Prevention of Venous Thromboembolism

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Introduction

Venous thromboembolism (VTE), which can present clinically either as deep venous thrombosis (DVT) or as pulmonary embolism (PE), is observed quite frequently, often complicating surgery. In orthopaedic and trauma surgery it has been estimated that, without anti-thrombotic prophylaxis, the rate of DVT was 45%–57% (23%–26% proximal) in total hip replacements, 40%–84% (9%–20% proximal) in total knee replacements, and 45%–50% in proximal femoral fractures [1-3]. An accurate evaluation of the incidence of VTE in patients with lower limb fractures or soft tissue injuries is difficult at the present time, due to the lack of research on this topic. A reliable estimate of VTE incidence in lower limb fractures is 6%–45 % (4%–8% proximal). Exact data on the frequency of VTE in upper limb fractures are not available; nevertheless, the risk of PE in conjunction with DVT of the upper limb is considerable. With regard to the injuries of the soft tissues, such as tendons, it has been calculated that the DVT rate in these injuries is about 50% of the rate in bone injuries [3].

DVT must be rapidly diagnosed, not only in order to establish a suitable therapeutic strategy in the acute stage but also to prevent relapses and further complications. Without adequate and rapid medical treatment, the risk of relapse seems to be 40% in the first month after the primary event and 10% during the second and the third month [4].

Since a possibly fatal PE can follow DVT, it is mandatory that the clinical clues of such a disease not be underestimated. Edema, more or less associated with skin color alterations and pain (described sometimes as cramp and sometimes as heaviness and which increases upon local pressure) actually are not signs or symptoms specific for DVT; in fact, they can obscure a vascular disease of different origin, for example, superficial thrombophlebitis, lymphedema, or vasculitis. They can also be the expression of orthopaedic diseases such as stretching, muscular, or tendon ruptures or rupture of a synovial cyst [5].

However, these symptoms become increasingly significant in the presence of risk factors predisposing to thrombotic events by themselves.

Risk Factors

Among the so-called permanent risk factors (i.e., risks always present even without clinical evidence) are congenital factors such as anti-thrombin III, protein C, and protein S deficits. Anti-thrombin III deficit seems to be related more to venous thromboembolic risk than the two others. Homozygous carriers of protein C or protein S deficit are susceptible for severe clinical diseases, such as porpora fulminans, whereas heterozygous carriers can suffer DVT episodes before 45 years of age even at uncommon sites such as upper limb veins.

Other congenital risk factors include mutation of the Leiden factor, which is responsible for protein C-activated resistance, and mutation of prothrombin G20210A, which determines a 30% increase in circulating prothrombin.

Age, neoplasms, anti-phospholipid antibodies, and previous episodes of DVT represent permanent, acquired risk factors.

Moreover, in some clinical cases the thromboembolic risk is hardly detectable, such as in cases of hyperhomocysteinemia, hyperfibrinogenemia, and an increase in factor VIII, IX, and XI levels.

Among the most easily detectable transient risk factors are surgery (mainly orthopaedic surgery or neurosurgery), multiple trauma, prolonged immobilization, pregnancy, and oral contraceptive use [4].

Instrumental Diagnosis

If clinically suspected, especially in patients in whom these factors have been detected, further investigations are indispensable for a detailed diagnosis and an appropriate therapy. The significance of the investigations depends on the anamnestic and clinical data in combination with the evidence for risk factors: an accurate study of these parameters is required for a precise diagnosis and appropriate therapeutic procedure.

By scoring the symptoms, clinical signs. and other possible diagnoses the patient can be classified as being at clinically low, medium, or high risk for DVT [5–7].

Venous Doppler Ultrasonography (DUS), hematological investigations, and contrast venography are the instrumental investigations commonly used for diagnosis. A different role is played by impedance plethysmography, angio-CT scan, and angio-MRI.

DUS, which demonstrates the venous system through high-resolution ultrasonography, is the most universally accepted test for the diagnosis of proximal DVT of the lower limbs [8]. This examination is fast, inexpensive, and, most importantly, harmless, and because of these features it can be repeated soon, if necessary. In this test the probe is put on the common femoral vein, at the inguinal ligament level. Then it is moved distally along the superficial femoral vein path; at the back of the knee joint, the popliteal vein is followed until it trifurcates into anterior and posterior tibial veins and peroneal vein.

The venous areas are examined with the patient in different positions. The diagnostic criterion is the lack of compressibility of the vein's lumen under probe pressure: if the vein is compressible, its walls collapse and it does not contain a thrombus. Venous compressibility, better detectable in transverse scans, is difficult to perform at some sites (superficial femoral vein in the Hunter canal and deep femoral vein) for anatomic reasons. However, the introduction of color Doppler and power Doppler ultrasonography has improved the diagnostic accuracy even at those sites. The quality of the examination at distal sites closely depends on the operator and on employing adequate instruments.

For hematological investigation in suspected DVT the D-dimer levels are evaluated (products of stabilized fibrin degradation) [9]. A high level of D-dimers is nevertheless not highly specific for thrombosis since it can be detected in many other conditions, too (neoplasm, IMA, infections, and surgery). Therefore the levels of those substances is more significant for excluding thrombosis when the value is normal rather than confirming it when the value is high.

Contrast venography is performed by injecting contrast medium into a superficial vein of the back of the foot. Then, numerous radiograms of the limb are taken in different positions [8, 10]. An alternative procedure uses a tourniquet at the limb root, making it possible to adminster a lower quantity of contrast medium. Compared with the other technique, however, it is less accurate in visualizing gastrocnemius veins and anterior tibial and deep femoral veins.

The presence of a thrombosis is identified by a defect in lumen filling, evident in each projection. The sensitivity of this technique is 100% for lesions of 0.5 cm or more in diameter. In spite of the high resolution and accuracy of this procedure, venography has many limitations, related to the cost and the invasiveness of the technique, which can also be painful and involve complications.

Immediate side effects, whose incidence varies according to the contrast medium concentration and quality, are mostly minor reactions such as nausea, vomiting, and itching, sometimes associated with skin reactions; less frequently systemic complications such as anaphylactic reactions occur, which

can cause heart arrest. Some cases of PE developing during venography have been reported, due to thrombus mobilization. The delayed side effects include postphlebitic syndrome, characterized by pain, warmth, and edema of the proximal calf and which resolve in few days, or a true thrombophlebitis, usually at the leg veins. For these reasons, in spite of the high resolution and accuracy, contrast venography cannot be considered the examination of choice.

Among the instrumental investigations, impedance plethysmography plays a particular role. Plethysmography records blood volume alterations inside the leg veins [11, 12]. The examination is performed by placing electrodes sensitive to this parameter at the site. A tourniquet is then inflated at the limb root to stop the venous blood flow and then deflated to restore the flow. In normal limbs the blood stagnation produced during the early stage creates an increase in blood volume, which rapidly decreases as soon as the tourniquet is deflated. If there is a thrombosis in the thigh, the volume increase is slower because the flow is already congested due to the thrombus and the emptying of the calf will be slower as well.

Plethysmography cannot detect most of the isolated thrombi: its sensitivity was evaluated at 95% in the 1970s and 1980s but now has been reduced to 70%. Therefore this technique has now been almost completely abandoned [5].

From the radiological point of view, angio-CT scan and angio-MRI play a very important role because they offer undoubted advantages to traditional phlebography. With these techniques, sites formerly difficult to investigate can be visualized, reducing side effects thanks to the very low quantity of contrast medium employed and obtaining very good results in terms of sensitivity and specificity. The limitations of these techniques are related to costs and high radiation exposure of the angio-CT scan [4].

As already mentioned, the choice of the instrumental investigation and its predictive value change according to the combination of clinical data and evidence of risk factors. In patients showing signs and symptoms of DVT, the first choice is DUS. If findings are positive, a diagnosis is made and it is necessary to initiate adequate therapy. If the DUS findings are negative, clinical data are not significant, and there are no associated risk factors, this examination must be repeated within 5–7 days if symptoms get worse. It is important to remember that a distal DVT becomes proximal in 30% of cases in about 1 week, and thus it can be better assessed by DUS. If, otherwise, clinical evidence is strong and associated risk factors are present, the use of an aggressive means of investigation such as phlebography is justified from the start because it provides a definite diagnosis.

Whereas phlebography, due to its typical features, is performed just once, DUS can be repeated to monitor DVT development until total vessel recanalization or stabilization of the thrombus dimensions has been achieved.

These data are important to determine the duration of anticoagulant therapy; moreover, they are indispensable in cases of suspected DVT relapse, which should be documented by the presence of a new thrombus (in case of a previously negative DUS) or by increased dimensions (of at least 4 mm) of a known thrombus [4].

Therapy

Once DVT is diagnosed, adequate therapy must be established as quickly as possible to prevent thrombus enlargement, detaching of emboli, and distant complications. Treatment is based on drugs interfering with coagulative mechanisms such as unfractionated heparin (UH), low-molecular-weight heparins (LMWHs), oral anticoagulants, and use of fibrinolytics and caval filters [4]: the two latter methods will not be discussed here.

Unfractionated heparins are composed of a heterogenic mixture of polysaccharide chains of different molecular weights of between 6,000 and 30,000 Daltons. Heparin directly interferes with coagulation, by locking a plasmatic factor (ATIII) and therefore inactivating the FXa and FIIa (thrombin) [13]. The two main activities of UH are performed by polysaccharide chains of different length: low-molecular-weight chains in particular are enough to obstruct FXa action, while heavier molecular chains are required to inhibit thrombin.

The anticoagulative effect, monitored by the aPTT dosage, is obtained when scores are 1.5–2.5 times the basal rate. LMWHs are derived from heparin digestion by chemical or enzymatic means and have a relatively low molecular weight, between 3,000 and 8,000 Daltons [14]. Their anticoagulative effect is a result of a link with ATIII producing an anti-Xa effect similar to that of heparin. However, because of the different molecular weights, they have a reduced anti-IIa activity.

LMWHs have a limited plasmatic protein link, which improves their bioavailability at low doses, makes the anticoagulant action predictable, and enables a once daily administration, without monitoring.

The use of LMWSs, even if prolonged, is associated with a lower rate of plateletpenia and osteoporosis than the use of unfractionated heparin. These features are common to all LMWHs, although they differ in average molecular weight, specific anti-Xa and anti-IIa activity, and anti-Xa and anti-IIa rate.

Oral anticoagulants interfere with vitamin K metabolism, inactivating the vitamin K-dependent coagulation factors (II-VII-IX-X). The most commonly used drugs of this family are warfarin and acenocumarol, which have different pharmacokinetics but not different clinical effects. Although oral administration makes these drugs easy to use, the individual variability in anticoagulative effect requires accurate and prolonged monitoring and exact thera-

peutic adjustment of the drug. The prothrombin time (PT) must be determined, which is sensitive to the reduction of only three of the four vitamin K-dependent coagulative factors, but not to factor IX variations.

Since the therapeutic effect is evident when all the factors are inactivated, variations in PT are not a reliable measure of anticoagulant efficacy in the early stages of therapy. Moreover, its value can vary according to the reagent employed in the laboratory test. This problem was resolved by the introduction of a standardized system called INR (International Normalized Ratio). In most cases, therapy is considered effective at INR values of between 2.0 and 3.0 [6, 15].

DVT therapy is based on the inhibition of coagulation mechanisms. Since oral drug efficacy is evident a few days after beginning treatment, the antithrombotic effect is initially obtained with simultaneous heparin administration and then maintained until the therapeutic anticoagulant levels have been reached (INR 2–3); heparin is generally administered for 5–7 days.

Until recently, heparin was given intravenously with frequent aPTT dosages; that is why DVT therapy was performed exclusively under hospitalization in the past and was only continued at home after therapeutic dosages had been reached.

Since the efficacy of UH and LMWHs has been demonstrated to be similar, the therapy can also be given to patients at home in the early phases of DVT, using subcutaneously administered LMWHs until INR therapeutic levels have been reached using the oral anticoagulant drug [15].

The therapy must be continued for a variable period of time (depending on whether it is the first episode or a relapse, and on the presence or absence of risk factors), but for at least 3 months and at most 12 months, or forever in cases of relapsing idiopathic DVT or in individuals with persistent risk factors.

In some exceptional cases, in which it is impossible to use oral anticoagulant therapy, LMWHs at therapeutic dosage are employed for the period mentioned above. DVT therapy is crucial to prevent immediate and delayed complications such as PE and fatal PE, relapses, and postphlebitic syndrome.

Prophylaxis

Prophylaxis is as important as therapy itself. Epidemiological studies, which have demonstrated the high incidence of the disease, and the fact that the disease is silent in the early stages represent the rationale for prophylactic measures in patients at risk.

In orthopaedic surgery prophylaxis consists of early mobilization, use of elastic stockings with graduated compression, and intermittent pneumatic

compression. Such measures can represent the only prophylaxis in some kinds of surgery, but more invasive orthopaedic surgery requires drug therapy [6, 15].

LMWHs are very effective in reducing the risk of DVT, with a lower risk of major bleeding than UH [16]. A major bleeding is clinically evident and associated with a decrease of at least 2g/dl of hemoglobin and requires blood transfusion. It may be subperitoneal or intracranial or located in critical organs, or it causes death of the patient.

A minor bleeding such as epistaxis or macrohematuria is not associated with the features mentioned above.

Various LMWH belong to a homogeneous drug group, but differ from each other in molecular weight, bioavailability, and antiXa-IIa rate. These differences determine their differing efficacy and safety profiles.

Studies conducted on the use of LMWHs in orthopaedic surgery have shown them to be superior to UH in reducing both thromboembolic events and major bleedings; however, definitive data to help distinguish between the different LMWHs are lacking. Some clinical randomized trials defining symptomatic DVT relapse as an endpoint compared safety and efficacy of subcutaneously administered enoxaparin and nadroparin with intravenous UH in patients affected by proximal DVT. In both cases LMWHs were demonstrated to be as effective and safe as UH. Reviparin sodium and parnaparin also showed good efficacy and clinical tolerance. The dosages are different according to the molecule and (in some cases) to the weight.

Among the new anti-thrombotic drugs, those that were most highly developed in clinical phase III trials are fondaparinux (synthetic pentasaccharide, which specifically links anti-thrombin, improving its Xa factor inhibition capacity) [17], and the oral thrombin inhibitors (synthetic molecules, among which the most studied is melagatran, a direct inhibitor of thrombin active site, can be administered orally every 12 h at fixed dosages) [18].

Fondaparinux can be administered subcutaneously; it has a plasmatic half-life of about 17 h and thus can be given daily. Specifically, among the drugs commonly used, fondaparinux can be given for prophylaxis but does not seem to be indicated for DVT long-term therapy. Here, melagatran seems to be more promising [19].

A discussed problem is the duration of administration, particularly in patients who have undergone subarachnoidal anaesthesia. The American College of Chest Physicians (ACCP) recommendations [2] call for particular attention to patients whose history reveals coagulation alterations or bleeding risk factors. In these patients, in case of spinal anesthesia, anti-thrombotic administration may cause hematoma and bleeding that may lead to neurological deficits (sometimes permanent).

Since the risk seems to be related mainly to the procedures of placing and removing the catheter, regional anesthesia should be considered for both pre-

and postoperative prophylaxis, provided that the time of drug administration is far enough from such manuevers.

As for the duration of prophylaxis, it is necessary to remember that some patients may develop a DVT after discharge. Therefore, it is useful to continue the prophylaxis for a sufficient time and corresponding to the kind of surgery [19].

According to the most recent recommendations of the American College of Chest Physicians [2], in patients who are candidates for a total hip replacement or total knee replacement, prophylaxis must be started with LMWHs at full dosage 12 h before surgery or 12–24 h after surgery, or 4–6 h after surgery at half dosage and at full dosage from the day after.

An alternative may be to start the administration of fondaparinux 6–8 h after surgery or the administration of vitamin K antagonists, whose dosage must maintain the INR at 2.0–3.0, in the preoperative period or on the evening of the day of surgery.

As for the prophylaxis duration, there is near consensus that it must be continued until the patient can move by himself, i.e., for a period of about 4–6 weeks.

For the so-called minor orthopaedic surgical procedures, which involve patient immobilization, guidelines are not as accurate; in any case, there are sufficient indications to suggest the use of LMWHs for at least 2 or 3 weeks or until the patient can move by himself [2].

Finally, even respecting the guidelines, it would be useful for all clinics to develop personal multisubject operative procedures, based on wise preoperative study of the patient and in consideration of all the possible human and technical resources to optimize the diagnostic-therapeutic course.

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