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Perioperative Management in Patient Receiving Antithrombotic Therapy: Minimalized the Risk of Thrombosis and Bleeding

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ABSTRACT

The Management of cardiovascular disease mostly uses antithrombotics, either antiplatelet or anticoagulant, to prevent thrombosis. These may become a problem whenever the patient needs surgery, especially a non-cardiac procedure, due to the risk of bleeding related to antithrombotic use. Unfortunately, discontinuing this medication carelessly will also give a thrombotic risk that may be fatal. Managing cardiac patients with this condition is important to avoid the risk of thrombosis due to discontinuing medication perioperatively and minimizes the bleeding risk intra-procedure caused by the continuation of therapy. Perioperative management of cardiac patients receiving antithrombotic must depersonalize depending on each patient's condition. Furthermore, balancing the risk and benefit of continuing or stopping antithrombotics in cardiovascular patient who need to undergo surgery is a challenge in clinical setting. Hence, this review will show the perioperative management of cardiovascular patients by considering the balance of bleeding and thrombosis risks.

INTISARI

Antitrombotik merupakan salah satu hal yang paling dibicarakan dalam dunia kardiovaskular. Antitrombotik yang dimaksud disini adalah antiplatelet maupun antikoagulan dengan tujuan mencegah terjadinya trombosis. Hal ini mungkin menjadi masalah ketika pasien tersebut membutuhkan tindakan operasi, terutama prosedur non-bedah jantung. Masalah ini muncul disebabkan risiko perdarahan yang disebabkan penggunaan antitrombotik. Meskipun demikian, penghentian obat-obatan tersebut juga berisiko menimbulkan trombosis yang fatal sehingga harus dilakukan secara hati-hati. Pengelolaan pasien dengan kondisi ini penting dilakukan untuk menghindari risiko trombosis karena penghentian obat anti trombotik sebelum tindakan dan meminimalisir risiko perdarahan intra-prosedur yang meningkat karena pemberian antitrombotik itu sendiri. Perlu diingat bahwa pengelolaan perioperatif pada pasien jantung dengan antitrombotik harus disesuaikan dengan kondisi dari masing-masing pasien sehingga dalam menghitung risiko keuntungan dan kerugian merupakan tantangan tersendiri bagi klinisi. Tinjauan pustaka ini akan mengulas terkait tatalaksana perioperatif pada pasien dalam terapi antitrombotik terutama yang diberikan karena indikasi penyakit jantung baik penyakit jantung koroner (PJK) atau penyakit jantung lainnya.

Introduction

Antithrombotic can be divided into antiplatelet and anticoagulant. Antiplatelets can be classified according to how they act to their receptors. The antiplatelet which act on the Adenosine 5'-Diphosphate (ADP) receptor is aspirin. Another antiplatelet which acts on the P2Y12 inhibitors receptor are Clopidogrel, Ticagrelor and Prasugrel. When both of this antiplatelets were given to the patient (ADP receptor and P2Y12 inhibitors receptor), it was known as Double Anti Platelet Therapy (DAPT). If

only one of them was given to the patient, it was known as Single Anti Platelet Therapy (SAPT).[1,2]

The oral anticoagulants can be distinguished from Vitamin K-Antagonists (VKA) such as warfarin/cumarin and Non-Vitamin K Direct Oral Anticoagulants (NOACs)/ Direct Oral Anticoagulant (DOACs) such as dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa) and betrixaban (Bevyxxa). NOACs/DOACs are categorized into 2 main classes: oral direct factor Xa inhibitors (ie, rivaroxaban, apixaban, edoxaban and betrixaban) and direct thrombin inhibitors (ie, dabigatran).[3]

The management of cardiovascular disease mostly uses these antithrombotic drugs. The use of antithrombotic can be a single antiplatelet, double antiplatelet or anticoagulant and even a combination of oral antiplatelet and anticoagulant. Antiplatelets are widely used in coronary heart disease cases, especially who have done Percutaneous Coronary Intervention (PCI).[2] While anticoagulants are widely used in atrial fibrillation cases or postoperative valve replacement, especially mechanical valves.[3]

The aimed of antithrombotic therapy is to prevent thrombosis in cardiovascular diseases. But the management of antithrombotic therapy could be a problem if the patient is going to undergo a surgery. This problem is closely related to the risk of bleeding during the surgical procedure if antithrombotic is continued or the risk of thrombosis if antithrombotic therapy is discontinued before the surgery. In surgical procedures with low bleeding risk, every effort should be taken not to discontinue DAPT perioperatively. In surgical procedures with moderate bleeding risk, patients should be maintained on aspirin while P2Y12 inhibitor therapy should be discontinued whenever possible. More challenging decision making is to be faced among patients on DAPT who undergo high bleeding risk non-cardiac surgeries, including vascular reconstruction, complex visceral procedures neurosurgery and transbronchial operations.[2]

As a case illustration. The first case, a 60-year-old man was consulted to the Cardiology Department regarding the use of double antiplatelet therapy (DAPT) aspirin and ticagrelor. This patient had urinary retention due to benign prostatic hypertrophy and urological surgery was planned. Two months earlier, the patient had an acute myocardial infarction and a Primary Percutaneous Coronary Intervention was performed using two coronary stents-Drug Eluting Stent (DES). The second case, a 40-year-old woman was scheduled for tooth extraction. This female patient had a history of taking warfarin 4 mg daily because of metallic mitral valve replacement surgery with atrial fibrillation rhythm. The female patient was consulted to the Cardiology Department due to warfarin management in patient who undergo a tooth extraction surgery.

The purpose of this paper is to discuss the management of cardiovascular patients receiving antithrombotic therapy who undergo non-cardiac surgical procedures, how to avoid the risk of thrombosis because discontinuation of antithrombotic therapy before the surgery but also minimalized the risk of bleeding during the surgical procedure because of the continuation of antithrombotic therapy.

Discussion

Until the present decade, more than 500,000 coronary stents were implanted each year due to coronary heart disease.[4] Coronary stent implantation in coronary arteries has consequences for the use of antiplatelet therapy. In the first 1 year, the patients have to use double antiplatelet therapy – DAPT (Aspirin + Clopidogrel / Ticagrelor / Prasugrel) and continued with a single antiplatelet therapy (SAPT) for long life 2. Patients who had coronary stenting, 1.8% of them will undergo coronary bypass surgery (CABG) within 1 year. While within 1 year, 11% will undergo non-cardiac surgery. In 2 years, as many as 20% of this population, will undergo a noncardiac surgery4 and in 5 years 5-25% will undergo noncardiac surgery.[1]

The duration of DAPT in cases of coronary stenting in coronary heart disease is depend on the indication of PCI itself and the generation of coronary stents. If the indication of PCI is due to an Acute Coronary Syndrome (ACS), the use of DAPT is recommended for 12 months using either a Bare Metal Stent (BMS) or a Drug Eluting Stent (DES). If the indication of PCI is due to Chronic Coronary Syndrome (CCS) or Stable Ischemic Heart Disease, the duration of DAPT in coronary angioplasty procedures without stent implantation is recommended for a minimum of 14 days only.[5] If BMS stent is used, the duration of DAPT is recommended for a minimum of 1 month, but if DES is used, the duration DAPT is recommended for at least 6-12 months.[2,6,7] In certain cases, such as in patients with a high bleeding risk or with the potential for surgery in the future, the newest generation of DES is a necessity. By choosing the newest stent generation, the duration of DAPT can be shortened into 3-6 months.[8] If the duration of DAPT is optimal according to the indications, of course, antiplatelet therapy with Single Anti Platelet Therapy (SAPT) will be continued in long life for a secondary prevention.[2,6]

The risk of bleeding due to DAPT in coronary stenting can be determined using scoring system from PRECISE-DAPT (PREdicting bleeding Complication In patients undergoing Stent implantation and subsEquent Dual Antiplatelets Therapy)[9] or the High Bleeding Risk from Bleeding Academic Research Consortium.[10] The BARC score consists of 20 clinical variables and divided into 14 major clinical criteria and 6 minor clinical criteria. If 1 major criteria or 2 minor criteria are obtained, the patient is included into the high risk bleeding category. It means that the patient has a bleeding risk > 4% in 1 year and has bleeding type 3 or bleeding type 5. Bleeding type 3A is bleeding with drop of hemoglobin value between 3-5 g/L and required a transfusion. Bleeding type 3B is bleeding with drop of hemoglobin value < 5 and required a surgery to control bleeding or a vasoactive agent. Bleeding type 3C

is intracranial hemorrhage with evidence of bleeding in imaging, autopsy, lumbar puncture or eye bleeding that interferes with vision. Bleeding type 5 is fatal bleeding.[10]

Management of patients on DAPT who are referred for surgical procedures involves consideration of: (1) the risk of stent thrombosis (particularly if DAPT need to be interrupted); (2) the consequences of delaying the surgical procedure and (3) the increased intra and periprocedural bleeding risk and possible consequences of such bleeding if DAPT is continued.[2] Base on a meta-analysis of randomized control trial, the PCI operator in the cardiac catheterization room should determine the type of stent that will be implanted in the coronary arteries. If the patient has a high bleeding risk, the newer generation of DES is recommended, so the duration of DAPT can be shortened to 3 months until 6 months than the standard duration.[8]

The use of DAPT in patients with Percutaneous Coronary Intervention is indicated to prevent re-infarction, target vessel revascularization and prevent stent thrombosis. Discontinuation of DAPT and switching into SAPT earlier than the recommended duration can increases the risk of life-threatening intrastent thrombosis. Intrastent thrombosis itself is more dangerous than intrastent restenosis. Early discontinuation of DAPT was a predictor of intrastent thrombosis, and stenting technique was also a predictor of intrastent thrombosis. The predictors of intrastent thrombosis are left main stenting, bifurcation stenting, overlapping long stenting, small stent diameter, and improper stent position. Diabetes mellitus and impaired of left ventricular function can also increase the risk of intrastent thrombosis.

Patient wo had coronary stents installed and undergo a surgery, the surgical plan should be postponed until the duration of DAPT treatment has been completed. For example, if a patient has angioplasty without stent implantation, the minimum duration of DAPT is 14 days. If the duration of the DAPT has over, the surgical operation can be performed without stopping the SAPT. If the risk of intrastent thrombosis is low or moderate, DAPT can be replaced with SAPT by waiting a few days depending on the type of P2Y12 inhibitor therapy used. If the P2Y12 inhibitor is clopidogrel, surgery can be delayed by 5 days from the last dose of Clopidogrel, 5 days from the last dose of Ticagrelor and 7 days from the last dose of Prasugrel. The DAPT can be discontinued and continue antiplatelet therapy with SAPT. It will be a problem if the surgical operator wants to discontinue SAPT. It must be considered between the risk of bleeding during surgery if SAPT is still given to the patient or the risk of intrastent thrombosis if SAPT is discontinued.[2,5]

In situations where the surgery cannot be postponed until the completion of DAPT therapy (12 months for ACS cases), the duration of DAPT can be shortened by waiting for the P2Y12 inhibitor used to finish as 5 days from stopping Clopidogrel, 5 days from stopping Ticagrelor and 7 days from stopping Prasugrel.[5] Surgery is recommended to be performed in a hospital with cardiac catheterization room facilities which are open 24 hours a day in 7 days (24/7). In situations where patients are at high risk of intrastent thrombosis and cannot stop DAPT prematurely, bridging therapy using antiplatelet injection therapy such as Glycoprotein IIb/IIIa Inhibitors (GP IIb/IIIa Inhibitors) can be performed. The choice of injection of GP IIb/IIIa Inhibitors is to avoid the risk of intrastent thrombosis due to the discontinuation of P2Y12 inhibitor. The short half-life of GP IIb/IIIa inhibitor was chosen to avoid intrastent thrombosis and minimalized the risk of bleeding. The scheme of bridging therapy between GP2b/IIIa inhibitors and DAPT is shown in Figure 2.[4]

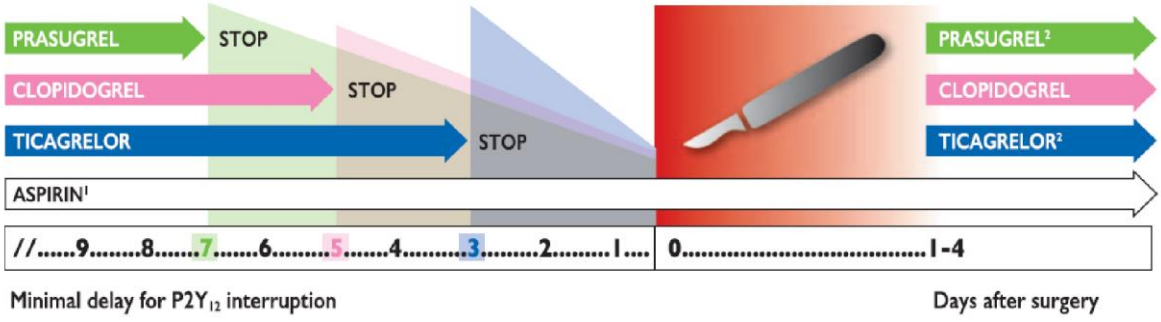

Figure 1: Minimal discontinuation and re-implementation times frame of DAPT for patients undergoing elective surgery. In patients not requiring oral anticoagulant.[2]

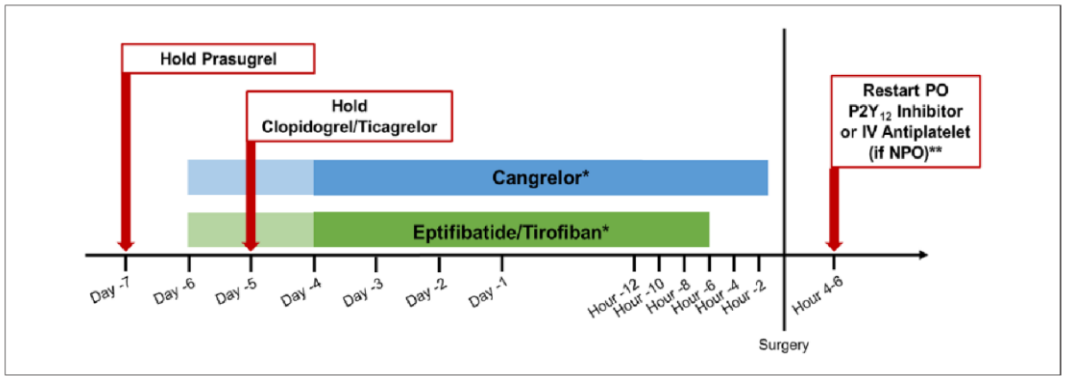

Figure 2: Perioperative discontinuation and initiation antiplatelet medications.[4]

Low-Molecular-Weight Heparin (LMWH) is not recommended for bridging therapy. The guidelines also did not recommend to assess the platelet function score to determine the cut-off bleeding. The DAPT is recommended to be started again immediately after 4-6 hours of surgery.[4,5]

Another antithrombotic therapy that often used in cardiovascular disease is anticoagulant therapy. Anticoagulants can be distinguished into Vitamin K Antagonist (VKA) and Non-Vitamin K Antagonist Direct Oral Anticoagulants (NOACs). The indications of oral anticoagulants in the cardiovascular diseases are to prevent thrombosis and prevent thromboembolism. Patients at high risk for thromboembolism are patients with atrial fibrillation with a CHA2DS2-score > 4 (Cardiac Failure, Hypertension, Age >75 (doubled), Diabetes, Stroke (doubled), Sex Female); mechanical prosthetic heart valve replacement, newly biological prosthetic heart valve replacement, first 3 months of mitral valve repair surgery, recent venous thrombo-embolism (within 3 months) or thrombophilia.[1,3]

Patient at risk for thromboembolism will be given VKA such as warfarin with adjusted doses to the target of International Normalized Ratio (INR), especially for Atrial Fibrillation (AF) patients, apart from using VKA, the NOACs such as Dabrigatan, Rivaroxaban, Apixaban or Edoxaban can also be used.[3]

Patients who received oral anticoagulant therapy and will be undergo a surgery, the risk of thromboembolism and bleeding should be considered. If the risk of bleeding is small due to surgery, oral anticoagulants do not need to be discontinued but the INR value must be less than 1.5. However, if the patient is in the high risk of thromboembolism and also high risk of bleeding due to surgery, bridging therapy using an anticoagulant injection can be performed.[1]

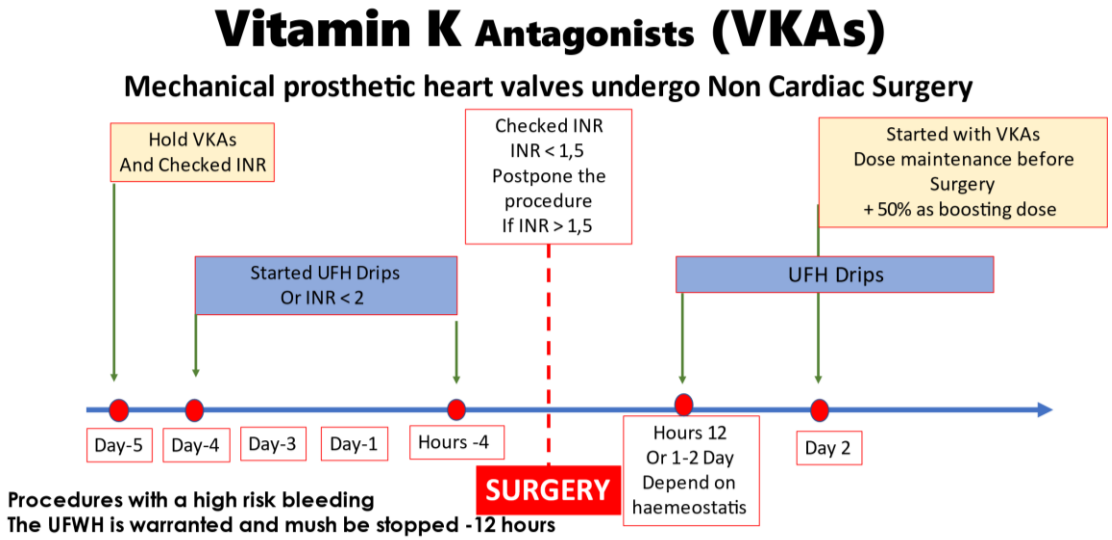

Figure 3: Bridging therapy with Unfractionated Heparin on patient with high risk of thrombo- embolism who underwent to non-cardiac surgery.[1]

Non Vitamin K Antagonists-NOACs (Direct Oral Anticoagulants)

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa (thrombin)	Xa	Xa	Xa
Application	Oral	Oral	Oral	Oral
Hours to C^{max}	1.25–3	2–4	3–4	1–2
Pro-drug	Yes	No	No	No
Food interactions	No	No	No	No
Bioavailability (%)	6.5	80–100	50	62
Drug interactions	P gp inhibitors or inductors	CYP3a4 inhibitors or inductors P gp inhibitors or inductors	CYP3a4 inhibitors or inductors P gp inhibitors or inductors	P gp inhibitors
Median half-life (hours)	12–14	7-11 (11–13 in the elderly)	12	6-11
Renal clearance (%)	85	33	27	37-50
Dose regimen	b.i.d.	q.d.	b.i.d.	q.d

Figure 4: Pharmacological features of Non-Vitamin K-Antagonist Oral Anticoagulant.[1]

The management of bridging therapy using anticoagulant injection is as follows. The oral VKA discontinued 3-5 days before surgery, then the INR value should be evaluated every day. If the INR value is less than 2, the anticoagulant injection is given until the wash out of VKA is completed. The recommended anticoagulant injection is Low Molecular Weight Heparin (LMWH) besides Unfractionated Heparin (UFH). Patients with high risk of thromboembolism were given LMWH twice per day but patients with low risk of thromboembolism were given LMWH injection once per day. In patients with prosthetic mechanical valves, UFH is more potently used as bridging therapy up to 4 hours before surgery. The INR value must be evaluated on the day of the operation and the safe value if the INR < 1.5.[1]

At least 12 hours or 1-2 days after the day of surgery, another injection of LMWH or UFH is given depending on the static bleeding. For oral anticoagulants VKA can be given again with a loading dose with a dose such as the maintenance dose before surgery plus 50% of the maintenance dose. This loading dose is given for 2 days and then the INR value is adjusted.[1] The scheme of anticoagulant injection bridging therapy as shown in Figure 3.

Patients on NOACs therapy do not require bridging therapy using anticoagulant injections because of 'on and off' action properties of NOACs agent. If the surgical procedure has a small risk of bleeding, the NOACs can be discontinued 2-3 times of the half time of the drug. In addition, if the surgical procedure has a high risk of bleeding, the NOACs are discontinued 4-5 times of the half time of the drug. The NOACs can be started again 1-2 days after surgery, even in some cases, starting on the 5th postoperative day until bleeding due to surgery can be minimized. Figure 4 shows some examples of NOACs with their median half-life (hours).[1,3]

In certain conditions, where the surgical procedure cannot be postponed until the wash out period of the VKA drug was achieved, it is recommended to give a low dose of Vitamin K injection (2.5-5.0 mg IV). If a reversal of VKA is urgently needed, Prothrombin Complex Concentrate (PCC) can be given in addition to the vitamin K injection. In other situations, bleeding due to NOACs therapy can also be managed clinically. First, the hemoglobin level, APTT value and creatinine function were evaluated. If the bleeding is minor, only stop the NOACs. However, if the bleeding is moderate, supportive therapy such as fluid replacement, blood transfusion and mechanical compression can be carried out. If there is heavy bleeding, PCC or hemofiltration/hemodialysis can be considered.[1]

Conclusions

In patient who receive antithrombotic therapy and will undergo non-cardiac surgery:

- Single Antiplatelet on indication of coronary stenting is still given unless surgically necessary.
- Patients with DAPT on indication of coronary stenting should be postponed until at least 3-6 months.
- Patients with DAPT on indication of coronary stenting and surgery cannot be delayed, DAPT is stopped and bridging therapy is carried out with injection of GP IIb/IIIa Inhibitor.
- Patients on VKA treatment can undergo a surgery without stopping VKA with INR value < 1.5.
- Patients with high risk for thrombo-embolism and VKA cannot be stopped during surgery, bridging therapy is carried out using an anticoagulant injection.
- Patients on NOACs can be discontinued 2-3 times the half-life of the drug before the surgery.

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