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Case Scenario: A Patient on Dual Antiplatelet Therapy with an Intracranial Hemorrhage after Percutaneous Coronary Intervention

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PERCUTANEOUS coronary intervention (PCI) is a common procedure being performed approximately 600,000 times annually in the United States alone. PCI refers to balloon angioplasty with or without stent placement. The safety and efficacy of stents in reducing restenosis following angioplasty was highlighted by the Belgian Netherlands Stent (BENESTENT) and Stent Restenosis Study (STRESS) studies.[1,2] Following these landmark studies, the rate of stent placement has increased exponentially, with stenting being performed in up to 84% of PCI procedures.[3] Stenting necessitates the use of dual antiplatelet therapy (DAT) to prevent stent thrombosis (STH). However, the period when uninterrupted DAT is required, which is up to 1 yr in the case of drug-eluting stents (DES), can be problematic if surgery is required or if a bleeding complication occurs. This article discusses the indications for PCI, the evolution of stent therapy, and the management of an intracranial hemorrhage (ICH) while on DAT.

Case Report

A 59-yr-old man with a history of coronary artery disease, hypertension, and hyperlipidemia reported sudden onset headache, mild dysmetria, and severe nausea. Medical history included a PCI performed 2 weeks ago for symptomatic coronary artery disease with placement of two platinum–chromium everolimus-eluting (PROMUS Element; Boston Scientific, Natick, MA) DES in the left anterior descending and circumflex artery. Left ventricular ejection fraction was 60%. DAT with aspirin and clopidogrel was initiated postprocedure.

On admission to the intensive care unit, the patient was normotensive with a 1 Glasgow Coma Scale of 15. Computed tomography (CT) scan demonstrated a left paramedian cerebellar hemorrhage measuring 29 × 18 mm with partial effacement of the fourth ventricle (fig. 1). The lateral and third ventricles were within normal limits with no evidence of hydrocephalus.

After consultation with the cardiologist, neurosurgeon, and neurointensivist, a decision was made to hold clopidogrel and continue aspirin. Due to the very recent placement of the DES, the cardiologist believed that stopping all antiplatelet therapy would significantly increase the risk of a major cardiovascular event. No platelets were administered to reverse the effects of the antiplatelet drugs. Hourly clinical neurological evaluations and a repeat CT scan was performed 12 h after the admission CT. This scan demonstrated no enlargement of the ICH or ventricular dilation. Both clinical and biochemical indicators of cardiac ischemia were absent during aspirin monotherapy.

After 1 week, with the absence of any clinical or radiological deterioration, the cardiologist and neurosurgeon believed that the risk of stent thrombosis was greater than the risk of worsening ICH. Clopidogrel was restarted and a repeat CT scan following recommencement demonstrated a stable ICH with no radiological features of enlargement. The patient was discharged home without any further complications.

Indications for PCI

The major indications for PCI are to relieve anginal symptoms, and in the case of an ST-segment elevation myocardial infarction, to improve survival. For symptomatology improvement with one or more significant anatomical (≥70% diameter stenosis) lesions and unacceptable angina, despite maximal goal-directed medical therapy, PCI is a Class I recommendation (Level of Evidence: A).[4] Other indications for PCI are when medical therapy is not tolerated or contraindicated and where there is ongoing angina or ischemia postcoronary artery bypass graft, despite maximal medical therapy.

This article is featured in "This Month in Anesthesiology," page 3A.

Submitted for publication December 23, 2013. Accepted for publication June 2, 2014. From the Department of Anesthesiology (B.I.N., Z.Z.), Division of Cardiovascular Medicine (E.C.K.), Department of Neurology (D.R.G.), University of Virginia, Charlottesville, Virginia.

 Anesthesiology 2014; 121:644–53

Clinical Factors and Choice of Revascularization

Certain clinical factors play an important role in determining the type of revascularization procedure that is performed. Diabetes mellitus, for example, is associated with an increased incidence of diffuse, multivessel disease. In these patients, evidence supports coronary artery bypass graft over PCI as a revascularization strategy.[4] Similarly, observational studies and subgroup analysis support coronary artery bypass graft for patients with severe renal dysfunction. Finally, the ability to comply with and complete DAT plays a major role in the type of revascularization offered. If the risk of early termination of DAT exists, coronary artery bypass graft and/or optimizing medical therapy is the preferred strategy.

Percutaneous Coronary Interventions and Stents

PCI has undergone an evolution from a stand-alone angioplasty to the placement of either nonmedicated or medicated stents following angioplasty. An understanding of the acute, subacute, and chronic vascular changes that occur after angioplasty has fueled this evolution.

The controlled mechanical compression of an obstructive atheromatous plaque is associated with an increase in the cross-sectional vessel diameter and improved coronary blood flow. There is a risk of early vessel closure and late restenosis following balloon angioplasty. Acute vessel closure occurs in 6–8% of angioplasties, with a significant amount of periprocedural morbidity and mortality risk.[5] The pathophysiology of acute vessel closure is multifactorial. They include denudation of the endothelium, creation of a local thrombogenic nidus, disruption of the atheromatous plaque with changes in the intima and media, vascular elastic recoil, and early vascular remodeling.[6]

Angiographic restenosis is defined as greater than 50% reduction in the postprocedural luminal diameter and occurs in 30–60% of cases following balloon angioplasty.[7,8] Restenosis is caused by an exuberant inflammatory response at the sentinel dilation site. Target vessel revascularization is required in 20–30% of cases following angioplasty secondary to restenosis.[6] To combat both early and late vessel closure, the Food and Drug Administration approved the use of bare metal stents (BMS) in 1993. BMS provides structural support to prevent the early vessel recoil and restenosis seen with balloon angioplasty alone. Due to its scaffolding properties, acute vessel closure (minutes to hours following the procedure) is virtually eliminated and restenosis is reduced by 10% with placement of a stent.[1,2]

Despite a reduction in restenosis, a new problem plagued the BMS stent: in-stent restenosis. Similar to balloon angioplasty alone, deployment of a BMS provokes a local inflammatory response that over time results in neointimal hyperplasia and luminal loss. This effect peaks at approximately 3 months after stent deployment and reaches a plateau between 3 and 6 months. In-stent restenosis for BMS varies between 16% and 44% with long lesion length and small vessel diameter of the involved vessels being significant predictors.[8]

To reduce the risk of in-stent restenosis and target vessel revascularization, DES were developed. DES are coated with a polymer that "elutes" an antiproliferative agent over several weeks that inhibits neointimal hyperplasia.[9,10] Stettler *et al.*[10] reported a significant reduction in the need of target vessel revascularization with both sirolimus (hazard ratio: 0.30 [0.24–0.37]) and paclitaxel (hazard ratio: 0.42 [0.33–0.53]) DES compared to BMS. Kastrati *et al.*[9] analyzed 14 trials comparing sirolimus-eluting stent and BMS and showed a hazard ratio for death, myocardial infarction, or reintervention at 0.43 (95% CI, 0.34–0.54; $P < 0.001$). Currently, four Food and Drug Administration–approved stents are available. They include the first-generation sirolimus-eluting and paclitaxel-eluting stents that have a permanent polymer coating potentially causing increased local inflammation, delayed endothelialization, and hypersensitivity reactions. Second-generation zotarolimus- and everolimus-eluting stents have a more biocompatible polymer, which reduces local inflammation and in-stent restenosis.[11] Although placing an antiproliferative drug in a stent reduces the risk of in-stent restenosis, the unintended consequence is attenuated stent endothelialization and an increased risk of STH.

Advances in PCI Therapy

Recent advances in stent technology, imaging modalities, and antiplatelet therapy may potentially alter the risk profile of the triad of in-stent restenosis, STH, and early termination of DAT. The replacement of stainless steel with cobalt chromium scaffolding potentially results in a thinner-profile stent with less risk of stent restenosis.[12] In addition, the introduction of biocompatible or even biodegradable polymers, which are responsible for the "elution" of the antiproliferative drug, causes less local inflammation and subsequent vessel narrowing.[12,13] Intravascular ultrasound and optical coherence tomography are imaging modalities performed during coronary angiography that allow the clinician to determine the amount of neointimal coverage that has occurred post-PCI.[14] Quantifying the degree of endothelium coverage in a newly placed stent has significant implications on risk modeling during unanticipated termination of antiplatelet therapy. The limitation of these imaging modalities, however, is that follow-up coronary angiography, an invasive procedure, must be performed, which is not standard of care in an asymptomatic patient.

Antiplatelet Therapy and Stents

Stent thrombosis remains a rare but devastating complication seen with both BMS and DES, with a 10–30% mortality in patients with proven thrombosis.[13,15] The incidence of STH is similar with BMS and DES and varies between 0.6% and 3.6%.[10,16] The risk of early (<30 days) and late (1 month to 1 yr) STH is equivalent with BMS and DES. However, divergence in STH incidence is seen with very late STH (>1 yr), which is significantly greater with DES. Based on data from three large registries (Rotterdam-Bern group, the SCAAR [Swedish Angiography and Angioplasty Registry] registry, and

the Pinto Slottow *et al.* registry) the risk of very late STH with DES varies between 0.36% and 0.6% per year for up to 5 yr.[17–19] With DES, the presence of the antiproliferative agent is a double-edged sword: inhibition of neointimal hyperplasia at the cost of delayed coverage of the stent struts. Other risk factors for STH include nuances of the native coronary anatomy, procedural and device-related factors, and patient's comorbidities. Central to the pathophysiology of STH is the exposure of the nonendothelized stent struts to the systemic circulation. Platelets bind to the foreign material *via* the GPIb/IX/V complex and von Willebrand factor. Adhesion results in a cascading effect of thromboxane production and serotonin and adenosine diphosphate (ADP) release from the platelets, which facilitate platelet aggregation. ADP then binds to both $P2Y_1$ and $P2Y_{12}$ receptors, resulting in a conformational change of the glycoprotein IIb/IIIa receptors and increased binding of the receptors to fibrinogen, fibronectin, and von Willebrand factor. To prevent STH, multiple anticoagulation regimens have been studied. However, the combination of an ADP-receptor antagonist with aspirin has proven to be most efficacious. Leon *et al.*[20] compared three antithrombotic regimens in 1965 patients after coronary artery stenting. The primary endpoint (death, revascularization of the target lesion, angiographically evident thrombosis, or myocardial infarction within 30 days) was observed in 3.6%, 2.7%, and 0.5% of patients in the aspirin, aspirin–warfarin, and aspirin–ticlopidine groups, respectively. The relative risk of hemorrhagic complication was higher in the aspirin–ticlopidine arm *versus* the aspirin-alone group (3.06 [1.57–5.97], $P < 0.002$) but was comparable to the aspirin–warfarin group.[20] Based on the aforementioned study, the combination of aspirin and clopidogrel (an ADP-receptor antagonist with less side effects than ticlopidine) became the mainstay of post-stenting antithrombotic therapy. Two new $P2Y_{12}$ ADP-receptor inhibitors, prasugrel and ticagrelor, have demonstrated a lower risk of STH compared to clopidogrel. Prasugrel and ticagrelor had a 1.13% *versus* 2.35% and 1.3% *versus* 1.9% risk of STH in the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38 and PLATelet inhibition and patient Outcome trial (PLATO) trial, respectively.[21,22] Furthermore, ticagrelor has the distinct advantage of being a reversible inhibitor of the $P2Y_{12}$ receptor with a shorter duration of action ($t_{1/2}$ = 7 h).[23] The rapid onset and offset of ticagrelor have significant benefits compared to the nonreversible inhibitors, prasugrel and clopidogrel, in the event of a major bleeding complication.

Duration of Antiplatelet Therapy

The two factors that determine the duration of DAT is the type of the stent (BMS *versus* DES) and whether it was placed during a PCI for acute coronary syndrome (ACS) or for a nonacute indication. All individuals who have a coronary stent should be on lifelong aspirin.[4] If a stent (BMS or DES) is placed for ACS, $P2Y_{12}$ therapy should be given for at least 12 months. For non-ACS indications, $P2Y_{12}$ therapy should be continued for a minimum of 1 month after BMS placement and 12 months after DES placement.

Early termination of antiplatelet therapy increases the risk of developing a major cardiovascular event. Airoldi *et al.*[24] and Spertus *et al.*[25] reported a significantly increased risk of STH (hazard ratio, 13.74; 95% CI, 4.04–46.68; $P < 0.001$) and mortality (7.5% *vs.* 0.7%, $P < 0.0001$; adjusted hazard ratio = 9.0; 95% CI, 1.3–60.6) with early termination (<6 months) of thienopyridines. Their findings are further strengthened by case series of major cardiovascular events in the perioperative period with early termination of DAT.[26,27]

The nature and urgency of the surgical procedure or hemorrhagic complication, duration on DAT, procedural-related risk factors (stent in the left main coronary artery position), and patient-specific comorbidities determine how DAT will be managed. Consultation with the anesthesiologist, surgeon, hematologist, and interventional cardiologist is paramount. For elective procedures, surgery must be delayed until DAT is completed (4–6 weeks for BMS and at least 1 yr for DES). With BMS, elective surgery should ideally be performed after 90 days post-PCI as this time period is associated with the lowest risk of adverse cardiac events.[28] However, the perioperative physician must be cognizant of the increasing risk of neointimal hyperplasia and restenosis the longer surgery is delayed.[29] Following completion of DAT, elective or nonemergent surgery can proceed with aspirin as monotherapy if not contraindicated from a surgical perspective. If an isolated balloon angioplasty is performed, elective surgery can be performed after 2 weeks on aspirin only.[30] With urgent or emergent surgical procedures or life-threatening hemorrhagic complications, all antiplatelet therapy is held or monotherapy with aspirin is continued based on the risk-benefit ratio. Platelet transfusion based on the platelet function assay and the severity of bleeding should be considered in these situations of emergency as discussed in the section Platelet Transfusion Post-ICH.[4]

Post-PCI ICH

The "Bleeding Academic Research Consortium" has put forward a standardized definition for post-PCI bleeding.[31] This is shown in table 1 with ICH being defined as a Type 3C bleed.[31] The risk of ICH associated with DAT is related to the individual and summative potency of the agents. In the Stent Anticoagulation Restenosis Study, the risk of major hemorrhagic complications was 1.8%, 5.5%, and 6.2% in patients on aspirin, aspirin–ticlopidine, and aspirin–warfarin, respectively.[20] In the PLATO trial, risk of major bleeding with ticagrelor and clopidogrel were 11.6% and 11.2%, respectively.[32] In this study, the incidence of ICH was 0.34% for ticagrelor-treated patients and 0.19% for clopidogrel-treated patients. In the TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial, 0.3% of prasugrel-treated patients and 0.4% of clopidogrel-treated

Table 1. Definition of Bleeding in Cardiology Trials: Bleeding Academic Research Consortium

Type 0	No bleeding
Type 1	Bleeding not requiring action (studies or treatment)
Type 2	Overt signs of bleeding requiring hospitalization for evaluation and medical (nonsurgical) treatment
Type 3	
Type 3A	Overt bleeding with 3–5 g/dl decrease in hemoglobin Any transfusion requirement
Type 3B	Overt bleeding with >5 g/dl decrease in hemoglobin Cardiac tamponade Bleeding requiring surgical intervention Bleeding requiring intravenous vasoactive agents for hemodynamic instability
Type 3C	Intracranial hemorrhage Intraocular bleed with vision changes
Type 4	Coronary artery bypass grafting–related bleeding
Type 5	
Type 5A	Probable fatal bleeding without autopsy or imaging confirmation
Type 5B	Definite fatal bleeding with autopsy or imaging confirmation

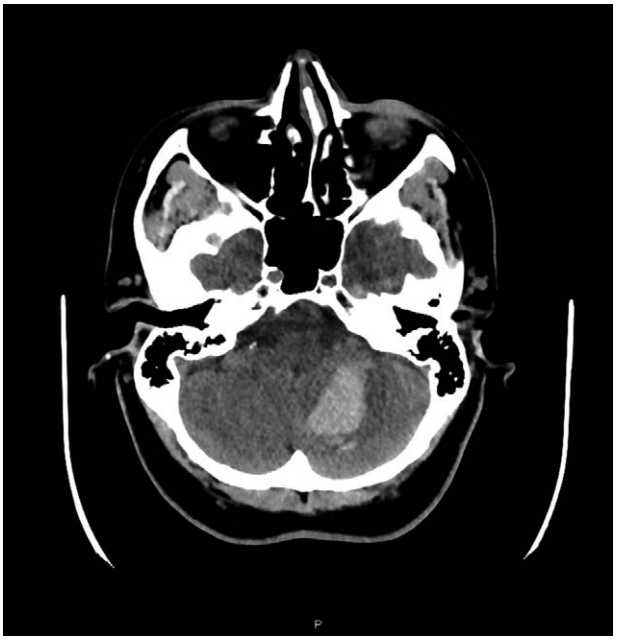

Fig. 1. Computed tomography image of a 29 × 18 mm paramedian left cerebellar hemorrhage.

patients developed an ICH.[32,33] A model from existing registry data has recently been developed to help predict the risk of post-PCI bleeding. The National Cardiovascular Data Registry CathPCI Bleeding Risk Score uses 10 variables and the associated scoring system to estimate the risk of bleeding following PCI.[34] The CathPCI Bleeding Risk Score may provide an additional tool for risk stratification for those patients who may require nonelective surgery prior to completion of DAT.

Although the risk of ICH is small, the possibility of a fatal outcome with this complication is high (55% in the ticagrelor arm of the PLATO trial).[32] These significant levels of morbidity and mortality are related to several pathophysiologic changes of the brain injury following an ICH. The initial injury is related to direct tissue destruction and mechanical compression of the adjacent brain tissue. The second is due to ongoing bleeding and hematoma expansion after initial ICH. The pathophysiology of hematoma expansion remains unclear, but emerging evidence suggests the presence of ruptured vessels surrounding the initial bleeding site.[35] With spontaneous ICH, hematoma expansion occurs at least 30% of the time over the first 24 h and likely more commonly in those on DAT. The neurologic injury is further complicated by hydrocephalus, either from mechanical compression of the cerebrospinal fluid drainage pathways or obstruction of those pathways by intraventricular blood. The cranial cavity is fixed with a finite volume, filled by brain, cerebrospinal fluid, and blood. The additional mass of the ICH initially displaces cerebrospinal fluid from the intracranial to the intraspinal compartment and then a progressive decrease in cerebral venous volume. When these compensatory processes are exhausted and hematoma expansion continues, ischemic brain injury can occur as cerebral perfusion becomes impaired. Ultimately a brain herniation results from the progressive mass effect. Late neuronal injury is thought to occur due to toxic effects of extravascular iron on the surrounding brain tissue.[36] Iron is implicated in causing oxidative injury to brain tissues. The role of iron chelation after ICH has demonstrated some promise in early animal studies and the results of a larger Phase II clinical trial is eagerly anticipated.[37]

General Management of Post-PCI ICH

The management of an ICH with DAT following PCI is currently based on expert opinions and requires the input from multiple specialists. The fundamental management includes close neurological monitoring and early intervention for ongoing ICH expansion while avoiding any major

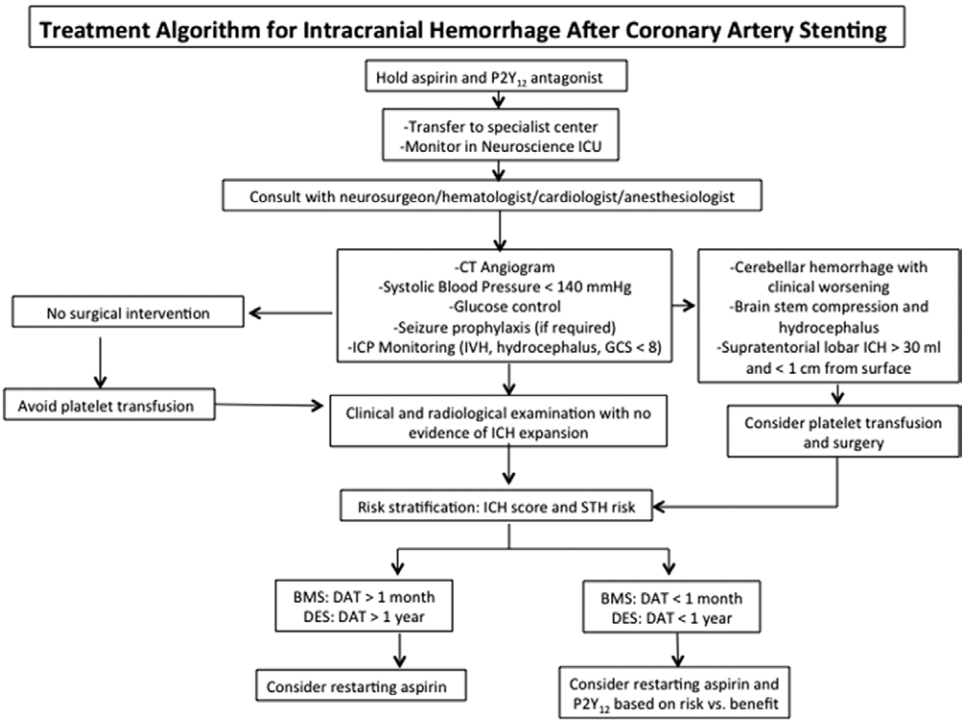

Fig. 2. Suggested treatment algorithm for intracranial hemorrhage (ICH) after coronary artery stenting. BMS = bare metal stent; CT = computed tomography; DAT = dual antiplatelet therapy; DES = drug-eluting stent; GCS = Glasgow Coma Scale; ICP = intracranial pressure; ICU = intensive care unit; IVH = intraventricular hemorrhage; STH = stent thrombosis.

cardiovascular events during temporary interruption of DAT. A treatment algorithm for the management of an ICH on DAT following PCI is proposed in figure 2.

The first step in the management of this complication is to consider transferring the patient to a center that has both neurosurgical and interventional cardiology capability. These patients are ideally managed in an intensive care unit, preferably a neuroscience intensive care unit, where hourly neurological checks can be performed to monitor for subtle neurological deterioration, such as increased somnolence. As much as 30% of patients with an ICH will require intubation for neurological deterioration, which is significantly higher than in patients with an ischemic stroke (5.8%).[38]

As much as 28–30% of patients with an ICH will demonstrate up to a 33% increase in the size of the ICH within 3 h after the first neuroimaging, whereas up to 48% of patients will demonstrate hematoma expansion within 6 h.[35,36] Ongoing hematoma expansion is associated with a poorer long-term neurological outcome. Davis *et al.*[39] reported that with every milliliter increase in ICH volume from baseline, patients were 6% more likely to increase 1 point on the modified Rankin Scale. Furthermore, intraventricular extension of an ICH occurs in 40% of patients with a supratentorial ICH, which significantly increases mortality.[40] Tuhrim *et al.*[41] reported a 30-day mortality rate of 43% compared to 9% in those without ventricular extension.

Therefore, a repeat CT scan within 6 h should be considered to monitor for subtle expansion of the ICH, intraventricular extension, and worsening hydrocephalus, which may not be detected clinically.[42] In addition, an admission CT angiography or contrast-enhanced CT can have important diagnostic and prognostic value. The presence of a "spot sign," a focus of enhancement within an acute ICH, is highly predicative of hematoma expansion.[43] Wada *et al.*[43] reported a sensitivity and specificity of 91% and 89% for hematoma expansion with a positive "spot sign." Furthermore, contrast-enhanced CT can identify undiagnosed vascular abnormalities such as an arteriovenous malformation or an aneurysm, which can impact the management of the ICH.

In addition to the ongoing neurological evaluation, cardiac monitoring is critical while DAT is interrupted. Clinical and electrocardiographic features of myocardial ischemia must be actively sought. For the latter, a two-lead continuous ST-segment monitor can be of great value as an early indicator of STH in patients with an impaired level of consciousness.[44]

Platelet Transfusions Post-ICH

A quantitative platelet count and a qualitative assessment of platelet function, if available, can assist with managing these cases. Naidech *et al.*,[45,46] in their two studies, demonstrated intracranial hematoma expansion and worse functional outcome in the presence of dysfunctional platelets. However, 9–21% patients with ICH on admission demonstrate no platelet inhibition by functional assay despite a positive history of antiplatelet use.[47,48] In the absence of any

demonstrable platelet dysfunction on the aspirin or $P2Y_{12}$ assays, platelet transfusions should be withheld. Withholding the platelet transfusion is of particular importance when the risk of ICH is weighed against the risk of major cardiovascular events during the "vulnerable" nonendothelialized period following stent placement.

The role of prophylactic platelet transfusions in the setting of an ICH with antiplatelet therapy has not been clearly defined. In a systematic review of adult patients with traumatic ICH and preinjury antiplatelet use, Nishijima *et al.*[49] reported conflicting data on the benefits of a platelet transfusion. By contrast, Naidech *et al.*[50] reported improved functional assays with smaller final hemorrhage size and better functional outcome with early platelet transfusion. A single apheresis unit was administered in 37% of patients while 28% received more than 1 unit during a single transfusion. There was, however, no correlation between platelet activity before and after transfusion and the number of platelet units administered. The major limitation of this study was its small sample size (n = 32). The ongoing Platelet Transfusion in Cerebral Haemorrhage (PATCH) study, a prospective randomized multicenter study with open treatment and blind endpoint evaluation will potentially provide clarity on the role of platelet transfusions in ICH.[51] Currently, according to the American Heart Association/American Stroke Association guidelines for the management of spontaneous ICH, platelet transfusion for patients with a history of antiplatelet use is a Class IIB level of evidence B recommendation.[36]

We suggest measuring both quantitative and qualitative platelet activity, if possible, prior to platelet administration and titrating the transfusion requirements based on these parameters.

Blood Pressure Management

Judicious blood pressure control (systolic blood pressure <180 mmHg) is paramount during the acute management of an ICH and may require invasive blood pressure monitoring. A recent study by Anderson *et al.*[52] demonstrated that a more aggressive blood pressure management strategy commenced within 6 h of an ICH (target systolic level of <140 mmHg within an hour) did not change the primary outcome of death or severe disability (odds ratio 0.87; 95% CI, 0.75–1.01; P = 0.06). However, functional outcomes (modified Rankin score 0–2) were better in the aggressive blood pressure management group. The ongoing Acute Cerebral Hemorrhage (ATACH II) trial will provide clarity on the role of aggressive blood pressure control (target systolic level of <140 mmHg) initiated earlier (<3 h) after an ICH on death and major disability.[53]

Intracranial Pressure Monitoring

Intracranial pressure (ICP) monitoring may be of value when the Glasgow Coma Scale is 8 or less with features of raised ICP, intraventricular hemorrhage, or the presence of hydrocephalus on neuroimaging.[36] A parenchymal or ventricular catheter can be used to monitor the ICP. The parenchymal monitors have less bleeding risk with insertion, but a ventricular catheter has the added advantage of allowing for cerebrospinal fluid drainage when an intraventricular hemorrhage with hydrocephalus is present.

Extreme care should be exercised when placing these devices in patients who are on DAT therapy. In older studies, the incidence of hemorrhage with placement of an ICP monitor in the absence of a coagulopathy varied between 2.1% and 3%, but increases to 15% when a coagulation abnormality is present.[54,55] However, in more recent studies the incidence of postventriculostomy hemorrhage is reported to be as high as 31–41%.[56,57] This higher rate is likely related to advances in imaging technologies with detection of smaller, more subtle bleeds. Performing the functional assays for aspirin and $P2Y_{12}$ inhibitors previously mentioned and correction of the qualitative platelet dysfunction may be of value prior to the placement of ICP monitor. Goals of therapy with ICP monitoring are to maintain a cerebral perfusion pressure between 50 and 70 mmHg. There are limited data on the ideal target cerebral perfusion pressure with ICH, and the aforementioned recommendations are extrapolated from the traumatic brain injury guidelines.[58]

Seizure Prophylaxis

Based on the American Heart Association/American Stroke Association guidelines for the management of spontaneous ICH, there is currently no indication for prophylactic anticonvulsants.[36] Patients with a known history of seizures, observed clinical seizures, and subclinical seizures detected on continuous electroencephalography will benefit from anticonvulsant therapy.[36]

Glucose Control

Admission hyperglycemia has been shown to independently predict mortality in both diabetic and nondiabetic patients with an ICH.[59,60] Maintaining normoglycemia is critical; however, extreme caution should be exercised in avoiding hypoglycemia. In a meta-analysis evaluating the benefits and risks of tight glucose control *versus* usual care, Wiener *et al.*[61] reported a 13.7% *versus* 2.5% (relative risk, 5.13; 95% CI, 4.09–6.43) incidence of hypoglycemia in critically ill adult. The Intensive *versus* Conventional Glucose Control in Critically Ill Patients Study comparing intensive (81–108 mg/dl) with conventional (<180 mg/dl) glucose management in 6,104 critically ill patients demonstrated an increased mortality in the intensive treatment arm (27.5% *vs.* 24.9%).[62]

On a cellular level, in severe brain injury, Oddo *et al.*[63] reported reduced extracellular glucose availability and brain energy crisis, defined as cerebral microdialysis glucose less than 0.7 mmol/l with a lactate/pyruvate ratio more than 40, for tight (80–120 mg/dl) *versus* intermediate (121–180 mg/dl) glucose control. Based on current evidence, we suggest maintaining blood glucose at less than 180 mg/dl in those patients requiring insulin therapy.

Surgical Management of ICH

The role of surgical evacuation of an antithrombotic-induced ICH remains controversial. The location of the ICH, size of the hemorrhage, and the underlying coagulopathy are important considerations in the decision-making process. Cerebellar hemorrhage with neurological deterioration, brainstem compression, and/or hydrocephalus from ventricular obstruction is best managed surgically.[36] Supratentorial lobar clots greater than 30 ml and within 1 cm of the cortical surface are also best managed surgically. In a meta-analysis of 10 trials with 2,059 patients, Prasad *et al.*[64] reported that surgery added to medical management for supratentorial hemorrhage was associated with a statistically significant reduction in death at final follow-up (odds ratio, 0.74; 95% CI, 0.61–0.90; $P = 0.003$).

New minimally invasive procedures with stereotactic guidance have demonstrated promising early results for the management of large ICH. The minimally invasive procedures offer the advantage of less injury to healthy brain tissue compared to traditional craniotomy. Barlas *et al.*[65] demonstrated a 60% reduction in both mean midline shift and edema volume ($P = 0.005$) with a minimally invasive technique for ICH removal. Furthermore, in a small study comparing medical management *versus* medical management plus stereotactic endoscopic hematoma evacuation, Miller *et al.*[66] demonstrated a 30% absolute reduction in mortality in the surgically managed group.

However, prior to any operative intervention, any underlying qualitative and quantitative platelet abnormality must be corrected, as the risk of hematoma recurrence remains high in the uncorrected patient.[67]

Anesthetic Considerations

During induction of anesthesia, attention must be paid to avoid extreme hypertension or hypotension. Blood pressure variability can increase the risk of further intracranial bleeding or compromise cerebral perfusion pressure if intracranial hypertension is present. An osmotic diuretic such as mannitol and mild hypocapnia ($Paco_2$ 32–35 mmHg) may help to acutely reduce intracranial hypertension until hematoma evacuation is performed.[68] Volatile agents produce direct cerebral vasodilation and can potentially increase ICP. These effects are negligible when the volatile concentration is maintained below one MAC. However, in the setting of critical intracranial hypertension with exhaustion of all compensatory mechanisms, volatile anesthesia should be avoided.[69]

Antiplatelet Therapy Post-ICH

There is limited evidence on the appropriate time to restart antiplatelet therapy following ICH in the setting of a recent PCI. Weighing the potential risk of hematoma expansion *versus* STH requires a quantifiable risk metric. The ICH score is a tool that can assist with mortality prediction with ICH. The Glasgow Coma Scale on admission, ICH volume, infratentorial origin of the ICH, intraventricular hemorrhage on CT scan, and age is used to determine an ICH score (range: 0–6).[70] Hemphill *et al.*[70] reported a 30-day mortality of 0%, 13%, 26%, 72%, 97%, and 100% when the ICH score was 0, 1, 2, 3, 4, and 5, respectively.

The periprocedural PCI risk factors (ACS *versus* non-ACS), type of stent, and duration of completed DAT therapy are important factors influencing the risk of developing ST with early termination of DAT.

If DAT has been completed (>1 month for BMS and >1 yr for DES), only aspirin monotherapy is required (Class I, Level of Evidence: A).[4] If DAT is terminated early (<1 month for BMS and <1 yr for DES) but the risk of morbidity and mortality from bleeding outweighs the benefit, then P_2Y_{12} therapy can be discontinued early according to the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Intervention guidelines (Class IIa, Level of Evidence: C).[4]

Using the ICH score and comparing it to data on STH and major cardiovascular events risk following DAT therapy interruption allow for a quantifiable risk calculation to be performed.[24,25] This risk calculation can guide the management team on the risk-benefit ratio of restarting antiplatelet therapy. Even with these data, the timing of restarting antiplatelet therapy with an ICH post-PCI is debatable and requires the input of the multidisciplinary team, family, and patient if possible.

Knowledge Gaps/Conclusion

There are limited data on the management of ICH while on DAT following PCI. The risk of a life-threatening bleeding, particularly in a critical location as demonstrated by our case, must be counterbalanced by the devastating complication of STH. The latter risk is significantly reduced with stent coverage by the native endothelium, a process that is significantly prolonged in the case of DES. Currently, there are no noninvasive methods available to determine the amount of protective endothelium present following stent deployment. Existing data from prospective studies and registry data may help provide a mathematical model that can predict the rate and degree of stent endothelialization. By knowing the extent of stent coverage, the multidisciplinary team may have an additional tool that can guide the decision whether one or both antiplatelet agents can safely be discontinued following an ICH.

In conclusion, although the risk of ICH after PCI and on DAT is small, there is significant morbidity and mortality associated with this complication. A collaborative team effort from multiple specialties with adherence to specialty-specific guidelines can mitigate the risk of both cardiovascular and neurological complications.

Acknowledgments

Supported by the National Institutes of Health, Bethesda, Maryland (HL97074 to Dr. Keeley), and the American Heart Association, Dallas, Texas (13IRG14560018 to Dr. Keeley). Dr. Zuo is supported

by grants (R01 GM065211 and R01 GM098308) from the National Institutes of Health; by a grant from the International Anesthesia Research Society (2007 Frontiers in Anesthesia Research Award), Cleveland, Ohio; a grant from Voices Against Brain Tumor (Investigator-initiated Project), New York, New York; and the Robert M. Epstein Professorship endowment, University of Virginia, Charlottesville, Virginia.

Competing Interests

The authors declare no competing interests.

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