MAEDICA – a Journal of Clinical Medicine
2013; 8(2): 189-194

MÆDICA - a Journal of Clinical Medicine

STATE-OF-THE-ART

Venous Thromboembolism Following Major Orthopedic Surgery

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ABSTRACT

Venous thromboembolism (VTE) is an important complication of major orthopedic surgery (total hip arthroplasty-THA, total knee arthroplasty-TKA, hip fracture surgery-FHS) and is associated with significant morbidity and mortality. Despite this, not all patients receive an appropriate prophylaxis, often due to a disproportionate fear of bleeding complications. A challenge in the management of VTE prophylaxis is to balance the benefits of the treatment with the risk of bleeding. In this article, we review the latest guidelines recommendations regarding prevention of postoperative VTE in patients undergoing orthopedic surgery.

INTRODUCTION

VTE is an important complication of major orthopedic surgery. Current data suggest that deep venous thrombosis (DVT) represents the most frequent postoperative complication in TKA (1), pulmonary embolism (PE) being responsible of half of postoperative deaths in THA (2).

Although VTE can develop after any major surgery, orthopedic patients are more vulnerable due to the involvement of several prothrombotic processes: i.e. coagulation activation from tissue and bone injury; venous injuries; heat due to cement polymerization; reduced venous emptying intra-or post-surgery; immobilization (3,4).

Clinical, pathological and epidemiological evidences suggest that the risk period for VTE begins at surgery and extends well beyond hospitalization; therefore thromboprophylaxis must be prolonged (5). Initially, the thrombosis appears in the lower leg, but the formation of the thrombus can take several days or weeks, and most symptomatic DVT usually occur after hospital discharge. Unfortunately, there is currently no way to predict which orthopedic patients will develop VTE.

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Article received on the 30th of January 2013. Article accepted on the 15th of April 2013.

Evaluation of risk factors for VTE

There are several patterns available for estimating VTE risk (Caprini Score, Padua Prediction Score), but none has been extensively validated (5,6). Both the surgical interventions and the characteristics of the patients are involved in risk estimation. The most used risk classification scale is the one described by Geerts that includes (7):

- Surgery, major trauma or lower-extremity injury
- Cancer
- Venous compression, central venous catheterization
- Pregnancy and post-partum period
- Contraceptive, selective estrogen receptor modulators
- Erythropoiesis-stimulating agents
- Acute medical illness, inflammatory bowel disease
- Immobilization, lower-extremity paresis
- Nephrotic syndrome, thrombophilia
- Paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders
- Obesity, increasing age, previous VTE

General recommendations for VTE prophylaxis in major orthopedic surgery

The prophylaxis methods are of two types: pharmacological and mechanical. It is recommended to begin prophylaxis as soon as possible postoperatively and to continue it until the risk fades;

- As the risk/benefit ratio for bleeding after the pharmacologic prophylaxis is different with every patient, ideally the type of thromboprophylaxis should be customized according to risk.

The guidelines of thromboprophylaxis in major orthopedic surgery

The thromboprophylaxis is clearly recommended by the latest guidelines such as the 2012 American College of Chest Physicians (ACCP), the 2011 American Academy of Orthopedic Surgeons (AAOS) and the 2011 National Institute of Clinical Excellence (NICE), but the optimal strategy remains debatable. The adherence to one or another set of guidelines may vary from country to country or according to clinical practice (8).

The primary changes in the 2012 ACCP is the stratification of the patients' risk for VTE or bleeding (9) and the recommendation of aspirin use in VTE high-risk patients.

The 2012 ACCP guideline includes the following recommendations (9):

- the use of one of the following antithrombotic prophylaxis (Grad 1A): low molecular weight heparins (LMWHs); fondaparinux; dabigatran, apixaban, rivaroxaban (TKA or THA, but excluding HFS); low-dose unfractionated heparin (UFH); adjusted-dose vitamin K antagonist (VKAs); aspirin (all Grade 1B); or an intermittent pneumatic compression device (IPCD) (Grade 1C) for a minimum of 10 to 14 days, suggesting extending prophylaxis for up to 35 days (Grade 2B);
- The use of LMWHs as preferred to other alternative agents (Grade 2C/2B) and adding an IPCD during the hospital stay (Grade 2C);
- The use of IPCD or no prophylaxis in patients with increased bleeding risk, (Grade 2C, as well as in the AAOS - *Grade of Recommendation: Consensus*);
- The use of apixaban or dabigatran in patients who decline injections (Grade 1B);
- The non-use of inferior vena cava filter placement for primary prevention in patients with contraindications to both pharmacologic and mechanical thromboprophylaxis (Grade 2C);
- The non-use of Doppler ultrasonography screening before hospital discharge (Grade 1B, as well as in the AAOS - *Grade of Recommendation: Strong*).

The latest AAOS 2011 includes the following recommendations (10):

- in further assessing VTE risk in orthopedic patients (who are already at high risk for VTE due to the type of surgery) current evidence is not clear about which factors other than a previous VTE increase this risk, and cannot recommend for or against routinely assessing these patients. (*Grade of Recommendation: Inconclusive*);
- in order to assess which patients are at increased risk for bleeding, known bleeding disorders like hemophilia and the presence of an active liver disease clearly increase the risk (*Grade of Recommendation: Consensus*); current evidence is not clear about other factors to increase the chance of bleeding and it is unable to recommend for or against using them to assess this risk. (*Grade of Recommendation: Inconclusive*);

- It suggests that patients should discontinue antiplatelet medication before elective arthroplasty (*Grade of Recommendation: Moderate*);
- It suggests the use of prophylaxis even in patients who are not at a higher risk beyond that of the surgery itself (*Grade of Recommendation: Moderate*); current evidence is unclear about which prophylaxis is optimal/suboptimal; therefore, the guideline is unable to recommend for or against a specific prophylaxis in these patients. (*Grade of Recommendation: Inconclusive*); in the absence of reliable evidence about how long to employ these strategies, it is being considered that patients and physicians discuss the duration of prophylaxis. (*Grade of Recommendation: Consensus*);
- In the absence of reliable evidence, patients who had a previous VTE should receive both pharmacologic and mechanical prophylaxis (*Grade of Recommendation: Consensus*);
- In the absence of reliable evidence, patients should undergo early mobilization (*Grade of Recommendation: Consensus*);
- It suggests the use of neuraxial anesthesia to help limit blood loss; even though evidence suggests that it does not affect the occurrence of VTE. (*Grade of Recommendation: Moderate*);

The methods of VTE prophylaxis

The prophylaxis therapy includes the following:

1. General methods:

- Active or *passive mobilization:* should begin on the first postoperative day (11);
- Adequate *hydration:* especially for immobilized patients.

2. Pharmacological methods:

- *Aspirin* is not a new therapy for the prevention of VTE, but the previous ACCP guidelines recommended against using it as the single agent for prophylaxis. In the current edition, aspirin is indicated as a prophylaxis option – although not typically the agent of choice –in major orthopedic surgery (9). The 2011 AAOS recommends a dose of 325 mg twice daily in patients at increased risk for major bleeding and at standard or increased risk for PE (10).
- *Heparins:* activate factor X (F Xa) by an antithrombin (AT)-dependent mechanism and inactivate thrombin, preventing fibrin formation and inhibiting thrombin-induced activation of platelets and of V and VIII factors. Heparin prophylaxis does not reduce the mortality, although has an undeniable benefit (11).
  - *UFH:* is given in a 5000 U SC fixed dose every 8 or 12 h, has a T½ 1.5 h, a binding to plasma proteins variable, and does not require laboratory monitoring. The heparin-induced thrombocytopenia and osteopenia can occur at any dose, especially in prolonged administration (12).
  - *LMWHs:* have stronger anti-Xa activity as compared to UFH; reduced binding to plasma proteins and cells is responsible for more predictable dose-response relationship, longer T½ and lower complications; they are excreted renal and do not require laboratory monitoring (Table 1).

Every LMHW has a unique pharmacokinetics, and it is not recommend changing them during the treatment. Although prophylaxis with LMWHs is associated with higher costs, its cost- effectiveness compares favorably to other interventions (13);

- *Vitamin K antagonists (VKAs)* need a strict laboratory and clinical control to ensure efficacy and safety, implying a weekly INR monitoring aiming at a 2-3 INR value range. Their advantages are the oral route of administration and low price, but they are challenging to use in practice because of a narrow therapeutic window, variability in dose-response, interaction with drugs and diet; also the laboratory control of the therapeutic level of anticoagulation requires a good doctor-patient communication (14);
- *Fondaparinux* (Arixtra®): is a pentasaccharide with highly inhibitory effect on Factor

Type of LMWHs	Dose and administration
Dalteparin (Fragmin®)	5000 UI/day SC, at 12 h postoperative
Enoxaparin (Clexane®)	4000 UI/day SC, at 12 h postoperative
Nadroparin (Fraxiparine®)	2850-5700 UI/day SC, depending on weight, at 12 h postoperative
Tinzaparin (Innohep®)	3500UI/day SC, in medium risk patients 4500UI/daySC, in high risk, at 12 postoperative
Reviparin(Clivarin®)	1432 UI/day SC, low and medium risk 4200 UI/day SC, high risk, at 12 h postoperative

TABLE 1. The type, dosage and administration of LMWHs.

Xa; it has 100% bioavailability, a long T½ 17-20 h that ensures a prolonged effect, but also the drawback of a lack of a quick reversibility. It is excreted renal and the daily dose is 2.5 mg SC, the first dose at 6-8 h postoperatively (15). The PENTAMAX study pointed out a higher rate of bleeding with Fondaparinux compared to Enoxaparin (2.1% versus 0.2%; P = 0.06), although Fondaparinux is superior to Enoxaparin in preventing VTE (16);

- *New oral anticoagulants:*

The guidelines recognize the recent clinical trials of new oral anticoagulants, that are equivalent to LMWH in terms of safety and efficacy, and have advantages as compared to AVK: a rapid onset of action without need for bridging therapy, a fixed dosing without requiring monitoring, the absence of food or drug interactions, and the patient's ease to self-manage the treatment (17,18). Their primary drawback is the lack of specific antidotes to reverse the anticoagulants effect, particularly for those with a long T½.

- *Dabigatran etexilate* (Pradaxa®), a direct inhibitor of thrombin, has a maximum effect within 2-3 h due to a rapid absorption and a T½ of 12-14 h. The treatment starts with one 110 mg capsule at 1-4 h postoperatively and continues with two 110 mg capsules once a day. A lower dose has been used in patients over 75 years or with kidney problems, or in association with amiodarone, quinidine or verapamil. In the USA, a 150 mg dose was approved twice daily for patients with a creatinine clearance (ClCr)>30 ml/min and a half-reduced dose for ClCr 15-30 ml/min. Studies RE-MOBILIZE and RE-MODEL show a similar incidence of bleeding with Enoxaparin (19-21).
- *Rivaroxaban* (Xarelto®): is a selective oral Factor Xa inhibitor with a high bio-availability, that inhibits not only free FXa, but also prothrombinase activity and clot-associated FXa activity. It is well tolerated, has a rapid onset of action, a T½ about 5–9 h, and a predominantly renal excretion (22). In a fixed, unmonitored, once-daily dose of 10 mg in the RECORD 1 and 2 trials for THA, and in the RECORD 3 and 4 for TKA, it proved to be a superior antithrombotic to Eenoxaparin, and with similar rates of bleeding (23, 24).
- *Apixaban:* is a selective inhibitor of both free and prothrombinase-bound F Xa, with a high bio-availability, a quick absorption, and a T½ of 13 h; it is administered in a single 2.5 mg daily dose, with minimal drug interaction, and has a renal and fecal excretion. The ADVANCE 1, 2 and 3 trials showed a similar bleeding rate and efficiency compared to Enoxaparin (25,26).
- *Betrixaban:* is a direct Factor Xa inhibitor with a T½ of about 23 h, a ClCr of 17% of the absorbed dose. It has 34% bio-availability and a binding to plasma proteins ratio of 60%. There is a trial in progress (APEX) comparing betrixaban 80 mg/day to enoxaparin 40 mg/day; the results of the study will be published in 2015 (27).

Bleeding is a major complication of antithrombin treatment, and this risk must be taken into account when starting the prophylaxis: active gastro-duodenal ulcer, age >85, hepatic or renal failure, bleeding <3 months prior to ad-

Anticoagulants	Use and timing of dural puncture or epidural catheter insertion
Rivaroxaban	• Puncture / KT Insertion – at least 18 h after the last dose • Removal – at least 18 h after last dose • Subsequent dose at least 6 h after epidural catheter insertion or removal • If traumatic puncture occurs, delay administration for 24 h
Dalteparin/ Enoxaparin	• Prophylactic dose, single daily dosing • Insertion – at least 12 h after the last dose. •Subsequent dose at least 4 h after epidural catheter insertion • Removal – at least 12 h after the last dose. • Subsequent dose at least 4 h after epidural catheter removal • Prophylactic dose, twice-daily dosing • Insertion epidural catheter - not recommended • Removal – twice-daily dosing at least 4 h after epidural catheter
Fondaparinux	• Insertion – fondaparinux not recommended prior to insertion • Removal – at least 36 h after the last dose of fondaparinux • Subsequent dose at least 12 h after epidural catheter removal
UFH	• Insertion – at least 4 h after the last dose • Removal – at least 4 h after the last dose • Subsequent dose at least 1 hour after epidural catheter removal
VKAs	• Insertion – no consensus regarding highest acceptable INR • Removal – within 48 h of initiation of warfarin and INR <1,5

TABLE 2. The administration of anticoagulants and neuraxial blockade.

mission, platelet count <50,000. are contra indications to this type of treatment (28).

Neuraxial blockade is not a contraindication for pharmacologic thromboprophylaxis (29), but it is important to consider the use and the timing of anti-thrombotic drugs in these patients, due to the concern about the occurrence of perispinal hematoma, a rare but serious complication (Table 2).

3. Mechanical methods

Their individual benefit remains unclear, due to the combined use with other prophylaxis methods.

- *The graduated compression stockings:* reduce the DVT rates up to 60% in case of moderate thrombotic risk, but are contraindicated in patients with severe peripheral arteriopathy, neuropathy or dermatological diseases located in lower limbs (30).
- *Intermittent pneumatic compression:* remains an alternative in patients at high risk, where anticoagulants cannot be used (9, 10). ❑

CONCLUSION

The guidelines of anti-thrombotic therapy, including the selection of drugs, the degree of anti-coagulation and the duration of prophylaxis continue to evolve. However, their implementation is still a problem, despite the detailed European or American guidelines consensus, because of the poor awareness of post-surgical thrombosis risk, the concerns about bleeding and the complexity of anti-coagulation with current agents.

Perioperative thromboprophylaxis with extended duration at discharge from hospital for, 28-35 days can reduce the risk for VTE and improve outcomes for these patients. Simplifying therapy, such as once-daily fixed dosing, could change attitudes to anticoagulant use and improve adherence to guidelines. ❑

Conflict of interest: none declared.
Financial support: none declared.

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