Perioperative Thromboprophylaxis

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Summary

Background: Venous thromboembolism (VTE), a composite of deep vein thrombosis and pulmonary embolism, is a preventable cause of morbidity and mortality in surgical patients. **Method:** National and international treatment guidelines and major clinical trials on mechanical or pharmacological VTE prophylaxis in surgical patients were reviewed. **Results:** The risk of perioperative VTE is dependent on patient- and surgery-related risk factors. Based on a thorough and individualized risk assessment, each surgical patient should be assigned a low, intermediate, or high risk of VTE. Whereas basic (e.g. early mobilization and avoidance of dehydration) and mechanical (i.e. graduated compression stockings) measures are appropriate for most low-risk patients, visceral surgical patients at intermediate or high risk of VTE should receive pharmacological thromboprophylaxis for at least 7–10 days. The risk of VTE should be balanced against the risk of bleeding. Low-molecular-weight heparin (LMWH) offers several advantages over low-dose unfractionated heparin and should be administered for prolonged periods in patients undergoing particularly high-risk (i.e. cancer) surgery. **Conclusion:** Perioperative VTE prophylaxis should be carried out in an individualized and risk-adapted manner. In visceral surgical patients with a moderate-to-high risk of VTE and a low risk of bleeding, pharmacological thromboprophylaxis with LMWH is a standard of care.

Schlüsselwörter

Chirurgie · Thrombose · Niedermolekulares Heparin ·
Karzinom · Thromboseprophylaxe

Zusammenfassung

Hintergrund: Die venöse Thromboembolie (VTE), die vor allem die tiefe Bein-/Beckenvenenthrombose und die Lungenarterienembolie umfasst, ist eine vermeidbare Ursache von Morbidität und Mortalität in der Allgemein- und Viszeralchirurgie. **Material:** Es erfolgte eine zusammenfassende Bewertung von verschiedenen nationalen und internationalen Leitlinien sowie von größeren klinischen Studien zur mechanischen oder pharmakologischen Thromboseprophylaxe bei chirurgischen Patienten. **Ergebnisse:** Das perioperative VTE-Risiko ist sowohl von patienteneigenen als auch von eingriffsbedingten Faktoren abhängig. Auf der Basis einer gründlichen und individualisierten Risikoeinschätzung sollte jedem chirurgischen Patienten ein niedriges, mittleres oder hohes VTE-Risiko zugeordnet werden. Während Basismaßnahmen (z.B. frühe Mobilisierung und Vermeidung von Exsikkose) und mechanische Methoden wie medizinische Thromboseprophylaxestrümpfe für die meisten Patienten mit niedrigem Risiko ausreichend sind, sollten viszeralchirurgische Patienten mit höherem Risiko eine pharmakologische VTE-Prophylaxe über mindestens 7–10 Tage erhalten. Dabei ist das Thrombose- gegen das Blutungsrisiko abzuwägen. Niedermolekulare Heparine (NMH) bieten gegenüber niedrigdosiertem unfractioniertem Heparin zahlreiche Vorteile und sollten bei besonders hohem VTE-Risiko (z.B. bei größeren tumorchirurgischen Eingriffen) über einen prolongierten Zeitraum verabreicht werden. **Schlussfolgerung:** Die perioperative VTE-Prophylaxe sollte in einer individualisierten und risikoadaptierten Art und Weise erfolgen. Bei viszeralchirurgischen Patienten mit einem mittleren bis hohem VTE- und einem niedrigen Blutungsrisiko ist die pharmakologische Thromboseprophylaxe mit NMH ein etablierter Standard.

Introduction

Venous thromboembolism (VTE) is a preventable cause of morbidity and mortality in surgical patients. It is estimated that, without appropriate mechanical or pharmacological thromboprophylaxis, approximately 15–40% of patients undergoing general, gynecological, or urological surgery will experience either symptomatic or asymptomatic deep vein thrombosis (DVT) [1–3]. In major orthopedic surgery such as elective hip or knee arthroplasty, postoperative rates of DVT in untreated patients may even approach 40–60%. The risk of VTE is also particularly high in patients undergoing surgery for malignant disease [4, 5]. In these patients, postoperative rates of isolated and mostly asymptomatic calf vein thrombosis are estimated to be 40–80% in the absence of routine thromboprophylaxis, while approximately 10–20% of patients will develop proximal DVT. Symptomatic pulmonary embolism (PE) may occur in up to 4–10% of surgical cancer patients, and previous case series suggest that 1–5% of patients undergoing major surgery for cancer will die from PE [3]. Overall, surgery for cancer confers a nearly 7-fold higher risk of perioperative PE when compared to similar surgical procedures for benign disease [6]. In contrast to the characteristic symptoms of established DVT resulting from painful vessel wall distension, inflammation, and/or venous blood flow obstruction, there are no clinical signs that reliably indicate early DVT development and could thus prompt physicians to initiate postoperative thromboprophylaxis on an individual basis [1]. On the other hand, even asymptomatic DVT harbors a significant risk of developing a postthrombotic syndrome, and most fatal PEs occur without clinical notice. Therefore, routine thromboprophylaxis in surgical patients considered at risk for VTE appears warranted. However, both the indication and the choice of thromboprophylaxis should be individualized and adapted to each patient's specific situation [1].

Risk Assessment

When assessing the risk of VTE in surgical patients, both patient- and surgery-related risk factors should be considered [1, 7]. Patient-related factors conferring a moderate-to-high risk of VTE include previous VTE, malignancy, age >60 years, a positive family history of VTE (i.e. VTE in a first-degree relative), known thrombophilia (e.g. antiphospholipid syndrome or activated protein C resistance), overweight (i.e. body mass index > 30 kg/m²), heart failure, and acute systemic infectious or inflammatory conditions. Although thrombophilia increases the risk of VTE, routine laboratory screening for inherited or acquired thrombophilia in surgical patients is not recommended. In addition, there is no established value of coagulation activation markers such as preoperative D-dimer or thrombin-antithrombin complexes in predicting

Table 1. Venous thromboembolism (VTE) risk categories and estimated incidence rates of deep vein thrombosis (DVT) and pulmonary embolism (PE) in surgical patients in the absence of appropriate thromboprophylaxis (adapted from [1])

Risk of VTE	Distal DVT, %	Proximal DVT, %	Fatal PE, %
Low	<10	<1	<0.1
Intermediate	10–40	1–10	0.1–1
High	40–80	10–30	>1

perioperative VTE occurrence in surgical patients [1]. Surgery-related risk factors are mainly determined by the indication for surgery and the magnitude of the surgical trauma. In this regard, extensive abdominal and pelvic procedures for malignant or inflammatory conditions as well as larger orthopedic procedures on the spine, hip, or knee confer a particularly high risk of VTE. While some guidelines put specific emphasis on the duration of the surgical procedure (with surgeries lasting >30 min being associated with a higher risk of VTE) [7], other guidelines conclude that this assumption is not sufficiently supported by randomized controlled trials [1]. There is general agreement, however, that laparoscopic procedures should be attributed a VTE risk similar to that of the corresponding conservative approaches. Based on the above patient- and surgery-related risk factors, each surgical patient should be grouped into one of the following three VTE risk categories: low, intermediate, or high risk. Estimated risks of VTE in the respective risk categories in the absence of appropriate thromboprophylaxis are summarized in table 1. It is important to note that patients undergoing low-risk procedures may be grouped into one of the higher VTE risk categories solely based on their predisposing comorbidities.

Perioperative Thromboprophylaxis

Basic Measures

All patients undergoing surgical procedures should receive basic measures of thromboprophylaxis (fig. 1). These include early mobilization, active or passive range of motion exercise, and avoidance of dehydration, and may be sufficient in most patients with a low risk of VTE. On an individual basis, basic measures may be complemented by elastic compression stockings. In surgical patients with a low risk of VTE, routine pharmacological thromboprophylaxis is not recommended [1, 7].

Mechanical Thromboprophylaxis

Mechanical methods of thromboprophylaxis include elastic stockings with graduated compression, intermittent pneumatic calf compression devices, and foot pumps. Of these,

Fig. 1. Simplified algorithm for venous thromboembolism (VTE) risk assessment and perioperative thromboprophylaxis. Each surgical patient should undergo a thorough risk assessment based on patient- and surgery-related risk factors. While patients in all VTE risk categories should receive basic measures of thromboprophylaxis such as early mobilization, active or passive range of motion exercise, and avoidance of dehydration, routine pharmacological thromboprophylaxis, preferably with low-molecular-weight heparin (LMWH), is only indicated in patients at intermediate or high risk of VTE. Unless there is a clear contraindication to systemic anticoagulation (e.g. due to an excessive risk of bleeding), mechanical methods such as elastic compression stockings (ECS) should not be used alone for VTE prophylaxis in the intermediate and high-risk categories, but may be a useful supplementation to pharmacological thromboprophylaxis in surgical patients at high risk of VTE.

elastic graduated compression stockings are most widely used in clinical practice. Elastic stockings should be carefully adapted. The correct pressure for primary VTE prophylaxis at the level of the ankle is 18–23 mm Hg, which is lower than the average pressure of 30–40 mm Hg used to prevent or treat the postthrombotic syndrome after established DVT [7]. Compared to thigh-length stockings, below-knee stockings may have some advantages such as in ensuring a proper fit, but based on indirect evidence from patients with stroke, thigh-length stockings may be more efficacious in preventing VTE than calf-length stockings [7, 8]. Elastic stockings should not be used in patients with critical peripheral artery occlusive disease, severe neuropathy, significant edema, or with local infections, necrosis, or trauma.

There is clear evidence in the literature indicating that mechanical methods such as elastic compression stockings are efficacious in preventing perioperative DVT, with an estimated risk reduction of 67%, but mechanical methods alone appear

much less efficacious in reducing the frequency of perioperative PE [4, 9]. Consequently, elastic compression stockings are not recommended as monotherapy in surgical patients at moderate-to-high risk of VTE unless there is a clear contraindication to pharmacological thromboprophylaxis such as an excessive risk of bleeding (fig. 1). However, additional implementation of mechanical methods in high-risk surgical patients already receiving appropriate anticoagulation can further decrease their risk of VTE and may thus be a reasonable supplementation to pharmacological thromboprophylaxis in particularly high-risk situations [1].

The insertion of a temporary or permanent inferior vena cava (IVC) filter may prevent potentially fatal PE in surgical patients at high risk of VTE in whom prophylactic anticoagulation cannot be commenced or who have developed proximal DVT despite appropriate pharmacological thromboprophylaxis. Because of the significant short- and long-term complications associated with this procedure, IVC filter insertion should be restricted to highly selected cases.

Pharmacological Thromboprophylaxis

Surgical patients with an intermediate or high risk of VTE should be considered for pharmacological thromboprophylaxis (fig. 1).

Low-Dose Unfractionated Heparin

Low-dose unfractionated heparin (UFH) is a mixture of mucopolysaccharides of various chain lengths with an elimination half-life of 1–2 h that exerts its anticoagulant effects mainly through the enhancement of antithrombin-dependent inhibition of thrombin and factor Xa. UFH is eliminated to a similar extent via the liver and the kidneys. An international multicenter trial originally published in 1975 and reanalyzed in 1977 randomly assigned more than 4,000 patients undergoing major surgical procedures to receive either no pharmacological thromboprophylaxis or low-dose UFH which was commenced 2 h preoperatively at a dose of 5,000 IU and then continued at $3 \times 5,000$ IU subcutaneously per day until the patient was fully mobilized. The primary endpoint of autopsy-proven fatal PE occurred in 15 of some 1,400 autopsied control patients as compared to none in some 1,300 autopsied patients receiving low-dose UFH ($p < 0.001$) [10]. Consistent with this finding, a meta-analysis published in 1988 concluded that pharmacological thromboprophylaxis with low-dose UFH (i.e. $2-3 \times 5,000$ IU or $2 \times 7,500$ IU subcutaneously per day) is highly efficacious in reducing perioperative VTE across a range of major surgical interventions, including general, orthopedic, and urological surgeries [5]. According to this analysis, low-dose UFH reduced the frequency of asymptomatic DVT, fatal PE, and total perioperative mortality by 67, 68, and 21%, respectively.

Low-Molecular-Weight Heparin

Low-molecular-weight heparins (LMWHs) are derived from UFH through various fractionating processes and have an average elimination half-life of 4–6 h. Similar to UFH, LMWHs inhibit factor Xa and, to a lesser extent, thrombin in an antithrombin-dependent manner and are excreted predominantly via the kidneys, which requires particular caution in patients with severe renal insufficiency. Compared to UFH, LMWHs have improved pharmacological properties including a more predictable bioavailability. For pharmacological thromboprophylaxis, most LMWHs are administered as fixed doses once per day (i.e. routine dose adjustments based on the patient's body weight are not required). However, for some LMWHs, different doses are available dependent on whether the VTE risk is considered high or low-to-intermediate. Several randomized controlled trials have compared LMWH with low-dose UFH for pharmacological thromboprophylaxis in surgical patients [1–3, 7]. Taken together, LMWH appears to be at least as safe and efficacious as UFH in this indication. In this regard, a recent randomized controlled trial deserves particular attention due to its size and design. In this double-blind study, some 23,000 surgical patients received either low-dose UFH ($3 \times 5,000$ IU per day) or the LMWH, certoparin, at a daily dose of 3,000 IU anti-Xa. The incidence of the primary efficacy endpoint of autopsy-proven fatal PE was similar between the two groups [11]. Based on their overall safety and efficacy profile, the significantly reduced risk of heparin-induced thrombocytopenia (and probably also of osteopenia), and the convenience of once daily injections, national guidelines favor LMWH over low-dose UFH for pharmacological thromboprophylaxis in surgical patients [1].

Fondaparinux

Fondaparinux is a synthetic pentasaccharide with an elimination half-life of 17 h that is excreted almost exclusively via the kidneys and specifically inhibits factor Xa in an antithrombin-dependent manner. At a dose of 2.5 mg per day, fondaparinux has shown safety and efficacy in preventing VTE in high-risk orthopedic and abdominal surgical patients [12, 13]. Compared to the LMWH, enoxaparin, fondaparinux is associated with an almost 50% reduction in thromboembolic events in patients undergoing major orthopedic surgery [12], but this superior efficacy may be somewhat counterbalanced by a slightly increased risk of bleeding, especially when the factor Xa inhibitor is administered too early (i.e. before 6 h) after surgery [1].

Direct Oral Anticoagulants

The direct oral thrombin inhibitor, dabigatran etexilate, and the direct oral factor Xa inhibitors, rivaroxaban and apixaban, which specifically and reversibly inhibit both free and clot-bound thrombin and factor Xa, respectively, are currently approved in Europe for the prevention of perioperative VTE in patients undergoing major orthopedic surgery (i.e.

elective hip or knee arthroplasty). From pooled analyses it may be tentatively concluded that rivaroxaban has a superior efficacy profile compared to the LMWH, enoxaparin [14], while the other two direct oral anticoagulants (DOACs) are associated with quite similar overall rates of thromboembolic events. However, none of the three drugs is currently approved for pharmacological thromboprophylaxis in other surgical indications, and their off-label use is strongly discouraged particularly in visceral surgical patients due to their currently unpredictable effects on hemostasis and wound healing in the immediate postoperative period.

Other Oral and Parenteral Anticoagulants

Although the platelet inhibitor, acetylsalicylic acid (ASA), at doses of 75–325 mg per day shows some efficacy in primary and secondary VTE prevention, it should not be used for perioperative thromboprophylaxis [1–3, 7].

Vitamin K antagonists (VKAs) such as warfarin or phenprocoumon are indirect anticoagulants that inhibit the production of functional clotting factors II, VII, IX, and X. VKAs are efficacious in preventing perioperative VTE, but their rather slow onset of action (2–3 days) and narrow therapeutic window necessitating regular monitoring of the international normalized ratio (INR) and frequent dose adjustments limit their use in clinical practice [1].

The heparinoid, danaparoid, is an antithrombin-dependent, heparin-free factor Xa inhibitor with a rather long elimination half-life of 22–24 h and is almost exclusively excreted through the kidneys. Prophylactic doses of danaparoid (i.e. 2×750 IU anti-Xa subcutaneously per day) have shown safety and efficacy for VTE prevention in stroke and trauma patients [1]. The current use of danaparoid for thromboprophylaxis in surgical patients is mainly restricted to situations in which heparin is contraindicated (e.g. due to drug allergy or a history of heparin-induced thrombocytopenia).

The recombinant hirudin, lepirudin, is a direct thrombin inhibitor with a renal route of elimination that is approved, at a subcutaneous dose of 2×15 mg per day, for primary VTE prevention after elective hip or knee arthroplasty. The use of lepirudin is problematic in patients with renal insufficiency and harbors the risk of alloantibody formation that may significantly delay drug excretion and may induce severe allergic reactions upon re-exposure. Lepirudin is still available on the market, but no longer produced for reasons other than safety concerns. Desirudin is another recombinant hirudin approved for VTE prophylaxis after major orthopedic surgery.

Initiation and Duration of Pharmacological Thromboprophylaxis

While in Europe perioperative pharmacological VTE prophylaxis with low-dose UFH or LMWH is typically commenced 2–12 h before surgery, in North America the first

dose is almost exclusively given postoperatively. There is no evidence to support the one over the other scheme with regard to safety or efficacy, albeit LMWH may be associated with less bleeding when the first dose is given 12 instead of 2 h before surgery, probably due to its increased elimination half-life compared to UFH.

Fondaparinux and the above-mentioned DOACs should always be started postoperatively. Postoperative initiation of prophylactic anticoagulation is also recommended in patients taking anti-platelet agents such as ASA or clopidogrel [1].

If, based on an individualized risk assessment, pharmacological thromboprophylaxis is indicated, it should be continued for at least 7–10 days postoperatively [1–3, 7]. For many surgical procedures, this standard duration of VTE prophylaxis already extends into the period of ambulation or rehabilitation. Moreover, recent epidemiological evidence suggests that the risk of VTE is significantly increased up to 6 weeks after in-hospital surgery [15]. Consequently, prolonged pharmacological VTE prophylaxis over 3–4 or even 5 weeks is recommended in patients at particularly high risk, including those with major cancer surgery or elective hip arthroplasty [1–3, 7]. At hospital discharge, it is thus mandatory to provide subsequent healthcare providers with detailed information on indication, intensity, and intended duration of prescribed anticoagulants in order to ensure continuation of pharmacological VTE prophylaxis.

Specific Patient Populations

Patients at Risk or with a History of Heparin-Induced Thrombocytopenia

Surgical patients receiving heparin for thromboprophylaxis, especially those after major orthopedic surgery, are at increased risk of developing heparin-induced thrombocytopenia (HIT). HIT is an adverse drug reaction typically occurring 4–14 days after surgery that is mediated by platelet-activating IgG antibodies to heparin-platelet factor 4 (PF4) complexes and may result in catastrophic arterial and/or venous thrombosis. The risk of HIT is significantly higher in patients receiving low-dose UFH as compared to those receiving LMWH (with estimated absolute risks of 1–3% and <0.1–0.3%, respectively), and it is negligible in patients receiving fonda-

parinux. The ACCP guidelines recommend monitoring of peripheral platelet counts every 2 or 3 days from day 4 until day 14 or until heparin is stopped (whichever occurs first), when the risk of HIT is estimated to be >1% [16]. Consequently, platelet monitoring may not be necessary during LMWH thromboprophylaxis and can be safely omitted in patients receiving fondaparinux. Surgical patients with a moderate or high clinical likelihood of HIT (according to the 4-T score) should undergo definite laboratory testing and be switched to alternative anticoagulation depending on either a positive test result or a high pretest clinical probability for HIT [17]. Surgical patients with a history of HIT in whom persistence of heparin/PF4 antibodies can be safely excluded (i.e. those diagnosed with HIT >3 months before the current presentation) should receive standard prophylaxis with a compatible non-heparin anticoagulant such as danaparoid, fondaparinux, or hirudin. Patients undergoing elective hip or knee arthroplasty may also receive one of the DOACs.

Cancer Surgical Patients

Cancer surgery is associated with a particularly high risk of VTE. Consequently, when LMWH heparin is used for perioperative thromboprophylaxis, doses approved for high-risk situations should be used. For example, in an early study by Bergqvist et al. [18], a daily dose of 5,000 IU anti-Xa dalteparin over 7–10 days was as safe but significantly more efficacious in preventing perioperative VTE in high-risk surgical patients when compared to a daily dose of 2,500 IU anti-Xa, with primary event rates of 8.5 and 14.9%, respectively. Furthermore, in patients undergoing major thoracic, abdominal, or pelvic cancer surgery, who have additional risk factors for VTE such as overweight, a history of VTE, or gross residual disease, prolonged postoperative pharmacological thromboprophylaxis over ≥ 3 –4 weeks is significantly more efficacious in preventing clinically relevant thromboembolic events than standard prophylaxis over 7–10 days, and is thus recommended in clinical practice guidelines [19–21].

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