Prophylaxis Against Thromboembolism in Spinal Surgery

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18.1 Introduction and Core Messages

Venous thromboembolism (VTE) is a common and clinically serious event, with an age-related incidence that increases from circa 1 case per 1000 person-years at age 50 years to circa 5 cases per 1000 person-years at age 75 years [1].

The rationale for prophylaxis of venous thromboembolism is based on the clinically silent nature of the disease, the relatively high prevalence among hospitalized patients, and the potentially tragic consequences of a missed diagnosis [2].

18.2 Venous Thrombosis and Pulmonary Embolism (PE) [3–5]

Superficial venous thromboses cause discomfort but generally not serious consequences, as do the deep venous thromboses (DVTs) that form in the deep veins of the legs or in the pelvic veins. Nevertheless, they can progress to the deep veins through the perforator veins, or they can be responsible for a lung embolism mainly if the head of the clot is poorly attached to the vein wall and is situated near the saphenofemoral junction. Complications can arise when a venous thromboembolism lodges in the lung as a pulmonary embolism [6]. Mortality from untreated PEs was said to be 26%. Deaths that are a result of VTE/PE were shown to be the most common cause of preventable hospital deaths. Autopsy results show that as many as 60% of patients dying in the hospital have had a PE, but the diagnosis has been missed in about 70% of the cases [6]. Hospitalized patients have between a 10% and 48% chance of developing a VTE [7]. 762,000 PEs/DVTs were reported in EU in 2004 [8, 2]. The incidence of a DVT in a hospital lies between 10% and 40% for medical or general surgical patients and 40% and60% following major orthopedic surgeries [2, 8, 9].

18.2.1 Diagnostics

The diagnostics of venous thrombosis due to clinical signs and symptoms is unreliable. Therefore, instrument-based diagnostics should be carried out immediately in the case of a suspected thrombosis or embolism, in order to objectively confirm or rule out this suspicion. Depending on the issue and the assumed localization of the thrombosis (pelvis, thighs, or lower legs), these diagnostic measures include the Duplex sonography, phlebography, perfusion scintigraphy, or CT and MR procedures.

18.3 Frequency of Occurrence of the Venous Thrombosis without Medication-Based Prophylaxis and Risk Factors [5, 2–10]

In the assessment of risk factors for specific procedure or injuries, it is important to remember the multifactorial etiology of venous thromboembolism. The frequency of occurrence of a deep vein thrombosis (DVT) in the cases

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where no prophylactic treatment is performed may be low, medium, or high, depending on the scope of the medical operation, the extent of the injury, and the factors of disposition. The patients at greatest risk for VTE are those undergoing major lower extremity orthopedic surgery and those who have experienced major trauma or spinal cord injury [9, 11, 12]. The definition of risk groups for determining an indication for thromboembolism prophylaxis is crucial, taking the benefit-risk assessment into account. In addition to the risks of thrombosis due to an operation, injury, and/or immobility (expositional risks), the risk factors brought about by the patient's disposition are to be taken into consideration in order to decide whether or not measures of thromboembolism prophylaxis are required (at all) and if so which type and intensity of such measures are to be implemented. Venous thromboembolisms that have occurred previously in the patient's own medical history or in the patient's medical family history as well as the previous exposure to antithrombotic agents including possible reactions to these are of particular importance. If the patient's medical history displays a positive result with regard to the aforementioned factors, an increased dispositional risk has to be assumed, and a laboratory analysis should be considered to clarify a coagulation disorder. The dispositional risk factors for venous thromboembolism may be venous thromboembolism in the patient's medical history, congenital or acquired thrombophilic coagulation defects, malignant tumors, a pregnancy and postpartum period, advanced age, a therapy where sex hormones are either administered or blocked, chronic venous insufficiency, a severe systemic infection, overweight (body mass index <30), cardiac insufficiency, or a nephrotic syndrome. Together with the expositional risk factors, the dispositional risk factors define a patient's individual risk of thrombosis. If we take into account the previous frequency of occurrence of thromboses of patients who have been operated and/or who are traumatized, which has been determined by means of objective detection techniques, plus the additional risk constellation that is not procedure-related, patients can be classified by a low, medium, and high risk of thrombosis. Risk factors for venous thromboembolism are patient-related factors (age, previous thromboembolism, obesity, hormonal treatment, varicose veins, etc.) and procedure-related factors (total hip arthroplasty, total knee arthroplasty, plaster cast immobilization, spinal trauma, etc.). The levels of thromboembolism risk in surgical patients without prophylaxis are [2, 9] the following:

- **Low risk**: Minor surgery in patients aged <40 years with no additional risk factors
- **Moderate risk**: Minor surgery in patients with additional risk factors, non-major surgery in patients aged 40–60 years with no additional risk factors, and major surgery in patients aged <40 years with no additional risk factors
- **High risk**: Non-major surgery in patients aged >60 years or with additional risk factors; major surgery in patients aged >40 years or with additional risk factors
- **Highest risk**: Major surgery in patients aged >40 years plus prior VTE, cancer, or molecular hypercoagulable state, hip or knee arthroplasty and hip fracture surgery, major trauma, and spinal cord injury

18.4 Incidence of DVT and PE in the Population of Patients Undergoing Spinal Surgery [11, 13]

There are no accepted guidelines recommending a specific protocol for VTE prevention. It is difficult to determine the incidence of postoperative VTE in these different types of spinal surgeries. On the other side, the North American Spine Society (NASS) published an evidence-based clinical guideline on antithrombotic therapies in spine surgery. The guideline addresses key clinical questions surrounding the use of antithrombotic therapies in spine surgery [2]. The guideline does not represent a "standard of care" nor is intended as a fixed treatment protocol (Table 18.1).

In contrast to other orthopedic surgeries, in spine surgery, there is no manipulation of the limbs, where thrombosis usually originates. Major surgery or trauma of the lower extremities triggers the coagulation cascade. In these patients, a reduced venous flow and impaired endothelial function further increase the risk of developing deep vein thrombosis and pulmonary embolism [14]. Minimally invasive spinal surgery procedures, but also spinal reconstructions that are complex to some extent, possibly may have a different impact on the development of a thromboembolic occurrence. Patients who undergo spinal surgery are generally at low risk for VTE compared with craniotomy patients (Royston). Almost half of all thromboembolic events in spinal surgery occur after hospital discharge. In a study conducted by Fang et al., in 27,730 patients undergoing spinal surgery and included in the 2005–2011 ACS-NSQIP database, DVT was reported on 0.7% and pulmonary embolism in only 0.4% at 30 days postoperatively

Table 18.1 Risk factors for a DVT and PE

• Previous episode of thromboembolism.
• Prolonged immobility.
• Cancer.
• Obesity
• Pregnancy
• Oral estrogen
• Fever
• Atrial fibrillation
• CHF, shock
• Varicose veins
• Over 60 years old
• Hematologic disorders
• Trauma
• Central lines
• Dehydration
• Hypovolemia
• Surgical patients

[15]. The figures relating to the prevalence of a deep vein thrombosis or pulmonary embolism in the context of spinal operations vary between 0.63% and 33%. A clinically manifest thromboembolic complication does not seem to be common with spinal operations. Most of the prospective observational studies use an ultrasound screening with incidences between 2% and 14% of asymptomatic deep vein thrombosis in the context of different spinal surgery procedures. Since most studies were either carried out on a retrospective basis or showed a low methodological quality, risk factors can only be specified with reservations. Localization of the procedure, in particular an operation on the lumbar spine, still is the most reliably proved predictor of an asymptomatic DVT. The data with regard to the relevance of age are contradictory. Overweight, the duration of the medical procedure, the sex, and the number of days of bed rest have not shown any significant impact in the studies published so far. Although the increased thrombosis rate in the case of spinal cord injuries is well supported, no studies on spinal surgery itemizing motor deficits as a risk factor can be found. Corresponding to the inhomogeneous epidemiological data situation, there are contradictory studies relating to the benefit of thromboembolism prophylaxis. Only one relatively small randomized study compares mechanical prophylaxis to a control group without any prophylactic treatment for 50 different spinal operations. The results do not show any significant reduction of the asymptomatic rate of venous thrombosis from 25% to 8.5%. The rate of symptomatic thromboembolism did not show any significant difference. There are no meaningful studies relating to the risk of thromboembolism following spinal injuries. Nevertheless, thromboembolic complications must be taken into account, depending on the type and extent of the injury and the degree of immobility. In a prospective randomized study, in spite of prophylactic treatment with LMWH (low-molecular-weight heparin) vs. UFH (unfractionated heparin) in combination with IPC, phlebographically proven thromboses exceeding 60% in each case were reported. A combination of prophylactic treatment with physical measures seems advisable. Spinal injuries with damage to the spinal cord are listed as a contraindication for the administration of heparins by most manufacturers. This, however, is not to be considered as a prohibition. If it is possible to apply physical treatment, a decision on additional medicinal VTE prophylaxis must be made on a case-by-case basis. In the case of complete or incomplete paraplegic syndromes as a result of a spinal paralysis, a strongly increased VTE risk has to be assumed. In particular, in the case of incomplete and progressive lesions of the spinal cord and a proven intraspinal hematoma, the risk of bleeding has to be taken into consideration. TED stocking in combination with acetylsalicylic acid (SA) is an option in elective spinal surgery to decrease the incidence of thromboembolic complications [8]. Most elective spinal surgeries done through a posterior approach are associated with a low risk of VTE. Chemoprophylaxis may not be warranted as it is accompanied by a risk of serious wound and bleeding complications. In combined anterior posterior spinal surgery, LMWH or low-dose warfarin may be used postoperatively. Lee et al. [16] published a prospective study to determinate the rate of DVT following major spinal surgery without antithrombotic therapy. All 313 patients were analyzed with duplex ultrasonography. Lee et al. reported a 1.3% incidence of a DVT, with a clinically symptomatic presentation in 0.3% of patients. When interpreting the figures, it has to be regarded critically that the statistics do not include an exact figure relating to children. On the other side, Oda et al. reported a prospective study that analyzed the prevalence of DVT after posterior spinal surgery without antithrombotic therapy. He found an incidence of 15.5% DVD (lumbar 26.5%, thoracic 14.3%, cervical 5.6%) but without clinical magnification. A risk factor in the population was the period of bed rest. Patients with a spinal cord injury represent another dignity with regard to risk for VTE which is among the highest among all hospital admissions [17].The incidence of DVT and PE within 3 months is 38% and approximately 5%, respectively [18]. The hypercoagulability state induced by traumatic injury, together with other

Table 18.2 Incidence of symptomatic deep vein thrombosis in the general population

Author	Population	Type of study	TVL/LE rate
Glynn et al., 2007 [6]	39,876 women, >45 years	Randomized, controlled study	TVL-0.12%
Naess et al., 2007 [22]	94,194 Norwegians, >18 years	Population-based, retrospective cohort study	TVT-0.093%; LE-0.050%
White et al., 2005 [23]	23.3 m, >18 years	Population-based, retrospective cohort study	TVT-0.093%
Oger et al., 2000 [14]	342,000 Frenchmen/Frenchwomen, >18 years	Population-based, retrospective cohort study	TVT/LE-0.124%
Silverstein et al., 1998 [24]	106,470 Americans, >18 years (1966–1990)	Population-based, retrospective cohort study	TVT/LE-0.117%
Nordström et al., 1992 [19]	366 Swedes, >18 years	Population-based, prospective cohort study	TVT-0.16%
Anderson et al., 1991 [25]	379,953 Americans, >18 years (1985–1986)	Population-based, prospective cohort study	TVT/LE-0.107%

factors such as obesity and prolonged immobilization, increases the VTE risk in patients with spine injuries [19] (Table 18.2).

The European guidelines on perioperative venous thromboembolism prophylaxis (ESA VTE Guidelines Task Force [20]) suggest for patients undergoing spinal surgery with no additional risk factors and no active thromboprophylaxis intervention apart from early mobilization. For patients undergoing spinal surgery with additional risk factors, the group recommends mechanical thromboprophylaxis, and the group suggests the addition of LMWH postoperatively when the risk of bleeding is presumed to be decreased [4].

18.5 Thromboembolism Prophylaxis

Thromboembolism prophylaxis may be provided by basic measures, based on physical and medication therapy.

18.5.1 Basic Measures and Physical Thromboembolism Prophylaxis

Basic measures are early mobilization; the provision of a critical diagnostic evaluation of measures that are immobilizing the patient, in particular with regard to the ankle and knee joint and to the pelvic region; requesting and instructing the patient to do exercises on his/her own muscle pump; reduction of the period of immobility; early operation, in particular in the case of injuries of the lower extremities, the pelvis and the thoracic spine and lumbar spine; and cardiovascular and respiratory therapy.

Some mechanical methods such as graduated stockings, foot pumps, and calf compressors have a good evidence base with studies showing a consist reduction in thrombosis. The ideal role is in conjunction with, rather than in competition with, chemical methods.

Physiotherapy, compression stockings, and early mobilization provide the basic measures which, however, cannot replace an indicated medication-based thromboprophylaxis. On the other hand, the basic measures are always additionally required if a medication-based thromboprophylactic treatment is performed. Both procedures complement each other to form an effective prophylaxis. Measures to prevent thromboses are active and passive movement exercises such as a bed pedal exerciser, a continuous passive motion device for mobilizing the ankle joint, and carefully fitted compression stockings (thigh-length/half stockings). Mechanical compression devices in the lower extremities are suggested in elective spinal surgery to decrease the incidence of thromboembolic complications.

18.5.2 Medication-Based Thromboembolism Prophylaxis [21]

The world of antithrombotic prophylaxis is a revolutionary phase due to the introduction of numerous compounds in the daily practice. Heparins are pharmaceutical products for medication-based thromboembolism prophylaxis (unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs)), but also with a sufficient or insufficient impact on thromboprophylaxis, and substances such as danaparoid, fondaparinux, thrombin inhibitors, hirudin, vitamin K antagonists (coumarins), and platelet inhibitors. These drugs, however, may involve increased bleeding complication following medical measures and in particular after surgery. When bleeding complications occur while medication-based thromboembolism

Table 18.3 Frequency of occurrence of deep vein thrombosis in operative medicine without medication-based prophylaxis in compliance with the International Consensus, 2001

	Studies, *n*	Patients, *n*	TVT, %	95% CI, %
Abdominal surgery	54	4310	25	24–26
Retropubic prostatectomy	8	335	32	27–37
Transurethral prostatectomy	3	150	9	5–15
Gynecology				
Malignant tumor surgery	4	297	22	17–26
Benign disease	4	460	14	11–17
Elective hip replacement	17	851	51	48–54
Multiple traumas	4	536	50	46–55
Knee replacement	7	541	47	42–51
Hip fractures	16	836	45	41–48
Neurosurgery	5	280	22	17–27

prophylaxis is performed, apart from the possibility of a surgical bleeding, also a drug accumulation, for example, renal insufficiency or wrong dosage of drugs, must be taken into consideration and must be clarified by laboratory tests. In order to ensure expedient diagnostics, for unfractionated heparins and thrombin inhibitors, the measurement of the aPTT (activated partial thromboplastin time) and for low-molecular-weight heparins, danaparoid and fondaparinux, and determination of the anti-Xa activity or performance of the HEP test are required. The intensity of the anticoagulation with vitamin K antagonists is recorded by the determination of the INR. If serious bleeding complications occur while prophylactically dosed anticoagulants are administered, the dose of anticoagulants has to be reduced or the treatment has to be interrupted, and in the case of pathologically altered coagulation tests under UFH or LMWH, antagonization by means of protamine has to be taken into consideration (Table 18.3).

18.5.3 Heparins

Heparins are mucopolysaccharides, the anticoagulative potential of which is mainly unfolded by potentiating the antithrombin effect. They are extracted from the pig's intestine mucosa. Various fragmentation processes generate low-molecular-weight heparins.

18.5.3.1 Unfractionated Heparin (UFH)

The subcutaneous administration of UFH two or three times a day ("low-dose heparin": 2–3 × 5000 or 2 × 7500 IE/day) is effective for patients with a medium risk of thrombosis. This form of prophylaxis is to produce a thrombosis reduction in general surgery from approximately 30% to 5–15% and in trauma surgery from approximately 50% to 25–30%.

18.5.3.2 Low-Molecular-Weight Heparins (LMWHs)

Thanks to their improved pharmacological properties, a reduced incidence of undesirable effects compared to UFH, and their antithrombotic efficiency as well as a high practicability, LMWHs provide advantages compared to UFH. The low-molecular-weight heparins are not a homogeneous substance group. They feature different antithrombotic efficiencies and dosage recommendations. Low-molecular-weight heparins display a lower risk of heparin-induced thrombocytopenia (HIT) than unfractionated heparins. There are various undesired drug effects with the application of heparin. There are two forms of heparin-induced thrombocytopenia (HIT): heparin-induced thrombocytopenia type I (HIT I) and heparin-induced thrombocytopenia type II (HIT II). The thrombocyte decrease in the case of HIT I is low to medium, temporary in most cases, and clinically irrelevant. It occurs a few days (1–3) after the start of the treatment and only rarely reaches a value of <100,000/µL. With HIT I, an interruption of the heparin treatment is not necessary, as the number of thrombocytes will increase again during the next days, even if the treatment with heparin is continued. HIT II, an immunologically mediated form of thrombocytopenia, is a dangerous complication of the heparin application which may involve venous and/or arterial thromboembolism. With the administration of unfractionated heparin, in approximately 10% of the cases, patients undergoing extensive surgical and/or orthopedic procedures have the risk of antibodies; in up to 2–3%, they suffer the risk of thrombocytopenia (HIT II). When low-molecular-weight heparin is administered, these risks are much lower. With HIT II, the decrease in thrombocytes usually occurs between the 5th and the 14th days, more rarely up to the 21st day after the initial application. The numbers of thrombocytes often drop below 80,000/µL or below 50% of the initial value. Checking the characteristic of the number of thrombocytes, in particular between the 5th and the 21st days of the heparin administration, is recommended. With the long-term use of UFH at a dosage of 15,000–30,000 IE/day, more rarely in the case of LMWH, exceeding 4–6 months, it is known that osteopenia may occur.

18.5.3.3 Danaparoid

Danaparoid is a heparin-free heparinoid that is also extracted from the pig's intestine mucosa and that has an anticoagulatory effect. It is an effective form of the medication-based thromboembolism prophylaxis in situations in which the use of heparins is not permissible or not possible.

18.5.3.4 Fondaparinux

Fondaparinux is a pentasaccharide that is produced synthetically, inhibiting antithrombin-mediated factor Xa. In the elective (hip replacement and knee replacement) and non-elective (hip fracture) high-risk surgery, in clinical studies at a dosage of 2.5 mg/day s.c., fondaparinux has proven to be antithrombotically superior compared to low-molecular-weight heparin. Prophylactic treatment with fondaparinux is started 6 h after the end of the operation. Under the influence of fondaparinux, neither heparin-induced thrombocytopenia (HIT II) was observed, nor a cross-reactivity with plasma of patients with HIT antibodies was proved.

18.5.3.5 Thrombin Inhibitors

In addition to the direct (i.e., effective without mediation by antithrombin) thrombin inhibitor hirudin, low-molecular-weight, also directly acting thrombin inhibitors are tested in clinical studies (e.g., melagatran/ximelagatran). They can also be administered orally. During hirudin treatment (2 × 15 mg/day s.c.), patients with an elective hip replacement showed substantially less deep vein thrombosis with a comparable risk of bleeding than under the influence of UFH or LMWH. Due to the missing cross-reaction with HIT type II antibodies, hirudin is used in particular for the medication-based thromboembolism prophylaxis for patients with HIT II.

Oral anticoagulants (vitamin K antagonists—coumarins), warfarin, and other vitamin K antagonists of the coumarin type are effective means for the perioperative prophylaxis of venous thromboembolism for patients with a medium or high risk. Due to the required laboratory tests (INR) and the increased risks of bleeding, in Europe, vitamin K antagonists are hardly used perioperatively; however, they are occasionally used for long-term prophylaxis (INR 2.0–3.0). For patients with a low risk of thromboembolism, physical measures and measures to quickly mobilize the patients again can be considered sufficient. For patients with a medium risk and, in particular, with a high risk of thromboses, in addition to the physical measures and measures to quickly mobilize the patients, a medication-based thromboprophylaxis is indicated. In contrast to North America, in Europe, the medication-based thromboembolism prophylaxis is usually started perioperatively or as soon as possible after a trauma. Fondaparinux is generally only administered postoperatively. Today, patients are often discharged early from inpatient care after operations or after a trauma. If there are relevant risk factors of venous thromboembolism that are still remaining after the hospital discharge, a post-hospital prophylaxis should be taken into consideration. For patients with a total hip endoprosthesis and hip fracture and following extensive operation of malignant tumors in the field of abdominal surgery, clinical studies have shown the benefit of a 4–5-week medication-based thromboembolism prophylaxis, so that prophylactic treatment that has been started in the hospital should also be continued as outpatient treatment on a case-by-case basis. The doctor responsible for further treatment has to be informed about the necessity of the prophylactic treatment. The present results of the clinical studies are not sufficient yet to allow for a generally binding recommendation regarding the duration of the medication-based thromboembolism prophylaxis. This duration depends on additional dispositional risk factors, the surgical trauma, and the degree of immobility.

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