Perioperative management of antithrombotic therapy

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Abstract: The management of patients who require temporary interruption of warfarin therapy because of elective surgery or another invasive procedures is clinically important because of the increasing prevalence of patients who are receiving warfarin and the availability of low-molecular-weight heparins, which facilitate out-of-hospital perioperative anticoagulation. The two main issues that need to be considered in perioperative anticoagulant management is the patient's risk of a thromboembolic event when warfarin therapy is interrupted and the risk of bleeding that is associated with the surgery or procedure. An assessment of these factors will determine the optimal perioperative anticoagulant management approach. The overall objective of this review is to provide a practical approach relating to perioperative anticoagulation which can be used in everyday clinical practice.

Key words: bleeding, bridging anticoagulation, perioperative management, thromboembolism, warfarin

INTRODUCTION

The perioperative management of patients who require temporary interruption of warfarin because of surgery or another non-invasive procedure, such as endoscopy or cardiac catheterization, is a common but challenging clinical problem [1]. Bridging anticoagulation refers to the use of a short-acting anticoagulant, which is usually therapeutic-dose subcutaneous low-molecular-weight heparin (LMWH) or intravenous unfractionated heparin (UFH), administered during the time when warfarin is interrupted and there is no therapeutic anticoagulation [2]. However, we acknowledge there is no standardized definition of "bridging anticoagulation" and other treatment regimens, including low-dose regimens with LMWH or UFH, have been used, particularly after surgery in selected patients at high risk for bleeding complications.

Although the absolute risk for arterial thromboembolism during temporary interruption of warfarin based on mathematical modeling has been estimated to be low [3], actual rates of thromboembolism in cohort studies of temporary warfarin interruption are higher, thereby suggesting that the risk during te 8–10 day period when warfarin anticoagulation is sub-therapeutic may be higher than anticipated [1]. Furthermore, the clinical impact of thromboembolism may be considerable. Thus, valve thrombosis can be fatal in 15–30% of patients and embolic stroke can be fatal or associated with major disability in 70% of patients [4,5].

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Received: March 25, 2008. **Accepted in final form:** March 31, 2008.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2008; 118 (4): 201-208

Counterbalancing the risk for thromboembolism is the risk for perioperative bleeding if there is too aggressive perioperative anticoagulation. In studies involving patients with a mechanical heart valve or atrial fibrillation, the case fatality of major bleeding is 8–9% [6,7]. The mortality of bleeding in a perioperative setting is not well documented and may be higher. Bleeding usually at operative site can result in increased morbidity resulting from the need for urgent or emergency surgery, an infected hematoma or abscess and potential long-term consequences related to scarring and chronic pain. Furthermore, bleeding may have the undesired effect of promoting thromboembolic events, due to prolonged interruption of warfarin. Thus, in studies of bridging anticoagulation with LMWH, approximately 50% of arterial thromboembolic events occurred in patients who developed postoperative bleeding [8-11].

Against this background, the objectives of this review are:1) to provide an approach to stratify patients according to their risk for arterial or venous thromboembolism if antithrombotic therapy stopped and the risk for bleeding associated with surgery or procedure; 2) to provide a practical approach to the perioperative interruption and resumption of antithrombotic therapy; 3) to provide a suggested protocol for the administration of bridging anticoagulation when required.

Overall patient management

In assessing patients who are receiving warfarin and are having elective surgery, the initial question should be: is interruption of warfarin therapy needed? In patients who are undergoing a major surgical or invasive procedure, warfarin interruption is required to minimize the risk for bleeding. On the other hand, in patients who are undergoing a minor surgical or invasive procedure, such as dental, dermatologic or ophthalmologic procedures, interruption of warfarin ther-

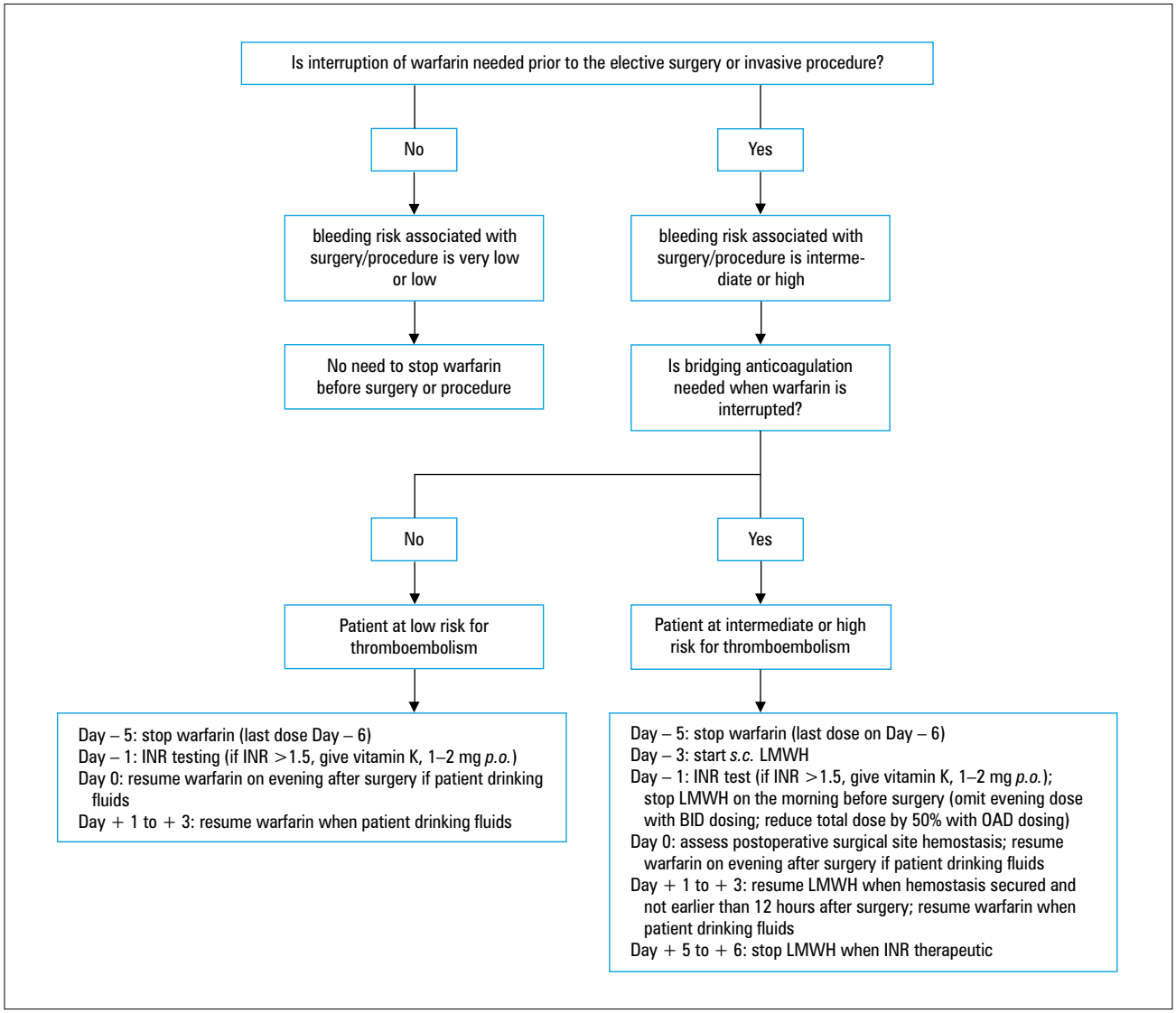

Fig. Suggested perioperative management of warfarin therapy. Abbreviations: BID – twice a day (*bis in die*), INR – international normalized ratio, LMWH – low-molecular-weight heparin, OAD – once a day

apy may not be required. Having addressed this initial question, the next question is: is bridging anticoagulation needed? The need for bridging anticoagulation is determined by patients' risk for thromboembolism during warfarin interruption. A suggested perioperative anticoagulant management algorithm is provided in Figure 1 and the various pre- and post-operative steps are discussed below.

Assessing patients' risk for thromboembolism

There are no validated schemes for stratifying patients according to their risk for perioperative thromboembolism. The suggested risk stratification, which is summarized in Table 1, is derived based primarily on data from non-perioperative settings.

Bridging anticoagulation should be considered in patients at high or moderate risk for thromboembolism whereas it is optional in patients at low risk for thromboembolism.

Mechanical heart valve

In patients with mechanical heart valves, the risk for thromboembolism is determined by the type and position of the valve and the presence of additional risk factors for stroke and intra-cardiac thrombosis [12,13]. In patients who are probably at high risk for thromboembolism, such as those with a recent (within 3 months) stroke or transient ischemic attack, a mechanical mitral valve, or an older generation valve (e.g., caged-ball, tilting disc), bridging anticoagulation is recommended [1,13]. In patients at moderate risk for thromboem-

bolism, such as those with a newer generation aortic valve (e.g., bileaflet) and ≥2 risk factors for stroke, bridging anticoagulant should be considered. Finally, in patients who are probably at low risk for thromboembolism, such as those with a bileaflet aortic valve and <2 risk factors for stroke, bridging anticoagulant therapy is optional and may not be required [1,2].

Chronic atrial fibrillation

Bridging anticoagulation should be considered in patients with chronic atrial fibrillation who are at high or moderate risk for stroke [14,15]. High-risk patients include those with a recent (within 3 months) stroke or transient ischemic attack and patients with rheumatic valvular heart disease. The $CHADS_2$ scoring system can be used to assess risk for stroke in patients with non-valvular atrial fibrillation and is calculated based on the presence or absence of one or more of the following risk factors: previous stroke or transient ischemic attack; congestive heart failure; hypertension; diabetes mellitus; and age >75 years [16]. Bridging anticoagulation is recommended or optional in patients with a recent (within 3 months) stroke or transient ischemic attack or a $CHADS_2$ score ≥3 and it is probably not needed in patients with a $CHADS_2$ score of 0–2 (no prior stroke or transient ischemic attack) [1,13].

Venous thromboembolism

Bridging anticoagulant therapy should be considered in patients with venous thromboembolism who are at high or moderate risk of disease recurrence. High-risk patients are those who have had a recent (within 3 months) episode of venous thromboembolism or have selected prothrombotic blood abnormalities (e.g., deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies or with multiple prothrombotic blood abnormalities) [17-19]. Moderate risk patients include those with previous venous thromboembolism during the last 3–12 months, in whom bridging anticoagulation should be considered. In patients with remote venous thromboembolism, occurring more than 12 months before the planned surgery, bridging anticoagulation is not probably needed.

Pre-operative management

Interruption of warfarin therapy

Patients should be assessed approximately 5 days before surgery to allow time for the anticoagulant effect of warfarin to be eliminated, after it is interrupted and to teach patients LMWH self-injection if bridging anticoagulation is used [2]. In patients who are receiving warfarin with a target international normalized ratio (INR) range of 2.0–3.0, stopping treatment 5 days before surgery will, in most patients, ensure a normal INR at the time of surgery [20]. However, as the pharmacokinetic properties of warfarin are age-dependent, a longer time for the INR to normalize after warfarin is stopped in the elderly and in such patients more than 5 days interruption before surgery may be required [21].

Preoperative INR monitoring

Whenever feasible, INR testing should be done the day before surgery to ensure the INR is normal (≤1.3) or is near normal (≤1.4). Patients with an INR ≥1.5 are at increased risk of postoperative bleeding and administering 1 mg oral vitamin K to such patients will hasten the normalization of the INR prior to surgery [22]. This low dose of vitamin K is unlikely to confer resistance to re-anticoagulation when warfarin is resumed after surgery [23]. In patients who receive vitamin K, it is also reasonable to measure the INR on the morning of surgery to confirm that the INR is normal because if the INR is measured only on the day of surgery, there is a small possibility that a patient will have an INR level that is too high for some types of surgery (≥1.5). In such patients, the patient may require 2–4 units of fresh frozen plasma to rapidly normalize the INR.

Interruption of antiplatelet therapy

Patients who are receiving warfarin may also be receiving antiplatelet therapy, typically acetylsalicylic acid (ASA), 81 mg/24h. Since ASA and clopidogrel irreversibly inhibit platelet function, there is an increased risk of perioperative bleeding when surgery is performed in such patients. Acetylsalicylic acid should be interrupted approximately 7–10 days (lifespan of a platelet) before surgery [2].

Initiating bridging anticoagulation with LMWH

Bridging anticoagulation is recommended in patients at high risk for thromboembolism and, probably, for moderate-risk patients, while in low-risk patients, bridging anticoagulation is optional. The emergence of LMWHs obviates the need for in-hospital perioperative anticoagulation. Bridging anticoagulation with LMWH typically is started 3–4 days before surgery [2].

Dosing of LMWH before surgery

If once a day (OAD) LMWH is used as bridging anticoagulant therapy (e.g., tinzaparin, 175 IU/kg OAD, dalteparin 200 IU/kg OAD), the dose should be administered in the morning, and with last preoperative dose given in the morning of the day before surgery or least 24 hours before surgery. If twice a day (*bis in die* – BID) LMWH is used (e.g., enoxaparin, 1 mg/kg BID, dalteparin 100 IU/kg BID), the evening dose on the day before surgery should be omitted. With either of these dose regimens, the last dose of LMWH should be given at least 24 hours before surgery to minimize the likelihood of a residual anticoagulant effect at the time of surgery.

Table 1. Patient stratification for thromboembolism risk

Suggested risk stratification scheme
High-risk (bridging anticoagulation recommended)
Any mechanical prosthetic mitral valve
Older generation (cage-ball, tilting disc) mechanical prosthetic aortic valve
Recent (within 3 months) arterial thromboembolism (stroke, systemic embolism, transient ischemic attack [TIA])
Recent (within 3 months) venous thromboembolism (deep vein thrombosis, pulmonary embolism)
Chronic atrial fibrillation and $CHADS_2$ score 5 to 6
Prior arterial or venous thromboembolism during interruption of warfarin
Selected prothrombotic blood abnormalities (deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies, multiple prothrombotic blood abnormalities)
Rheumatic valvular heart disease and chronic atrial fibrillation
Intermediate-risk (bridging anticoagulation suggested but optional)
Newer generation (bileaflet) mechanical prosthetic aortic valve and at least 1 major stroke risk factor
Bioprosthetic aortic valve
Chronic atrial fibrillation and $CHADS_2$ score 3 to 4
Prior venous thromboembolism within last 3 to 12 months
Low-risk (bridging anticoagulation not recommended)
Bileaflet mechanical aortic valve and no major stroke risk factor
Chronic atrial fibrillation and $CHADS_2$ score 0 to 2 (no prior stroke or TIA)
Prior venous thromboembolism over 12 months ago
$CHADS_2$ score based on 1 point for age ≥75 years, congestive heart failure, hypertension, diabetes and 2 points for prior stroke or transient ischemic attack

The anticoagulant effect of LMWH is measured by the anti-factor Xa level. Anti-Xa testing should not be routinely done in patients who are receiving LMWH because this testing is not done in many laboratories and the results may not be available for several hours, which is impractical in patients who are scheduled for surgery on the same day. Furthermore, since LMWHs have a predictable pharmacokinetic profile and elimination half-lives of 3–4 hours, there should not be a clinically important residual anticoagulant effect 24 hours after the preceding dose [2].

Postoperative management

Resuming bridging anticoagulation with LMWH

The decision to resume bridging anticoagulation with LMWH after surgery is based on whether there is adequate postoperative hemostasis and the bleeding risk associated with the surgery. A suggested bleeding risk stratification scheme is provided in Table 2. If there is ongoing bleeding after surgery, as detected for example by blood accumulation into a surgical drain, the resumption of LWMH should be deferred until the bleeding has subsided. Most postoperative bleeding will resolve within 24 hours after surgery. If there is adequate postoperative hemostasis after surgery, the decision to resume anticoagulants will depend on the bleeding risk associated with the surgery. In patients having surgery that is associated with a high risk of bleeding, such as prostatectomy or neurosurgery the resumption of LMWH should be deferred for at least 48–72 hours after surgery and, preferably, after consultation with the surgeon. In patients having surgery that is associated with a moderate risk for bleeding, such as intra-abdominal or intrathoracic surgery, the resumption of LMWH should be delayed until 24–48 hours after surgery, while in case of a low risk for bleeding, LWMH can be resumed 12–24 hours after surgery, usually the day after the surgery or procedure [2].

Patients at very-high risk for postoperative bleeding

There may be patients in whom bridging anticoagulation should be considered before but not after surgery. Such patients include those who have had excessive postoperative bleeding or have undergone a procedure associated with a very high risk for bleeding (e.g., intracranial neoplasm, coronary artery bypass surgery). It is always helpful to discuss such high risk patients with the attending surgeon to better understand patient-specific issues relating to bleeding risk and to discuss the initiation of postoperative anticoagulation.

The assessment of postoperative bleeding is subjective and will vary depending on the type of surgery. For example, patients who undergo prostatectomy routinely have postoperative hematuria, and this may persist for 24–72 hours after surgery [12]. In such patients, it is prudent to withhold LMWH

Table 2. Patient stratification for bleeding risk

Suggested risk stratification scheme
Very high-risk
Neurosurgery (intracranial or spinal surgery)
Cardiac surgery (coronary artery bypass or heart valve replacement)
High-risk
Major vascular surgery (abdominal aortic aneurysm repair, aortofemoral bypass)
Major urologic surgery (prostatectomy, bladder tumor resection)
Major lower limb orthopedic surgery (hip/knee joint replacement surgery)
Lung resection surgery
Intestinal anastomosis surgery
Permanent pacemaker insertion or internal defibrillator placement
Selected invasive procedures (kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)
Intermediate-risk
Other intraabdominal surgery
Other intrathoracic surgery
Other orthopedic surgery
Other vascular surgery
Low-risk
Laparoscopic cholecystectomy
Laparoscopic inguinal hernia repair
Dental procedures
Dermatologic procedures
Ophthalmologic procedures
Coronary angiography
Gastroscopy or colonoscopy
Selected invasive procedures (bone marrow aspirate and biopsy, lymph node biopsy, thoracentesis, paracentesis, arthrocentesis)
Very low-risk (warfarin interruption not needed)
Single tooth extraction or teeth cleaning
Selected skin biopsy or skin cancer removal
Selected cataract removal

until the hematuria is subsiding, that is, when the urine becomes pink-colored. In patients who undergo neurosurgery, a small amount of bleeding may be associated with serious complications such as intracranial hemorrhage. In such patients, anticoagulation should be delayed for at least 24–48 hours after surgery.

In patients who develop major postoperative bleeding, all anticoagulants should be withheld until the bleeding source has been identified and treated. The resumption of anticoagulants is superseded by the need to prevent further bleeding. If the cause of the bleeding is readily reversible, as with the repair of a severed blood vessel that inadvertently occurred during surgery, anticoagulants probably can be resumed within 24 hours. On the other hand, if the bleeding is unlikely to resolve quickly, as with a large gastric ulcer, the resumption of anticoagulants should be deferred for one to two weeks, or longer, depending on the size of the ulcer and whether there was active bleeding at the time of the gastroscopy. A repeat gastroscopy may be warranted one to two weeks after the start of anti-ulcer therapy to ensure that significant ulcers have healed and are not likely to re-bleed if anticoagulant therapy is restarted.

Bridging anticoagulation should be stopped when a patient's INR level is within the therapeutic range. Preferably, INR testing should be done on day 3, and day 5 after surgery. The timing of postoperative INR testing may vary by one day earlier or later, depending on the day of the week that the surgery was done and patient availability for blood testing. In most patients, with a target INR of 2.0–3.0, bridging anticoagulation will be required for 3 to 4 days after surgery, and in patients with a target INR of 2.5–3.5, approximately 5 days of bridging anticoagulation will be required.

Resuming warfarin therapy

As with the resumption of bridging anticoagulation, the resumption of warfarin should be predicated on the patient's

risk for postoperative bleeding. With most types of surgery or procedures that are associated with a low or moderate risk for bleeding, warfarin can be restarted on the evening after surgery since a clinically significant anticoagulant effect not occur for at least 48 hours after the initial dose of warfarin, and a full anticoagulant effect will not occur for 4–6 days [9,10]. In patients who are undergoing a surgical or other procedure associated with a high or very high risk for postoperative bleeding, the initial dose of warfarin can be resumed on the evening of the first or second postoperative day, 36–60 hours after the procedure, to anticipate the onset of a clinically important anticoagulant effect by the 4th or 5th postoperative day. Overall, the graduated approach to resuming warfarin should parallel the resumption of bridging anticoagulation and should be individualized based on a postoperative assessment of the patient's risk for bleeding.

The starting dose of warfarin can be the patient's usual dose, according to their pre-specified dose regimen. Consequently, the resumption of warfarin on the evening after surgery should not adversely affect postoperative hemostasis. If a patient has received high-dose vitamin K before surgery (i.e., 5–10 mg), this may result in resistance to re-anticoagulation when warfarin therapy is resumed. Because it is difficult to predict the warfarin dose requirements of such patients, it is reasonable to double their usual dose of warfarin for two consecutive days after surgery. If low-dose vitamin K (i.e., 1–2 mg) has been given before surgery, resistance to re-anticoagulation is unlikely but it is reasonable to double the first dose of warfarin.

Resuming antiplatelet therapy

In patients who are receiving antiplatelet therapy in addition to vitamin K antagonists (VKA) therapy, the antiplatelet drug, usually ASA, can be resumed on the same day when VKA is resumed.

SUMMARY

The management of patients who require temporary interruption of warfarin requires an individual assessment of both patients' risk for thromboembolism during warfarin interruption and patients' risk for bleeding associated with surgery. These considerations will determine whether patients receive bridging anticoagulation. For patients in whom bridging anticoagulation may be warranted, the risk for bleeding associated with the surgery or invasive procedure will determine when bridging is resumed after surgery. In recent years, much progress has been made in our understanding of the therapeutic benefits and risks of bridging anticoagulation through cohort studies and patient registries. However, several questions remain that are best addressed by randomized controlled trials. Most important, perhaps, is the need to address whether bridging anticoagulation is needed in patients who require temporary interruption of warfarin, especially in patients at low-to-moderate risk for thromboembolism who constitute the vast majority of patients assessed and in whom there is uncertainty about optimal practice. Additional unanswered questions relate to the timing of bridging anticoagulation before and after surgery and identifying types of surgery and procedures in which the risk for bleeding precludes bridging anticoagulation.

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