Catheter-Related Deep Vein Thrombosis in Critically Ill Cancer Patients

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Contents

Abstract

Cancer and **critical illness** are predisposing factors for the development of **catheter-related deep vein thrombosis**. This chapter discusses specific catheter-related factors that increase the risk of **thrombosis**, as well as strategies for prophylaxis against the development of these vascular complications. Treatment options will also be covered, including management of the **catheter** and options for pharmacologic therapy. Finally, consideration will be given to concomitant **thrombocytopenia**, a frequent comorbid condition in patients with malignancy.

Keywords

Cancer · Critical illness · Intensive care unit · Catheter · Thrombosis · Deep vein thrombosis · Catheter related thrombosis · Pulmonary embolism · Anticoagulation

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Introduction

The use of **central venous catheters (CVCs)** in the oncologic patient population is very common for a variety of reasons. They are often used for the administration of medications best suited to be delivered into the central, rather than peripheral, circulation. Long-term placement of central venous catheters is also used to enable patients to receive frequent chemotherapeutic treatments either during frequent outpatient visits or even for medication administration at home. CVCs are also commonly utilized in the critically ill patient population as well [1]. Unfortunately, the combination of being critically ill, suffering from cancer, and having a central venous catheter in place can significantly increase the risk of developing **deep vein thrombosis (DVT)**.

Not only does critical illness predispose patients to thrombosis formation, but the development of venous thrombosis in this population has also been associated with longer durations of mechanical ventilation, ICU stay, and hospital stay than patients who do not develop DVTs [2, 3]. In addition to being critically ill, patients in the **intensive care unit (ICU)** often have additional risk factors such as immobilization, surgery, sepsis, renal failure, and vascular injury.

The presence of cancer is also an independent risk factor for the development of **venous thromboembolism (VTE)** which encompasses both deep vein thromboses and pulmonary emboli (PE) [4]. The extent of increased risk can be variable and often depends on the type of malignancy, the location of disease, or the stage of the malignant process. Cancer patients also have additional risk factors predisposing them to the development of VTE. Not only do they have some of the conditions mentioned above, but treatment with antineoplastic agents, including traditional chemotherapy as well as newer molecular-targeted therapies, can also increase thrombotic risk in these patients [5].

Central venous catheters increase the risk of thrombosis to as high as 14–18% [6]. Many of these patients are already at increased risk because they have one or more of the risk factors mentioned above. Indeed, some of these factors may be the reason that a CVC is needed in the first place. But in addition to underlying patient risk factors, there is increased thrombogenic risk associated with the lines themselves and also with the technique and location of line placement as well.

Catheter-Specific Risk Factors

The classic factors predisposing to the development of thrombosis as elucidated by Rudolf Virchow in his eponymous triad include hypercoagulability, stasis, and endothelial injury. We have already discussed the fact that critically ill cancer patients have multiple reasons to be hypercoagulable, but an indwelling catheter may compound the problem by acting as a focus for thrombogenesis. In addition, the mechanical obstruction of vascular flow by the catheter likely contributes to some degree of stasis, and the infusion of viscous substances through the catheter, or abnormal limb positioning due to the catheter, may also impede blood flow to some degree. Finally, the placement or position of the catheter may contribute to the third component by potentially inflicting damage to the endothelial lining of the vessels. Other prothrombotic states as well as hormonal therapy may increase thrombotic risk as well. The aforementioned risk factors apply to all catheters in general, but there are also more specific components of catheters which play a role such as the location of the catheter, the catheter type, and the techniques of placement.

Catheter Location

Catheters placed in the central veins of the upper extremities are frequently associated with DVTs in these locations. In fact, secondary **upper extremity deep vein thrombosis (UEDVT)**, which includes cancer and pacemakers as predisposing factors in addition to central lines, accounts for about 75% of cases of UEDVT [7]. Multiple studies have also shown an increased risk when the CVC tip was found to be above the superior vena cava–right atrium junction [8–13]. There is also evidence that left-sided CVC placement and femoral insertion increase the risk of thrombosis as well [10, 14,

15]. Placement in the subclavian vein has also been shown to have an increased risk versus jugular vein implantation [13].

Catheter Type

A more recent trend in critical care has been an increasing use of **peripherally inserted central catheters (PICCs)**. A study by Bonizzoli and colleagues in 2011 found that the rate of DVT/1000 catheter days was 4.4 for traditional CVCs versus 7.7 for PICCs [16]. A large meta-analysis of five randomized controlled trials and seven prospective studies which included 5636 cancer patients with a central venous catheter also found that implanted ports were associated with a lower risk than PICCs [13]. The number of lumens in the catheter also plays a role, with an increased risk for triple-lumen versus double-lumen CVCs [8].

Catheter Placement Technique

The placement of central venous catheters also contains many variables, some of which have been shown to increase the thrombotic risk in patients. Multiple-line insertion attempts as well as previous CVC insertion increase the risk for **catheter-related thrombosis (CRT)** development [17]. The length of procedural time also affects the risk, with an increase for placement time greater than 25 min [15].

Clinical Implications of Thrombosis

Once catheter-related thromboses occur, they may lead to the development of **pulmonary embolism (PE)** in 10–15% of patients [18, 19]. In addition, they may lead to interruption of therapy, phlebitis, post-thrombotic syndrome, stenosis, and increased costs of care. These issues, along with unclear and potentially fraught management strategies, suggest that prevention of catheter-related DVTs in the first place is an important initial strategy.

Prevention/Prophylaxis

Based on the risk factors specifically related to catheters mentioned above, certain considerations can be made to take these risks into account and minimize the attendant thrombotic potential during catheter placement itself.

Regarding placement location, the International Society on Thrombosis and Haemostasis addresses this in their guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. They suggest that catheters, when possible, should be inserted on the right side, in the jugular vein, and with the distal portion of the catheter located at the junction of the superior vena cava and the right atrium [18].

Based on the above data, it would also seem to be prudent to minimize the duration of the procedure as well as the number of attempts made, although this is obviously the goal in most cases, but sometimes affected by factors outside of the procedurist's control. Consideration could also be given to minimize the number of lumens necessary, which again may be limited depending on the patient's intravenous supportive requirements.

With regard to chemical **prophylaxis**, the use of **anticoagulation** for the routine prophylaxis of catheter-related thrombosis is not recommended by the International Society on Thrombosis and Haemostasis [18]. This recommendation was based on a multitude of studies as detailed below.

In six randomized studies, the safety and efficacy of **vitamin K antagonists (VKAs)** versus placebo or no treatment in the prevention of catheter-related thrombosis in cancer patients were evaluated [20–25]. The study by Bern and colleagues actually found a significant decrease in any CRT with low-dose VKA (warfarin 1 mg beginning 3 days before catheter insertion and continuing for 90 days) versus no treatment (9.5% vs. 37.5%) as well as a decrease in symptomatic CRT (9.5% vs. 32.5%, $P < 0.001$) [20]. However, in three of the subsequent studies, VKAs were not significantly more effective than placebo or no treatment in preventing thromboses [21–23]. One study did find that the incidence of

CRT was lower in patients receiving warfarin at a target INR of 1.5–2.0 versus those receiving a fixed dose of warfarin (2.7% vs. 7.2%, $P = 0.002$), but this was in the face of a significant increase in the risk of major bleeding (3.4% vs. 1.5%, $P = 0.04$) [24]. In the sixth study, chemical prophylaxis was better than no treatment in preventing nonocclusive and asymptomatic CRT without an increased bleeding risk, but the rate of occlusive CRT did not differ between the treatment and non-treatment groups [25].

Only one study evaluated **unfractionated heparin (UFH)**, and it looked at 128 CVCs in 108 patients with hematologic malignancy randomized to either a heparin arm (continuous infusion of 100 IU/kg/day, with a maximal dose of 10,000 IU UFH daily) or a saline arm. The heparin arm had significantly fewer occurrences of CRT than the control arm (1.5% vs. 12.6%, $P = 0.03$) without a significant increase in severe bleeding risk [26].

Low molecular weight heparins (LMWHs) have also been evaluated in a variety of studies for the prevention of CRT [25, 27–31]. The results are mixed in these investigations as well. There is some evidence that LMWHs are better than no treatment at preventing asymptomatic CRT [25, 27], but in one of these studies, there was no difference in the rate of occlusive CRT. Additionally, three placebo-controlled studies [29–31] found no difference in either asymptomatic or symptomatic CRT between the LMWH and placebo groups. Of note, none of the studies found a significantly increased bleeding risk with LMWH versus placebo or no treatment. The International Society on Thrombosis and Haemostasis therefore concluded that LMWH did not increase the bleeding risk, but also did not show any benefit in preventing symptomatic thromboses [18].

Although the recommendations of the International Society on Thrombosis and Haemostasis are against routine chemical prophylaxis for CRT, one meta-analysis that should be kept in mind combined seven studies looking at anticoagulation in general (VKA, UFH, or LMWH) versus placebo or no treatment in oncologic patients with a CVC. They did actually find a significant 44% reduction in symptomatic DVT risk in the anticoagulated group, without an attendant significant increase in major bleeding incidence [32].

The use of **thrombolytics** for prophylaxis has also been investigated, although not extensively. One study of pediatric oncology patients found that the rate of CRT was significantly lower in the 15 patient group that received urokinase 10,000 IU infused in each catheter lumen for 4 h once a week versus the control group which was a historical series of 15 children who didn't get prophylaxis (44% vs. 82%, $P = 0.047$), and there were no reported bleeding complications [33]. A second study evaluated 160 cancer patients randomized to either urokinase 5000 IU over 4 h once a week or to saline placebo. The primary goal of the study was to evaluate catheter-related infection, but they also found that five patients in the saline group developed catheter-related thrombosis versus one patient in the urokinase group. They clarify, however, that the patients were not evaluated routinely with Doppler ultrasound or venography to assess thrombosis, and therefore the true incidence and risk reduction by urokinase for CRT are unclear from this study [34].

Treatment

Despite clinicians' best efforts at prophylaxis, catheter-related thromboses regardless unfortunately often develop. Once this occurs, the treating team is faced with the question of what to do with the catheter, as well as how to treat the thrombus.

As far as the CVC is concerned, the International Society on Thrombosis and Haemostasis recommends that the catheter can be kept in place if it is functional, well positioned with the distal tip at the junction between the superior vena cava and the right atrium, and not infected. There should also be good resolution of symptoms under close surveillance [18]. The data in this area is limited. However, a retrospective study of 319 cancer patients with CVCs found that 112 patients had evidence of thrombosis. The catheter was removed in 52% of these patients.

Only four patients did not have resolution of their presenting symptoms, and all of these were patients in whom the catheter was removed [35].

For treatment purposes, the International Society on Thrombosis and Haemostasis recommends anticoagulant treatment for a minimum of 3 months for the treatment of symptomatic CRT in cancer patients [18]. They suggest low molecular weight heparins (LMWHs), although they state that vitamin K antagonists (VKAs) can also be considered, given the lack of direct comparisons of these two modes of anticoagulation in this scenario. In the case of non-catheter-related thromboses in cancer patients, there is evidence that LMWHs are superior to VKAs and are therefore the agent of choice [7, 36], although there is accumulating evidence that **direct oral anticoagulants (DOACs)** may be equivalently effective [37–43]. However, when it comes to catheter-related thromboses in cancer patients, there is again a paucity of data regarding the use of anticoagulants; specifically there are no prospective randomized trials addressing this issue. One prospective but non-randomized study of 46 patients evaluated treatment of upper extremity DVT with dalteparin 200 IU/kg once daily subcutaneously for a minimum of 5 days and warfarin for a goal INR of 2.0–3.0. Of the study participants, 34 (74%) had cancer and 16 (35%) had a CVC. They were followed for 12 weeks after diagnosis and DVT recurred in only one patient (2.2%). None of the subjects developed pulmonary embolism (PE), and only one patient developed major bleeding [44]. In another study of 74 patients with solid tumors and confirmed CRT, treatment was given with dalteparin 200 IU/kg once daily subcutaneously for at least 5 days along with warfarin initiated on the 1st day with a goal INR 2.0–3.0. The follow-up period was 3 months and CRT recurred in three (4.7%) patients with major bleeding in seven (10.9%) patients, including one fatal event [45]. There was also one retrospective study looking at 498 patients in whom 899 CVCs were placed. Of these, 39 patients developed CRT, and 30 were treated with heparin, while 9 were treated with warfarin for 3 months. There were no recurrent events, PE, or bleeding events.

This group of experts also did not recommend routine administration of thrombolytic medications for CRT, because although data suggests improved vessel patency with thrombolytic therapy compared to anticoagulation alone, there is also a likely higher risk of bleeding complications [46, 47]. They do, however, suggest that thrombolytic therapy may be considered if the thrombotic risk is greater than the risk associated with complications from these medications, such as a superior vena cava thrombosis associated with recent, poorly tolerated, objectively confirmed vena cava syndrome, or if the maintenance of a CVC is imperative [18].

One of the complicating factors in cancer patients, particularly those who are critically ill, is the frequent presence of comorbid **thrombocytopenia**. This should of course be taken into account when considering the above therapies, and risk versus benefit should always be considered. The use of unfractionated heparin can also be an option in these cases, with the ability for closer monitoring, titration as needed, and reversibility. Alternatively, adjusted dosing of LMWH can be considered [48]. The National Comprehensive Cancer Network Guidelines Version 2.2018 suggest that for the management of anticoagulation for VTE in patients with chemotherapy-induced thrombocytopenia, full-dose enoxaparin be given at 1 mg/kg twice daily for a platelet count >50,000/mcL, half-dose enoxaparin be given at 0.5 mg/kg twice daily for a platelet count of 25,000–50,000/mcL, and enoxaparin be held temporarily for a platelet count <25,000/mcL [49]. In the event that any anticoagulation is contraindicated, retrievable IVC filter placement can be considered for lower extremity thrombi.

Summary

In summary, cancer and critical illness are predisposing factors for the development of catheter-related deep vein thrombosis. General prothrombotic risks are increased by a variety of factors associated with these two medical processes.

In addition, specific catheter-related factors increase the risk of thrombosis. These include an increased risk for placement of the CVC tip above the superior vena cava–right atrium junction, left-sided placement, and femoral or subclavian placement versus jugular placement. PICCs also increase the risk, and this is higher as the number of lumens increases. Finally, during placement, multiple attempts or a procedure time greater than 25 min increases the risk for thrombosis development as well.

Given the morbidity and poor treatment options associated with venous thromboembolic disease, prevention of the development of CRT is ideal. This goal can attempt to be achieved by placement of right-sided, jugular catheters in the appropriate position, with minimal attempts, as few lumens as are necessary, and a procedure time under 25 min when possible. The International Society on Thrombosis and Haemostasis also does not recommend the routine use of anticoagulation for prophylaxis [18].

If catheter-related thrombi do occur, the CVC can be maintained if it is functional, in good position, and not infected and if there is good resolution of symptoms. For the treatment of symptomatic CRT in cancer patients, the International Society on Thrombosis and Haemostasis recommends anticoagulant treatment for a minimum of 3 months, preferably with LMWHs. Routine thrombolytic therapy should not be given but can be considered in cases where the thrombotic risk is greater than the risk of bleeding complications [18]. Since thrombocytopenia is a frequent comorbid process in cancer patients, the risk versus benefit of anticoagulant therapy should always be considered, with the possibility of using alternative measures, such as unfractionated heparin, adjusted LMWH dosing, or temporary IVC filter placement.

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