

Percutaneous coronary intervention in patients with active bleeding or high bleeding risk

Aktif kanama ve kanama riski yüksek olan hastalarda perkütan koroner girişim

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ABSTRACT

There is a lack of evidence from randomized clinical trials (RCT) supporting percutaneous coronary intervention (PCI) in patients with high bleeding risk or active bleeding. The management decisions are based on extrapolation of subgroups data in RCTs or experts' opinions. Bleeding in the peri-PCI period also increases mortality. In general, PCI can be performed if bleeding can be stopped by mechanical means (compressing or ligating the artery) and the patient can tolerate 4 hours of anticoagulant without further bleeding. For patient with acquired or inherited high risk of bleeding, anecdotal reports showed that either unfractionated heparin or bivalirudin would be acceptable for PCI. For patients on chronic oral anticoagulants, PCI could be performed without new antithrombotic therapy if the international ratio (INR) is between 2 and 3. Antiplatelet therapy would be needed if new thrombi are detected at the index artery. Ultimately, the decision to perform PCI or treat the patient conservatively must be managed on a case-by-case basis. If the benefits outweigh the risk, then the patient can undergo PCI. (*Anadolu Kardiyol Derg 2013; 13: 165-70*)

Key words: Percutaneous coronary interventions, bleeding, ST-segment elevation myocardial infarction

ÖZET

Kanama riski yüksek veya aktif kanaması olan hastalarda perkütan koroner girişimi (PKG) destekleyen randomize klinik çalışmalardan (RKÇ) elde edilen kanıt eksikliği vardır. Takip kararları RKÇ'lerdeki subgrup analizine veya uzman görüşlerine dayanmaktadır. Kanama peri-PKG dönemdeki mortaliteyi de artırmaktadır. Genel olarak, kanama mekanik yöntemlerle (sıkıştırma ya da arterin bağlanması) durdurulabileceksen ve hastanın daha fazla kanaması olmadan antikoagülanı 4 saat tolere edebileceksen, PKG gerçekleştirilebilir. Edinsel veya kalıtsal kanama riski yüksek olan hasta için, anekdot raporları ya anfraksiyone heparin veya bivalirudinin PKG için kabul edileceğini gösterdi. Oral antikoagülanları kronik alan hastalar için, uluslararası normalleştirme oranı (UNO) 2 ve 3 arasında ise PKG yeni antitrombotik tedavi olmaksızın PKG yapılabilmektedir. Belirlenen arterde eğer yeni trombüs tespit edilirse, antitrombosit tedavi gerekli olmalıdır. Sonuçta, PKG gerçekleştirmek veya konservatif hasta tedavisi kararı her bir olgu için ayrı ayrı takibi gerektirir. Yararları risklerinden fazla ise o zaman hastaya PKG uygulanabilir. (*Anadolu Kardiyol Derg 2013; 13: 165-70*)

Anahtar kelimeler: Perkütan koroner girişimler, kanama, ST-segment yükselmeli miyokart enfarktüsü

Introduction

Acute coronary syndrome occurs in over 700,000 Americans every year and of those, it is uncertain how many patients present with active or recent bleeding in the central nervous system (CNS), gastrointestinal tract, or due to traumatic injury. Many interventional cardiologists also would be hesitant to rush these patients to the cardiac catheterization laboratory (CCL) for per-

cutaneous coronary intervention (PCI) while they were on multiple anticoagulants or antiplatelet drugs. Other factors which increase the risk of bleeding during PCI include thrombocytopenia, age >75 years, renal insufficiency, anemia, and female gender. If the decision is made to proceed with PCI, the practical aspects must be considered such as the site of vascular access, the selection of antithrombotic, and the prospect of late bleeding due to long-term dual antiplatelet therapy. Thus, it is impor-

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tant to look at the overall clinical scenario, especially the bleeding risk, when evaluating a patient for elective PCI or further bleeding possibility in patients who require urgent PCI and are having active or recent bleeding.

In this review, in the first section, the management with ST-segment elevation myocardial infarction (STEMI) in patients with active or recent bleeding is discussed. In the second section, many anti-thrombotic strategies for PCI in patients with inherited or acquired high risk of bleeding are presented (1).

Patients with active or recent bleeding

Recent surgery

Less than 4 hours after a left femoro-popliteal bypass, a 63 year old male patient developed ST-segment elevation in leads II, III, and aVF. The heart rate (HR) was 122 beats per minute and the blood pressure was 154/96 mmHg. The patient was given 5 mg IV metoprolol and taken emergently to the CCL. Selective coronary angiography revealed acute occlusion of the right coronary artery (RCA). The patient subsequently underwent balloon angioplasty of the RCA with standard dose of unfractionated heparin (UFH) to achieve an activated clotting time (ACT) of 250-300 seconds. No stent was used and no UFH was given following the procedure. Due to the short duration of UFH use, minimal bleeding was observed in the surgical site and there were no long-term negative sequelae.

In the treatment of patients with STEMI after surgery (periprocedure) (PMI), as there are no prospective randomized studies directed specifically at patients with PMI, most treatment strategies are derived from retrospective studies and observational data (2). After the initial generic medical management of patients with STEMI, the decision must be made whether to continue a medical management strategy or take the patient to the CCL for PCI. The dilemma therein lies in the fact that virtually all treatment strategies require some forms of anticoagulation, which may lead to bleeding at the surgical site.

In a study from the Mayo Clinic, Berger et al. (3) showed that immediate coronary angiography and direct angioplasty, if appropriate anatomy was present, was feasible and appeared to be safe in selected patients with PMI, mainly the STEMI patients (3). The absolute contra-indication is for patients with PMI after neurosurgery, in whom absolute hemostasis is required. Among the currently available anticoagulants, intravenous UFH is the drug of choice, due to the fact that its therapeutic effects can be reversed by protamine (1), if unacceptable bleeding in the surgical field occurs. So for the patients with PMI, the patients can undergo PCI if the lesion is not too complex, does not require stenting, nor prolonged antithrombotic therapy nor glycoprotein IIb/IIIa inhibition.

In general, the decision to perform PCI depends on two factors: (1) if the benefits of PCI outweigh the potential bleeding risks associated with anticoagulation, (2) if only plain balloon angioplasty suffices without need for stenting.

Gastrointestinal bleeding

A 65 year-old male patient arrives in the emergency room of St Mary Medical Center, Hobart Indiana, USA with chest pain. He developed recurrent ventricular fibrillations in the waiting room and was shocked 7 times. While gathering additional history, the patient's family mentioned that he vomited blood 3 days prior to presentation. Post resuscitation ECG showed ST-segment elevation in V2-V6. The patient was taken emergently to the CCL and balloon angioplasty was performed to the proximal left anterior descending artery. 5000 units of UFH and 81 milligrams (mg) of aspirin were given. UFH was selected due to the availability of protamine, a heparin reversal agent, in the event there was additional bleeding. Bivalirudin was considered, as it could cause less bleeding, however it has no antidote if anticoagulation needs to be reversed (4, 5). As no stent was deployed, no clopidogrel was given. The next day, the patient underwent esophago-gastroduodenoscopy which showed a healing ulcer and the patient was discharged later in stable condition.

Despite a wealth of evidence supporting PCI in patients with STEMI, very little data exists in the setting of concurrent STEMI and gastrointestinal (GI) bleeding. Although periprocedural bleeding has been identified as a major risk factor for subsequent mortality following PCI, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines remain vague on this subject (6). There is a Class I (Level of Evidence: C) recommendation, which states the following: All patients should be evaluated for risk of bleeding before PCI (7). This corroborated the instance taken by an expert committee from the American College of Cardiology (ACC), American College of Gastroenterology (ACG), the American Heart Association (AHA) and the European Society of Cardiology (ESC), in which they recommended assessing GI risk factors in patients on antiplatelet therapy, such as history of ulcers (and testing for and treating *Helicobacter pylori* infection if present), history of GI bleeding, concomitant anticoagulation therapy, and dual antiplatelet therapy (8). In addition, history of bleeding is a potent predictor of bleeding in acute coronary syndromes (ACS) (adjusted odds ratio 2.83) (9).

In general, an individualized approach is required to provide the best possible treatment of each patient in each differing clinical scenario. Choice of antithrombotic drugs used during PCI is very important. Antithrombotic agents with less bleeding side-effects and with available reversal agents are preferred. This has been shown in the case of bivalirudin vs. UFH + glycoprotein IIb/IIIa inhibitors in primary PCI, although thought must be given to the presence of protamine, a reversal agent for UFH, and the absence of a reversal agent for bivalirudin (4, 5).

In addition, post-PCI antiplatelet therapy must be tailored to the individual to prevent further GI bleeding. Aspirin has been shown to increase the risk of GI bleeding two- to three-fold when compared to placebo, even at low doses (4). In most patients, a thienopyridine (such as clopidogrel or ticagrelor) is needed in addition to aspirin therapy. A recent consensus docu-

ment from the ACC/ACG/AHA on the concomitant use of proton pump inhibitors (PPI) and thienopyridines highlights that PPIs are appropriate in patients with risk factors for GI bleeding who require antiplatelet therapy, including patients with prior upper GI bleeding, advanced age, simultaneous use of warfarin, corticosteroid, or non-steroidal anti-inflammatory drug (NSAID), or *H. pylori* infection (10).

Concurrent or recent stroke

A 65 year-old male presented to the emergency room of St Mary Medical Center, Hobart, Indiana, USA with complaints of difficulty with speech, right-sided facial droop and right hemiplegia after awakening from sleep. A CT scan showed no intracranial bleeding. As plans were being made to transfer the patient to the intensive care unit, the patient subsequently developed acute onset of substernal chest pain. A 12-lead ECG showed ST-segment elevation in leads I, aVL, V5, and V6. The patient was given fibrinolytic therapy and started on beta-blocker (BB), statin, aspirin, and clopidogrel. Within an hour, the neurological signs and chest pain improved with reversal of the ST segment elevation on EKG. The next day, the patient underwent successful PCI of the left circumflex artery. He was discharged from the hospital to a rehabilitation facility 4 days later.

In the presence of acute intracranial hemorrhage, the risk of worsening or fatal hemorrhage outweighs the benefit of PCI, due to the need of anticoagulation before, during, and after PCI. But what can we do for patients with ischemic stroke?

Three major concerns in the management of patients presenting with acute MI and ischemic stroke are: (1) the 1% risk of developing hemorrhagic stroke with the use of fibrinolytic drug for STEMI, (2) the conversion of ischemic stroke to hemorrhagic stroke with anticoagulant drug, and (3) the risk of cerebral emboli from protruding plaque in the aortic arch during PCI. Other important questions include (1) the risk of CVA during primary PCI for patients with history of recent transient ischemic attack (TIA) or cerebrovascular accident (CVA), (2) the selection of oral antiplatelet drugs and (3) the duration of its therapy.

Because there are no data from RCTs comparing specifically patients with new stroke, so the management decisions must be made from extrapolation of subgroup data from large RCTs.

First, the selection of a post-PCI antithrombotic strategy in this context should be based on individual patient characteristics, as retrospective analyses suggest that double therapy provides the best benefit-risk ratio, provided that thienopyridines co-treatment is kept as short as possible (11). Second, in patients with remote history of ischemic stroke and MI, it is reasonable to use DES for revascularization. The placement of a drug-eluting stents (DES) requires the concurrent use of dual antiplatelet therapy, such as aspirin and clopidogrel. This combination of drugs was shown to be comparable to the combination of aspirin and dipyridamole for the secondary prevention of stroke (11). Third, for patients with embolic strokes, in whom anticoagulation with warfarin or dabigatran is indicated, bare metal stent (BMS) would likely be preferred.

In the updates to the 2004 ACC/AHA guidelines for the management of patients with STEMI, prasugrel should not be used as an alternative to clopidogrel in STEMI patients with history of prior TIA/CVA (12). There are no data comparing bare metal stents (BMS) to DES specifically in stroke patients with MI, in patients with new versus old ischemic stroke, and in patients with new versus old hemorrhagic stroke.

Traumatic injury

A 57-year-old man had severe chest pain while driving on the interstate I-94, near St Mary Medical Center, Hobart Indiana USA. Because of severe pain and dizziness, he lost control of his car and had a head on collision with another vehicle. The left femur was fractured with moderate bleeding. When he came to the emergency department, his initial EKG showed ST-elevation in the anterior leads. The emergency room physician stabilized the leg and stopped the bleeding with pressure bandage. The orthopedic surgeon refused to do surgery due to ongoing MI. Because it was uncertain if the bleed from the patient's leg was due to a laceration of an artery or due to tissue injury, so the patient underwent first a femoral angiogram. The results showed no arterial extravasation of contrast, so PCI was started. The patient was given 5000U of UFH, 600mg of clopidogrel and had a BMS deployed into the proximal left anterior descending artery. After PCI, the patient underwent successful surgery to the left leg.

Acute myocardial infarction after a motor vehicle accident is either due to coronary artery disease or due to a coronary artery dissection from a chest contusion (13). In either case, the patient has an ischemic event and needs a coronary angiogram for evaluation. However, the dilemma is how the patient can undergo PCI which requires anticoagulation while having active bleeding.

The first question is if the active bleeding can be stopped. Any patient whose bleeding cannot be controlled should not undergo PCI because the patient will die from shock. Hemorrhagic stroke is also an absolute contraindication. The second question is if surgery can be delayed and PCI is to proceed, what is the risk of bleeding associated with short term anticoagulation and dual antiplatelet therapy. The third question is the risk of bleeding during surgery. There are no guidelines to dictate a correct management but expert consensus from the ACC/AHA guideline suggests 3 options:

1. Surgery risk of bleeding is not low and timing of surgery >365 days, perform PCI with DES. Treat with clopidogrel for at least 1 year and aspirin indefinitely.
2. Surgery risk of bleeding is not low and timing of surgery 30-365 days, perform PCI with BMS. Treat with clopidogrel for 30 days and aspirin indefinitely.
3. Surgery risk of bleeding is not low and timing of surgery is imminent, perform PCI with balloon angioplasty and provisional BMS if necessary. Treat with aspirin. Repeat PCI if necessary after surgical issues are resolved.

Urgent surgery complicated with MI should be collaborated with the surgeon to assess the overall risk and determine the benefits of revascularization. Balloon angioplasty with provisional bare metal stenting is a safe option to consider. During PCI, the patient can receive unfractionated heparin because its half-life is only 35 minutes. Two to three hours after PCI, while a 300 mg loading dose of clopidogrel will not have fully its therapeutic effect yet (80% of platelet inhibited), and the effect of heparin is negligible, the patient can proceed for surgery.

In case of patients on long term chronic thienopyridine following remote drug eluting stenting, there are concerns of higher risk of bleeding during surgery without stopping thienopyridine or concerns of acute occlusion of the coronary artery at the DES site if thienopyridine is discontinued. However, realizing the risk of acute occlusion of the coronary artery due to stopping thienopyridine, many surgeons are comfortable doing surgery for patients with clopidogrel on board. The surgeons just need to cauterize well all the bleeding points during surgery and before closing the surgical field.

Patients with inherited or acquired high risks of bleeding

Hemophilia A is a sex-linked genetic bleeding disorder resulting in deficiency of plasma factor VIII (FVIII) coagulant activity. These patients have depleted clotting factors to 1% of normal and tend to bleed frequently on minimal or unrecognized trauma (most frequently into the joints or muscle and less frequently intracranial). The management includes early treatment of bleeding with prophylactic use of FVIII concentrate.

MI's are rare occurrences in hemophilia but studies have shown that transfusions of FVIII can precipitate thrombosis formation resulting in MI or cerebral vascular accidents. So these patients should be carefully evaluated and monitored for such events when being transfused of FVIII (14).

For patients with hemophilia A presenting with AMI, the indications for left heart catheterization are the same as non-hemophiliacs. However there is no guideline recommendation for antithrombotic therapy in addition to clotting factor correction. Several case reports vary in administration of anticoagulant during PCI (15). Arora et al. (16) presented a case report of a hemophilia A patient with an AMI. The patient was administered FVIII pre and post operatively, and during catheterization, bivalirudin was selected due to its rapid onset of action, short half-life, lower risk of bleed, and no need for monitoring which allows a predictable response for sheath removal during the FVIII transfusion. The patient had a successful multi-vessel PCI with no complications.

However, Kim et al. (17) presented a similar case but instead of using bivalirudin, this author chose 70 units/kg of unfractionated heparin (UFH) and continued to stent multiple lesions using BMS.

Therefore, the management of the patients with hemophilia A during PCI includes replacement of the clotting factor deficiency with FVIII and antithrombotic therapy. The recommended

serum level of FVIII is 0.8 U/l pre-catheterization until 48 hours post-catheterization. To achieve this level, the initial bolus of FVIII should be 40 U/kg infused over 30 minutes with a factor recovery assay done 15 minutes later and once peak level is achieved, maintenance is done by slow infusion at 20 U/kg every 12 hours for 48 hours (15). Bleeding is the most common complication especially if attempting femoral access compared to radial access.

Hemophilia B, in contrast, is an inherited disorder caused by a mutation on the factor IX gene located on the X chromosome. Similar to hemophilia A, these patients have increased risk for hemorrhage and present with bleeding to joints or muscles due to mild trauma or occurring spontaneously. The recommendations for these patients are to transfuse factor IX at 80U/kg pre-catheterization to have a peak level of 0.8 U/l and once peak level is achieved, maintenance is with slow infusion at 20 U/kg every 12 hours for 48 hours post-catheterization (15).

Overall, care for the patient should be done in tandem with the hematologist. The goal is to minimize bleeding in these patients and there are multiple factors to consider during intervention such as femoral vs. radial access, bare metal vs. drug eluting stents, and choice of antithrombotic therapy to avoid bleeding complications while securing excellent good long-term outcomes.

von Willebrand's Disease: von Willebrand factor (vWF) is a large glycoprotein encoded on chromosome 12 produced by vascular endothelial cells and megakaryocytes (18). It plays a crucial role in causing platelet aggregation by binding to platelets via the GP Ib-IX-V and IIb/IIIa glycoprotein complexes and forms a clot at the site of injury. There are 6 subtypes of von Willebrand and clinical manifestations vary from features secondary to platelet dysfunction or factor VIII deficiency. Most commonly manifested symptoms are easy bruising and mucosal bleeding such as epistaxis, oral cavity bleeding, and menorrhagia. Severe cases of von Willebrand's disease (vWD) include gastrointestinal bleeding, hemarthroses, postoperative bleeding, and muscle hematomas.

There are multiple therapies for treating bleeding in vWD such as DDAVP, FVIII concentrates, tranexamic acid, and platelets. For patients undergoing major surgery, the goal of therapy is to treat with DDAVP or FVIII concentrates to maintain ristocetin cofactor levels between 50-100% for a period of 3-10 days and if the patient undergoes a percutaneous procedure, the length of treatment is shorter (18). There are no studies showing benefit for treating vWD patients pre and post catheterization and available case reports do not mention any administration of FVIII or DDAVP.

In general, most patients with vWD do not require prophylactic replacement therapy, especially for Type 1 disease or if the ristocetin cofactor levels are more than 50% of normal. However, there are reports that support prophylactic therapy with FVIII-vWF if the ristocetin level is less than 50% to achieve a goal of more than 50% of normal or if a patient presents with significant clinical bleeding (18).

Oral Anticoagulants: Patients on oral anticoagulants (OAC) pose a therapeutic dilemma in terms of anticoagulant management during PCI. It is often a fine balance between optimal anticoagulation and increased bleeding risk.

In patients who need absolute anticoagulant therapy, interventionalists often tend to stop OAC for the procedure and bridge them with heparin, as in patients with a mechanical prosthetic valve (19). In patients with AF, warfarin can be stopped easily about 5 days prior to the elective PCI. Most commonly used OAC therapy is warfarin and its therapeutic effect is monitored using international normalized ratio (INR). When the INR is between 2 and 3.0 (therapeutic range for most indications), it has been recommended that PCI can be performed in the "usual" fashion. There is an increased bleeding risk and caution should be exercised when obtaining arterial access. High INR is associated with peri-procedural bleeding. A meta-analysis by Popma et al. (20) showed that patients undergoing PCI with an INR of >3 had a 3 fold increased risk of bleeding events compared to those with $\text{INR} \leq 3$. There are no data on newer OAC such as dabigatran and rivaroxaban (Pradaxa or Xeralto in US).

In general, PCI can be performed safely in patients on warfarin with a therapeutic INR. However, warfarin does not have effect on platelets, so the patient still can have platelet aggregation. This is why the patients need to have either loading dose of oral antiplatelets prior to elective PCI or intravenous glycoprotein IIb/IIIa inhibitors if large thrombi are detected in the coronary arteries during PCI. There seems to be a trend towards increased local vascular access complications and vascular closure devices are effective in minimizing bleeding in this cohort (21).

Thrombocytopenia could be due to a variety of causes and is common in patients referred for PCI. Vaitkus et al. (22) showed that patients with thrombocytopenia due to advanced liver disease were able to undergo PCI safely. However, vascular complications tend to be high if the operator is not meticulous in vascular access.

Myelodysplastic syndrome (MDS) is a common cause of thrombocytopenia in elderly patients who are typically at higher risk of ACS. There are no randomized data guiding interventional cardiologists in treating patients with MDS who need PCI. However there are some case reports establishing the safety of PCI in these patients (23). These patients received UFH as the primary anticoagulant during PCI and were continued on dual antiplatelet therapy without any significant bleeding events. That being said, one should still exercise caution while performing PCI in these patients especially if the platelet count is less than 50.000 per cm^3 due to increased bleeding complications.

Idiopathic thrombocytopenic purpura (ITP) can cause bleeding and thrombosis in the same patient. In patients with ACS and ITP, there is an increased tendency to bleed with medications such as thienopyridines and glycoprotein inhibitors. Weight-adjusted heparin is the preferred anticoagulant.

Heparin induced thrombocytopenia (HIT) is a unique condition that is associated with severe thrombocytopenia and spontane-

ous thrombosis. This is an immunologically mediated reaction, which results in the formation of antibodies against heparin-platelet factor-4 complex, resulting in the formation of macro particles. In addition, there is increased platelet activation and adhesion that results in thrombus formation. Once the patients are diagnosed with HIT, PCI could be done using glycoprotein inhibitors or direct thrombin inhibitors as anticoagulants (24).

Conclusion

There is a lack of evidence from randomized clinical trials (RCT) supporting PCI in patients with high bleeding risk or active bleeding. The management decisions are based on extrapolation of subgroups data in RCTs or experts' opinions. Bleeding in the peri-PCI period also increases mortality. These bleeding problems clearly influence the decision of referring patients to PCI.

In general, PCI can be performed if bleeding can be stopped by mechanical means (compressing or ligating the artery) and the patient can tolerate 4 hours of anticoagulant without further bleeding. Ultimately, the decision to perform PCI or treat the patient conservatively must be managed on a case-by-case basis. If the benefits outweigh the risk, then the patient can undergo PCI (25, 26).

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