

Problematic issues surrounding deep vein treatment

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Abstract. Deep vein thrombosis (DVT) considered as a severe clinical problem. It caused by the formation of thrombi in deep veins, particularly in the lower limbs. Confirmation of DVT involving the use of Wells score, d-dimers examination and venous compression ultrasound. Anticoagulation proved to decrease mortality rate along with thrombus progression. However, despite major advances, clinician in daily care still poses various issues regarding optimal and best treatment for DVT patients. Anticoagulation (AC) is the backbone for the treatment during all phases of DVT treatment (acute, short term and long term) with the goals is to prevent thrombus progression and DVT complications. Unfractionated heparin (UFH) or low molecular weight heparin (LMWH) commonly used for in-hospitalized patient due to their short duration of action and anticipated antidote availability. Direct oral anticoagulants (DOACs) are also an option for the treatment of DVT patients. DOACs are preferred because they do not require monitoring and more practical in daily care. Furthermore, DVT in obese patients possess unique challenges to clinicians. Difficulty also exist in prescribe treatment for obese patient in term of appropriate dose of LMWH. The same also goes for cancer patients with thrombosis. It should be noted that all cancer-associated thrombosis (CATs) are different therefore, the optimal anticoagulant type, duration, and intensity for the treatment of CAT should probably be individualized. Travel-related DVT has been supported by scientific studies however, more aspects must be understood in order to present more accurate advice for travelers.

1. Introduction

Deep vein thrombosis (DVT) is a severe clinical entity characterized by the formation of thrombi in deep veins, notably in the lower limbs which consist of 80-95% cases. Inaccurate diagnostic or undertreatment for DVT or PE can have fatal complications. Frequent symptoms of DVT patients being presented are pain, swelling, and venous stasis. Some other less specific conditions may also present, such as hematoma, infections, joint and muscle injuries, and chronic joint disorders that made clinical examination alone is not enough to confirm the diagnosis or to exclude DVT patients [1,2]. Patients with 2003 version simplified Wells score of <2 points have a low probability of having DVT, and with ultrasound examination, only 5% of patients were found to have the disease [1,3]. If the Wells score is more than 2 and an elevated d-dimers, compression ultrasound is performed. When the patient has a low Wells score and negative d-dimers, DVT could be excluded, and ultrasound examination would be redundant in the diagnostic workup [4]. However, those with a Wells score of more than 2 and those with low Wells score but abnormal d-dimer must be directed for venous compression ultrasound. Once the patient confirmed with DVT, anticoagulation is the mainstay and is undisputed [1]. Several studies have proved that anticoagulant effectively reduces mortality rate as well as thrombus progression.



Despite major advances, clinician in daily care still poses several problematic issues regarding optimal and best treatment for DVT patients.

2. General consideration for DVT

Due to several DVT complications changes over time the knowledge of treatment phases for DVT patients is essential for making the correct option regarding timing and type of anticoagulation, for thrombophilia testing [1]. Before diagnosis can be made definitely with the suspicion of DVT, therapy for DVT is warranted until the diagnosis is made or ruled out. Once the diagnosis of DVT established an initial treatment phase starts and lasted for 5–10 days' post-diagnosis. Then continue with maintenance therapy or early secondary prevention. Maintenance phase lasts for three months following the initial therapy. Extended secondary prevention treatment phase starts three months after diagnosis, and the phase is slightly different among centers and across the DVT patients [1].

Anticoagulation (AC) is the backbone for the treatment throughout all phases of DVT treatment (acute, short term, and long term) with the goals is to prevent thrombosis progression and DVT complications. Now, there are several therapeutic options available to the clinician for anticoagulation therapy. Unfractionated heparin (UFH) or low molecular weight heparin (LMWH) are usually used in hospitalized patient due to their short duration of action and anticipated antidote availability. Another option for the treatment of DVT patients is Direct oral anticoagulants (DOACs). DOACs are preferred since they do not need monitoring and more practical in daily care. Thrombolytic therapy is specifically used for acute extensive proximal lower extremity DVT (phlegmasia cerulea dolens) or patients with anticoagulation failure [1,5]. Systemic thrombolytic therapy is usually reserved for patients with massive pulmonary embolism. Vena cava filter can be considered in patients at risk for PE if DVT patients are not suitable for anticoagulation because of contraindication or having high risk of bleeding [5].

It is recommended that DVT treatment should be individualized since different option of therapy available to meet specific clinical circumstances and patient preference and value [5].

2.1. Distal DVT

There is no absolute agreement regarding management of distal DVT which differs among centers and represents a major challenge. A group of experts agrees that all patients with distal DVT should be treated while others believe that a select of patients can avoid anticoagulation. A large study performed to assess whether available data could support either group and the research confirm the lack of scientific evidence supporting whether anticoagulation or no anticoagulation is preferred for distal DVT. American College of Chest Physicians, Australian Society of Thrombosis and Hemostasis, and the British DVT consensus group) have recommended anticoagulation for distal DVT. However, observation and duplex surveillance remains a commonly practiced in daily care in certain centers. A review supports this practical approach that in the lack of concrete evidence to support anticoagulation over imaging surveillance, either method must remain as current acceptable standards [6]. In specific condition distal DVTs resolve spontaneously without and at lower risk of embolization (approximately half the risk) than those with proximal DVT [7]. Also in many ways, distal DVT behave differently than proximal DVT, and this partially explains differences in manage patient with distal DVT. Distal DVT has a lower PE risk due to less propagates to proximal and also less likely to cause PTS [8]. Nonetheless, some studies reported that distal DVT with cancer was associated with propagation, whereas transient risk factors such as recent surgery and trauma were not; prior venous disease, cardiac disease, and hypercoagulable states were also not associated. However, when the decision is made, full therapeutic anticoagulation should be administered similarly to those with proximal DVT.

2.2. DVT in obese Patients

Improved awareness of VTE has enhanced the outcome in most patients with the condition. Clinical suspicion is critical in VTE diagnosis and treatment of obese patients with body mass index (BMI) >30 kg/m². Thus, in obese patients with body mass index (BMI) >30 kg/m², can present some unique challenges to clinicians [9]. Symptoms and signs of DVT in obese such as leg swelling and discomfort

as well as shortness of breath may not be valuable clinical features due to in part of the physiological changes linked to the increased BMI. Pulmonary function test profile of 63 obese individuals without underlying respiratory disease study identified two separate groups, one with significantly lesser lung function parameters and another group with normal values [9,10]. The study above shows that some obese patients may have peripheral airway disease that may be caused by higher BMI. Difficulty in prescribing treatment for an obese patient is in determining an ideal dose of LMWH. Dose capping has been recommended for some preparations which may result in under-dosing for obese patients. No available guidelines state dose recommendation for anticoagulation but expert opinion would recommend dosing patients on actual body weight [9,11,12]. Some studies have been published with those with BMI 30-40 kg/m², but there is no data in the morbidly obese patients (>40 kg/m²), which is also urgently needed [13]. Experts recommend close monitoring of anti-Xa levels, since this procedure has the theoretical disadvantage of causing drug accumulation [9].

2.3. DVT in cancer Patients

CAT (cancer-associated thrombosis) is associated with increased risk of mortality in cancer patients and often affects chemotherapy schedule [14,15]. CAT is more challenging to treat and have a higher risk of complications including recurrent CAT and major bleeding compared to patients without cancer [16]. Another abnormality that often encounters in CAT either due to chemotherapy-induced or myelosuppression. These thrombocytopenic patients pose clinicians with difficulty; whether to treat patient with anticoagulant where bleeding risk is increased or not, proper decision should be based on the severity of the CAT, duration of anticoagulation, level of thrombocyte as well as the availability of corrected measures. Despite major advances on CAT, some important knowledge gaps remain unresolved and deserve more attention. Such as the knowledge that not all CATs are the same due to differences in risk factors (e.g., hospitalization, surgery, central venous catheters, and so on) and various tumor types and stages. Cancer characteristics, the presence of additional risk factors, and underlying risk of future recurrent events all must be determined before decision being made to choose the optimal anticoagulant type (LMWH vs. DOAC vs. VKA), duration (i.e., short-term vs. indefinite), and intensity for the treatment of CAT. Every decision should probably be personalized and tailored to individual patients based on patient preferences and value. Patient with high risk for recurrent CAT and low risk should be treated. A risk stratification model is needed and be validated [17,18]. CATCH trial was unable to accurately confirm the clinical predictive model [19,20]. Biomarkers such as C-reactive protein, D-dimer and, factor VIII, tissue factor, and serum P- [21]. Prothrombin F1 + 2, D-dimer, and soluble P-selectin have been studied More studies are needed to focus on the risk factors and the stratification of the underlying risk for recurrent events and major bleeding for patients with CAT to personalize and facilitate anticoagulation decisions in this patient population. Anticoagulation for CAT should be treated with LMWH [22]. However, NOAC should be discussed with the patient since LMWH offers inconvenience for long-term phase. For patients not willing to tolerate LMWH injections in the maintenance phase, the same holds true. Whereas no specific NOAC trial for cancer-associated DVT has been done so far, the standard of care for the acute and long-term management of CAT is LMWH. Although the use of DOACs is attractive to clinicians, their use is discouraged until large randomized controlled trials are completed to compare DOACs to LMWH for this indication [1].

2.4. Travel-associated DVT

The term “economy class syndrome” invented by Cruickshank in the past. It was designed to describe travel-associated DVT when six case reports were being described by him. However, the term “traveler’s thrombosis” should be used, based on the Aerospace Medical Association’s Air Transport Medicine Committee [23]. Several conducted researches found that long term trip risking the travelers, regardless of what type of travel they use.

Furthermore, travel-associated DVT no longer is considered a scenario blown-up by media. It has been estimated that after flight of more than four hours, the incidence of DVT is 1 in 4656, while for more than eight hours flight, it is estimated as 0.5% in low and intermediate risk travelers. It should be

noted that the trip duration considered as the most important risk factor. For travel by air, the period of 4-8 hours and 8-12 hours may enhance the incidence of VTE by two-fold. Traveling for 12-16 hours related to the incidence rate ratios of 5.3 (95% CI 2.3-12.4) and traveling of > 16 hours is 5.7 (95% CI 2.0-16.5). Previous research found that the risk to develop travel-associated DVT remain significantly increase only for 4-8 weeks after traveling, and therefore travel-associated DVT should become as a diagnosis if it happens during this period. The occurrence of other concomitant risk factors associated with the increase of risk for air travel-associated DVT [24]. It should be noted that although the British Journal of Haematology has recommended guideline on travel-associated DVT [25], this condition needs further exploration to understand the pathophysiology of travel-associated DVT. This also could be used to present better preventive recommendations. For 'healthy' travelers, the risk to develop DVT after the long-distance journey is very low. Other risks may increase the chance for the traveler to suffer DVT. Travel-related thromboembolism remains as controversy, majorly when considering screening for lots of passengers, and subsequent prophylaxis, in which the side effects still has a potential to occur for long-distance travelers. For the time being, DOACs, as oral thromboprophylaxis, is not recommended until further investigation conducted.

2.5. *Thrombolysis for DVT*

Pathogenesis of venous thrombosis related with the defect on the venous valve, in which early deposit of thrombus may develop. Therefore, it is suggested that rapid removal and effective removal of acute thrombi, with the use of thrombolysis, may decrease the risk of PTS due to the fast restoration of blood flow in deep venous and prevent or decrease damage of valvular and vascular. Early lysis of thrombosis also could reduce the risk to develop PE and future recurrence risk. However, this hypothesis is in contrast with Cochrane review, in which it found that systemic thrombolysis was not associated with decreasing the risk of acute PE (risk ratio 1.7, 95% CI 0.55-5.4), severe PTS (risk ratio 0.48, 95% CI 0.12-1.9) and mortality (risk ratio 1.1, 95% CI 0.44-2.8), even though the venous patency is improved, and greater complete clot lysis were observed. Although thrombolysis may lead to 45% decrease of PTS risk of any severity (risk ratio 0.55, 95% CI 0.41-0.73), it was related with significant risk of major bleeding (12% vs 5.2%; risk ratio 2.2, 95% CI 1.4-3.5) [26].

For patients with phlegmasia, cerulea dolens or massive iliofemoral DVT or patients who fail therapeutic anticoagulation or massive PE with unstable hemodynamic, thrombolysis and thrombectomy are primarily used. It works effectively if symptoms were developed before 14 days (i.e., fresh clot), good functional status, and low bleeding risk [22]. Thrombolytic agents can be delivered systemically or with a catheter inserted to affected lower extremity vein (CDT=catheter-directed thrombolysis). It has been considered that catheter-directed thrombolysis, compared to systemic thrombolysis, may result in more rapid clot lysis and with lower doses, hence decrease risk for bleeding. Mechanical thrombectomy or surgical thrombectomy could be used as an adjunctive therapy, or alternative, for thrombolysis. It has been suggested that combined catheter-directed procedures (e.g., thrombolysis plus fragmentation) could minimize bleeding risk [27,28].

Thrombolysis and primarily CDT prove to improve the resolution of thrombus and patency rates. However, both of thrombolysis and CDT have not shown any benefit for critical long-term endpoints, including recurrent disease, severe PTS or mortality [22].

2.6. *Duration of long term extended anticoagulation for DVT*

General consideration such as the type of DVT (provoked and unprovoked DVT), recurrences risk and bleeding tendency should taken into account before deciding the optimal duration. According to the guideline, it has been stated that increasing the duration of anticoagulation beyond three months is considered in a few populations. However, there is still no agreed-upon best approach [29].

Whilst all DVT patients undertake at least initial and maintenance therapies, treatment during the extended phase (indefinitely) still under full debate especially in regards what agent to be used and for how long should be given. Moreover, the balancing of continuation or discontinuation of therapy is intricate in daily practice, and predictive scores which are at higher risk are off-hand [1]. There were

several groups of DVT patients when considering long term treatment phase. Group of patients with provoked DVT are at low risk for recurrence (less than 2% per year), and they do not need long term anticoagulation. Group of patients with recurrent provoked DVT, DVT with thrombophilia will need life-long anticoagulant. Though, for remaining group of patients including patients who resolved first episode of unprovoked DVT, DVT long-distance travel, mild leg trauma or oral contraceptive. In some occasions such as in patients with recurrent distal DVT, mild thrombophilia patients, and cancer patients who have developed DVT and have recently completed cancer therapy and currently in remission, how long they need to continue the DVT therapy? Should they continue for three months, six months, a year or forever? Also, which drug should be used, and at what dose? As this group has many varieties, we still need a simple and clear answer to these questions. In real practice, most scenarios may not lead to a definite determination of VTE recurrence risk and the decision to continue or to discontinue anticoagulation. As the consequence, the general risk for recurrence of DVT needs to be described to the patient and decisions with considering patient preferences should be made. In general, both of physicians and patients afraid for the risk of bleeding, in which it related to long-term anticoagulation. Along with the impact of using drugs or injections to the quality of life, it often drives the wish to stop anticoagulation and vice versa [1,30,31].

3. Summary

Despite major advances, there are several problematic issues regarding optimal and best treatment for DVT. There are differences in the treatment of isolated distal DVT among health providers and centers. The treatment for DVT still become a great challenge. There is a difference of opinion about using anticoagulant in DVT patient; some physician prefers all DVT patient use it. However, others agree that several patients can avoid the use of anticoagulant. In obesity patient, the sign and symptom of PE and DVT could be not specific. It may look like part of physiological change because of increasing BMI. Because of that, the diagnostic and therapeutic DVT in obese patient became more challenged. As well as in cancer with thrombosis, it is essential to keep in mind that all CATs are different. Therefore, the optimal anticoagulant type, duration, and intensity for the treatment of CAT should probably be individualized based on the cancer characteristics, risk factors, and risk of future recurrent events. Scientific studies have supported Travel-related DVT. However, many things have to be understood to present more accurate advice for travelers. Thrombolysis and CDT are known for increasing the patency rates, but they not reducing disease recurrences, severe PTS and mortality. Treatment duration during extended phase (indefinitely) is also problematic and still under full debate especially in regards what agent to be used and for how long should be given.

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