platelet function in uremia and in many, but not all, inherited qualitative platelet defects.¹⁹ In uremia, DDAVP normalizes the bleeding time in 75% of patients, with values returning to baseline in ~8 hours.¹⁸ It has also been shown to improve *ex vivo* platelet function after aspirin and glycoprotein IIb/IIIa inhibitors.²⁰ However, reversal of an aspirin effect is usually not needed before most procedures.

Because of its antidiuretic effect, the major side effect of DDAVP is hyponatremia and intravenous fluids should be limited in patients in whom DDAVP is used as a hemostatic agent. When given as an intravenous infusion, DDAVP is administered at 0.3 µg/kg and given over 15 to 30 minutes. In patients with type 1 VWD, mild hemophilia A, and responsive platelet function disorders, doses are often repeated at 12 to 24 hours. Because the increase in VWF and FVIII levels is due primarily to a release phenomenon, tachyphylaxis can occur, although this is variable and some response usually persists even after multiple doses.²¹

Fibrin Sealants

Fibrin sealants or fibrin glues have been used for years to obtain local hemostasis. Several virally inactivated plasma-derived products are available worldwide. They contain fibrinogen and thrombin, with different quantities of FXIII, antifibrinolytic agent (usually aprotinin), and calcium chloride.²² The thrombin and fibrinogen components are kept separate until application, usually using a dual-syringe method to allow fibrin formation at the site of current or potential bleeding. They have been used to aid in hemostasis in patients with congenital bleeding disorders in oral, general, and orthopedic surgery and in circumcision.^{23,24} Successful use of the agent Tisseel VH[®] (Baxter Healthcare, Westlake Village, CA) has been reported in interventional radiology procedures in closure of abdominal fistulas and sinuses and in biliary procedures.²⁵

Factor VIII and IX Concentrates

Virally inactivated high-purity plasma-derived and recombinant factor VIII (FVIII) and factor IX (FIX) products are available for replacement for patients with FVIII and FIX deficiency. Plasma-derived VWF-containing FVIII concentrates are available for treatment of VWD unresponsive to DDAVP. In hemophilic patients without inhibitors, these products effectively replace factor for procedures. A single institution reviewed their experience with TJLBs in 13 men with hemophilia or

other bleeding disorders.²⁶ The patients were given prophylaxis with hemostatic agents for 1–5 days, depending on their underlying disorder, and all were hospitalized for ≤48 hours. All patients did well and had no bleeding complications. Procedures in patients with inherited bleeding disorders should be managed in collaboration with hemophilia treatment centers or hematologists familiar in their management.

Activated Prothrombin Complex Concentrates and Recombinant Factor VIIa

Activated prothrombin complex concentrates (aPCCs; current product available in the United States is Feiba[®], Baxter Healthcare) and recombinant FVIIa (rFVIIa; NovoSeven[®], Novo Nordisk Pharmaceuticals, Princeton, NJ) are approved by the Food and Drug Administration for the treatment of hemophilic patients with inhibitors. These agents are also routinely used for the treatment of bleeding in patients with acquired antibodies to FVIII. aPCCs are virally inactivated plasma-derived concentrates of the vitamin K-dependent factors, with partial activation of the coagulation factors.²⁷ Both aPCCs and rFVIIa can result in thrombin activation independent of FVIII or FIX levels. aPCCs have been used for reversal of warfarin and in patients without hematologic disorders who have critical bleeding.

rFVIIa has been used to treat uncontrolled bleeding in patients without underlying bleeding disorders, including use in major trauma, liver transplantation, cardiopulmonary bypass, and thrombocytopenic bleeding and in reversal of warfarin. Most available data are from case reports and small series. At this time, many questions remain about the use of rFVIIa, including identifying the patients and clinical scenarios for which it is efficacious as well as defining the optimal dose and timing of administration.²⁸ Hampering progress is the fact that there is not a laboratory test that correlates with clinical efficacy. Administration of rFVIIa universally results in shortening of the PT regardless of response.

A small number of randomized clinical trials evaluating the use of rFVIIa for nonhemophilic bleeding have been completed. In a double-blind, placebo-controlled study of one dose of rFVIIa prior to retropubic prostatectomy, blood loss was decreased by 60% with a 40 µg/kg dose and by 50% with a 20 µg/kg dose.²⁹ In contrast, in liver transplantation and in partial hepatectomy, efficacy in decreasing blood loss was not demonstrated.²⁸ The dose approved for treatment of hemophilic patients with factor inhibitors is 90 µg/kg, and higher doses are under study for this indication. However, it appears from the prostatectomy study, case reports, and small series that a lower dose can be effective in nonhemophiliacs.

In terms of percutaneous procedures, Deveras and Kessler reported successful removal of an epidural

catheter, an arterial sheath, and a Hickman catheter after rFVIIa infusions in three patients with warfarin-induced coagulopathy with preprocedure INRs of 8.25, 3.37, and 1.85, respectively.³⁰ Four different doses of rFVIIa (5, 20, 80, and 120 µg/kg) were infused prior to laparoscopic liver biopsy in 71 coagulopathic patients with liver disease.³¹ All had platelet counts > 60,000/µL, and the PT was prolonged 3–15 seconds. All patients had shortening of the PT; none had bleeding complications.

There appears to be some increased risk of thrombosis with rFVIIa, particularly in patients with underlying cardiovascular risk factors. However, the risk appears lower than that seen with aPCC treatment. rFVIIa offers theoretical advantages over FFP because of a very small volume and more rapid availability. However, hemostatic levels of fibrinogen and prothrombin must be present, which would necessitate replacement. Normalization of the PT alone does not reflect correction of these factors. Taken together, the reports suggest that rFVIIa is more likely to be effective in microvascular bleeding and thus may not provide hemostasis with the puncture wounds produced in some interventional radiologic procedures.

CONCLUSION

Assessing a patient's bleeding risk is difficult because available testing may not accurately assess an individual's bleeding risk. There is a paucity of prospective randomized trials to guide therapy in patients, even in those with relatively common coagulopathies such as in liver disease. At this point, the best approach is to combine clinical evidence of a bleeding tendency; laboratory assessment, including specialized testing as indicated; and consideration of the procedure being performed.

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