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Risk factors of thrombosis in cancer : the role of microparticles
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3 deep vein thrombosis associated with central venous catheters- a review

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Introduction

Central venous catheters (CVCs) are frequently used in patients for a variety of indications such as cancer treatment, diagnostic monitoring, parenteral nutrition, hemodialysis, cardiac pacing, and administration of fluids, blood products or medication (1). The benefit derived from a CVC may be offset by thrombosis and associated complications, such as pulmonary embolism (PE), CVC dysfunction, infection or loss of central venous access. In the long term patients with thrombosis may suffer from a post-thrombotic syndrome (1;2).

The CVC-related thrombosis is an issue of importance to many clinicians, and insight into the different aspects is crucial to guide decisions in treatment in often vulnerable patients in daily practice. In medical literature, there is a lack of uniformity and uncertainty about several entities of CVC-related thrombosis. First, two types of CVC-related thrombosis must be clearly distinguished; i.e. clinically manifest and subclinical thrombosis. Furthermore, the type of thrombosis and the incidence is defined by the diagnostic strategy in patients with a CVC.

Anticipation of the risk of CVC-related thrombosis and the identification of certain 'high-risk' patients who are prone to develop thrombosis and secondary complications, is essential to initiate early preventive measurements such as prophylactic anticoagulation. The need for anticoagulant prophylaxis is however still a subject of discussion (3;4). Finally, for the treatment of established CVC-related thrombosis, several therapeutic options were evaluated in literature. General recommendations of anticoagulant treatment, and whether CVC removal is necessary or not, is warranted.

The primary aim of this review is to describe the diagnostic methods and their performance, the incidence and risk factors, complications, prevention and treatment of CVC-related thrombosis from a practical clinical point of view. English medical literature studies were retrieved by an extensive Medline search (Pubmed®) and bibliographies of the obtained studies were crosschecked where necessary. For each subject, only those studies with the strongest level of evidence, as defined and discussed in the subsequent paragraphs, were selected and reviewed.

Diagnosis of CVC-related thrombosis

In view of diagnosis of CVC-related thrombosis, two types of thrombosis can be distinguished; clinically manifest thrombosis and subclinical thrombosis. Clinically manifest thrombosis is defined as thrombosis objectified by diagnostic imaging (ultrasound, venography) upon overt symptoms and signs, such as pain or tenderness, warmth, swelling or edema, bluish discoloration or visible collateral circulation. Subclinical thrombosis, defined as thrombosis in the absence of signs and symptoms, is demonstrated by screening diagnostic imaging. Most thrombotic events associated with CVCs remain subclinical, or complications such as PE are the first presenting symptom (5-7).

Radiologically, thrombosis can have a typical appearance of enveloping sleeve surrounding the CVC (Fig 1) or be characterized by mural thrombosis adherent to the venous vessel wall (8). Mural thrombosis, present in approximately 30% of patients with CVCs, may cause subtotal stenosis (Figure 2) or occlusion of the venous lumen and lead to clinically manifest thrombosis or associated complications (6). Mural thrombosis is often found near the entry site of the CVC into the vessel or at the junction of large veins, although it may be extended or located into adjacent venous segments or the right atrium.

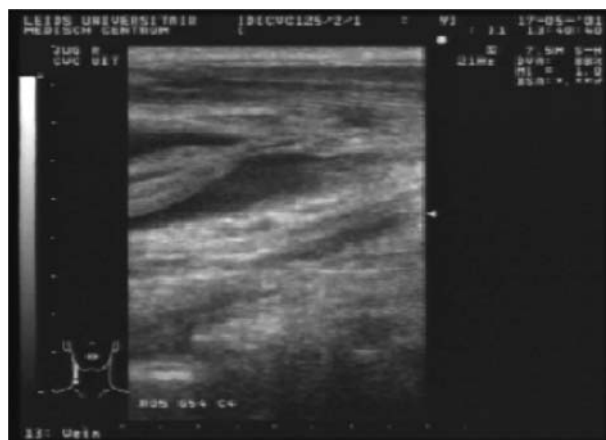


Figure 1. Ultrasonic appearance of a typical enveloping 'fibrin sheath' demonstrated immediately after central venous catheter removal (Jugular vein).

In the diagnostic work-up of CVC-related thrombosis, diagnostic imaging upon a clinical suspicion of thrombosis is mandatory. A diagnosis based solely on clinical symptoms and

signs of thrombosis is non-specific, as in deep vein thrombosis (DVT) of the leg. In only about a third to a half of all patients in whom thrombosis is clinically suspected, the diagnosis is confirmed (9-11).



Figure 2. Nearly occlusive mural thrombosis visualized by a flow defect, detected by Doppler Flow Imaging, just after central venous catheter removal.

Contrast venography is widely recognized as the reference standard in the diagnosis of thrombosis (12). However, ultrasound is most often used clinically, because it is non-invasive, does not expose to ionizing radiation, can easily be performed at the bedside and is well accepted by patients. In modern ultrasonography, real time gray-scale images (B-mode) are obtained and the criteria of non-compressibility (compression ultrasound) and direct visualization of thrombotic material in the venous lumen can be used to establish the presence or absence of thrombosis. Besides, real time changes in vessel diameter due to respiration may detect occlusive thrombosis more centrally located. In addition, Doppler techniques can add the advantage of evaluation of blood-flow. With pulsed Doppler signals added to gray scale imaging (Duplex ultrasound) qualitative and quantitative information of blood flow can be obtained. Color Doppler Flow Imaging (CDFI) displays blood flow in color in addition to gray scale imaging. A combination of all three modalities is called color duplex ultrasound.

In symptomatic lower extremity DVT, compression ultrasonography has been validated in clinical practice (13), but specifically for thrombosis associated with femorally inserted

CVCs, no studies are available in which ultrasound was compared with venography. With regard to the upper-extremity DVT, venography has high to moderate inter-observer agreement rates (71%-83%) and can be used as a reference test in clinical practice (14). In several studies the diagnostic accuracy of ultrasound in upper extremity thrombosis compared with venography was evaluated.

For the purpose of this review, we selected those studies in which ultrasound was compared with routine contrast venography in the diagnosis of upper-extremity DVT in the entire cohort of reported patients, and which results were independently interpreted by blinded observers. Overall, six studies were retrieved (Table 1) in which patients with CVCs were included. The reported sensitivity of ultrasound in the diagnosis of upper extremity DVT among these studies ranged from 56% to 100%, whereas the specificity ranged from 77% to 100% (10;11;15-18).

Table 1. Diagnostic accuracy of Doppler-ultrasound in the diagnosis of upper extremity thrombosis with routine contrast venography as the reference standard

Study (reference)	Patients (n)	CVC (%) [*]	Technique	Sensitivity (%)	Specificity (%)	Manifest/subclinical [†]
Prandoni <i>et al.</i> (10)	58	14	CUS	96	94	Manifest
Prandoni <i>et al.</i> (10)	47	NI	Duplex	81	77	Manifest
Prandoni <i>et al.</i> (10)	34	NI	CDFI	100	93	Manifest
Baarslag <i>et al.</i> (11)	99	NI	CDFI	82	82	Manifest
Baxter <i>et al.</i> (15)	19	74	CDFI	100	100	Manifest
Köksoy <i>et al.</i> (16)	44	100	CDFI	94	96	Mixed
Haire <i>et al.</i> (17)	43	100	Duplex	56	100	Mixed
Bonnet <i>et al.</i> (18)	40	100	Doppler	93	93	Mixed

CUS, compression ultrasound; CDFI, color Doppler flow imaging; NI, not indicated.

^{*}Percentage of patients with a central venous catheter (CVC).

[†]For definition manifest/subclinical, see text.

Reports specifically aimed at patients with CVCs are limited to three studies only (16-18), importantly, in patients with CVC-related thrombosis, thrombosis tends to be located more centrally than in patients with thrombosis not related to CVCs (4). As a consequence, the diagnostic technique of ultrasound, and therefore the accuracy, in patients with suspected thrombosis because of CVCs is different than those without (history of) CVC. In one study continuous wave Doppler without gray scale imaging only was used, a technique hardly applied nowadays (18). Applying modern techniques, Duplex ultrasound was reported to have an excellent specificity (100%), however the sensitivity was substantially lower (56%) (17). In another study, CDFI was found to be more sensitive (sensitivity 94% specificity 96%) (16).

Summary

In summary, reliable data on the accuracy of ultrasound in CVC-related thrombosis are limited. In lower extremity CVC-related thrombosis no studies are available. In upper extremity CVC-related thrombosis specifically, only three studies are available, of which CDFI had the best performance (sensitivity 94%, specificity 96%). In view of the advantages of ultrasound mentioned, and the high specificity, patients with clinically suspected CVC-related thrombosis, should undergo ultrasound initially. However, the safety of withholding treatment in case of a negative ultrasound in patients suspected for thrombosis is uncertain (19). As a consequence, in patients with normal ultrasound additional venography could be performed. Alternative strategies such as serially performed ultrasound, spiral CT or MRI may be useful and of potential interest, but are not validated yet.

Incidence and risk factors of CVC-related thrombosis

Incidence

In numerous studies the incidence of CVC-related thrombosis has been evaluated. In most studies, clinically manifest thrombosis was used as the primary endpoint. Among these studies incidences ranging from 0% to 28% were reported (20;21). However, the decision to refer for diagnostic imaging upon clinical signs and symptoms for thrombosis lacks uniformity and may be subjective. A more reliable estimate is given by studies in which

routine diagnostic screening (ultrasound or venography) was used in consecutive patients with CVCs to determine to assess a diagnosis of thrombosis. For the purpose of this review these studies are selected and summarized in Table 2, according to the indication for the CVC, i.e. the underlying disease and the type of thrombosis (subclinical, clinically manifest and overall) (5;6;8;22-44).

Overall, the reported incidences of CVC-related thrombosis in these studies ranged widely from 2% to 67% (Table 2). The wide range in observed incidence may be partly caused by different diagnostic modalities (venography, ultrasound), the used criteria, and patient- and CVC characteristics. On average, a 30% cumulative incidence can be found in hospitalized patients and the overall majority of thrombotic events remained subclinical (6). The percentage of clinically manifest thrombosis in these studies ranged from 0% to 12% (Table 2).

In some specific populations, such as patients with hemophilia, prospective (screening) studies are not available. In cohort-studies with merely clinical manifest thrombosis as an endpoint incidences ranged from 0% to 3% (45). Whether in patients with inherited bleeding disorders the risk of thrombosis is reduced as compared with other patients, is not known because of the lack of large studies in which all patients were screened systematically for thrombosis.

Risk factors

The individual risk of CVC-related thrombosis in a patient is the result of the interaction between patient characteristics, i.e. inherited and acquired risk factors; and the CVC (Figure 3). There are numerous studies in which risk-factor analysis of CVC-related thrombosis was performed. For inherited and common acquired risk factors cohort studies were considered to represent the highest level of evidence (level 1); case control studies as level 2. For CVC characteristics, randomized trials were considered to represent level 1 of evidence; cohort studies as level 2.

Table 2. Incidence of CVC-related thrombosis amongst studies with routine diagnostic imaging performed in consecutive patients (Doppler-Ultrasound or venography)

Study (reference)	Population	N	Technique	DVT % (manifest %) CVC	Location entry site
Chastre <i>et al.</i> (22)	ICU	33	V	67 (0)	Jugular vein
Durbec <i>et al.</i> (23)	ICU	70	V	36 (0)	Femoral vein
Timsit <i>et al.</i> (24)	ICU	208	D	33 (0)	Subclavian & jugular vein
Wu <i>et al.</i> (25)	ICU	81	D	56 (0)	Jugular vein
Joynt <i>et al.</i> (26)	ICU	124	D	10 (2)	Femoral vein
Martin <i>et al.</i> (27)	ICU	60	D	58 (2)	Axillary vein
Stoney <i>et al.</i> (28)	Cardiology	203	V	34 (3)	Cephalic & jugular vein
Goto <i>et al.</i> (30)	Cardiology	100	V	23 (0)	Cephalic & subclavian vein
Lin <i>et al.</i> (29)	Cardiology	109	D	6 (0)	Cephalic & subclavian vein
Antonelli <i>et al.</i> (31)	Cardiology	40	V	28 (5)	Cephalic & subclavian vein
Van Rooden <i>et al.</i> (32)	Cardiology	145	D	23 (2)	Cephalic & subclavian vein
Valerio <i>et al.</i> (33)	Oncology	18	V	33 (6)	Subclavian vein
Brismar <i>et al.</i> (34)	Oncology	53	V	36	Subclavian vein
Bozetti <i>et al.</i> (35)	Oncology	52	V	28 (0)	Subclavian vein
Haire <i>et al.</i> (5)	Haematology	35	V	63 (9)	Subclavian vein
Balesteri <i>et al.</i> (8)	Oncology	57	V	56 (0)	Subclavian vein
De Cicco <i>et al.</i> (37)	Oncology	95	V	66 (6)	Subclavian vein
Biffi <i>et al.</i> (38)	Oncology	302	D	4 (2)	Subclavian & cephalic vein
Luciani <i>et al.</i> (39)	Oncology	145	D	12 (3)	Subclavian vein
Harter <i>et al.</i> (40)	Oncology	233	D	2 (0)	Jugular vein
Lordick <i>et al.</i> (41)	Haematology	43	D	30 (0)	Jugular vein
Van Rooden <i>et al.</i> (42)	Haematology	105	D	28 (12)	Jugular & subclavian vein
Nowak-Gottl <i>et al.</i> (43)	Pediatrics	163	D	11 (11)	Subclavian vein
Beck <i>et al.</i> (44)	Pediatrics	93	D	18 (8)	Jugular & subclavian & femoral vein
Van Rooden <i>et al.</i> (6)	Mixed	252	D	30 (7)	Jugular & subclavian vein

V, venography; D, Doppler-ultrasound; DVT, deep venous thrombosis.
For definition of manifest, see text.

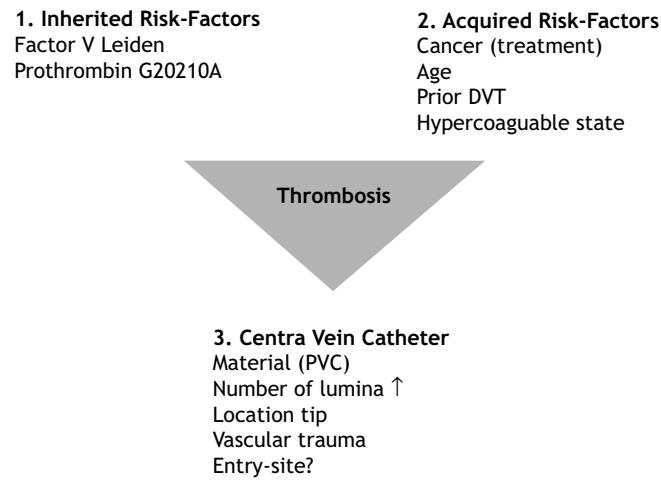


Figure 3. Interaction of inherited, acquired risk-factors of thrombosis with catheter characteristics play an important role the development of central venous catheter-related thrombosis.

Inherited coagulations disorders have been reported to contribute substantially to CVC-related thrombosis in large cohort studies (level 1). Factor V Leiden (FVL) was strongly associated with clinically manifest thrombosis in patients who underwent bone marrow transplantation ($n = 277$); *i.e.* 54% of patients with FVL developed thrombosis, in comparison with 10% of patients without (Cox proportional hazard ratio 7.7) (46). In a large hospital population of 252 patients, the presence of FVL and prothombin G20210A mutation increased the overall risk of CVC-related thrombosis almost threefold (6). Two other recent performed studies also suggested a contribution of these commonly inherited coagulations disorders (47;48). In contrast to these studies, a case-control study (level 2) reported no increased prevalence of FVL in patients with CVC-related thrombosis as compared with the general western population (49). In children, similar risk estimates as in adults have been reported. In cohort studies, the risk of thrombosis in FVL carriers in pediatric patients was substantial in patients with acute lymphoid leukemia, as well in mixed populations (43;50;51). With regard to common acquired risk factors of venous thrombosis there are numerous studies of different level of evidence. In cohort studies, the presence of cancer or active cancer treatment in both, adults and children (6;44), prior thrombo-embolism (32), acquired (temporary) hypercoaguable state (43;52) and a

high platelet count at CVC insertion (53) were associated with thrombosis. Age was also associated with CVC-related thrombosis; the risk was higher with increasing age, and in very young children (24;44).

Table 3. Studies in which the benefit from anticoagulant prophylaxis for CVC-related thrombosis was evaluated. Studies were classified into three categories: (i) randomized-controlled trials with routine mandatory diagnostic imaging; (ii) randomized-controlled trials with clinically manifest thrombosis or associated complications; and (iii) observational studies

Study (reference)	Population	n	Intervention	Thrombosis (%)	Thrombosis (controls) (%)	Endpoint
Randomized-controlled trials - mandatory diagnostic imaging						
Bern <i>et al.</i> (74)	Oncology	82	Warfarin 1 mg	9.5	42	Mandatory venogram
Monreal <i>et al.</i> (75)	Oncology	29	Dalteparin 2500 IU	6	62	Mandatory venogram
Abdelkefi <i>et al.</i> (76)	Hematology	128	UFH (100 IU kg ⁻¹)	1.5	12.6	Mandatory ultrasound
Brismar <i>et al.</i> (34)	Nutrition	49	UFH (5000 IU q 6 h)	21.7	53.8	Mandatory venogram
Ruggiero and Aisenstein (80)	Nutrition	34	UHF (1000 IU L ⁻¹)	53	65	Mandatory venogram
Fabri <i>et al.</i> (81)	Nutrition	46	UFH (3000 IU L ⁻¹)	8.3	31.8	Mandatory venogram
Fabri <i>et al.</i> (82)	Nutrition	40	UFH (3000 IU L ⁻¹)	0	0	Mandatory venogram
Macoviak <i>et al.</i> (79)	Nutrition	37	UHF (1 U ml ⁻¹)	17.6	15.6	Mandatory venogram
Pierce <i>et al.</i> (78)	Pediatr. Crit. Ill	209	UFH bonded CVC	8	0	Mandatory ultrasound
Massicotte <i>et al.</i> (77)	Pediatr. Oncology	158	Reviparin 30-50 IU kg ⁻¹	14.1	12.5	Mandatory venogram
Randomized-controlled trials - Clinical endpoints						
Heaton <i>et al.</i> (84)	Hemato-oncology	88	Warfarin 1 mg	17.7	11.6	Including PE & malfunction
Anderson <i>et al.</i> (85)	Oncology	255	Warfarin 1 mg	4.6	4	No PE or malfunction
Reichardt <i>et al.</i> (83)	Oncology	425	Dalteparin 5000 IU	3.4	3.7	No PE, malfunction

Study (reference)	Population	n	Intervention	Thrombosis (%)	Thrombosis (controls) (%)	Endpoint
Cohort studies (consecutive patients vs. controls)						
Boraks <i>et al.</i> (86)	Hemato-Oncology	223	Warfarin 1 mg	5	13	CMT
Lagro <i>et al.</i> (87)	Hemato-Oncology	323	Nadroparin 2850 IU	7	6	CMT
Lagro <i>et al.</i> (87)	Hemato-Oncology	323	Nadroparin 5600 IU	8	6	CMT

UHF, unfractionated heparin; RR, risk reduction; CMT, clinically manifest thrombosis; PE, pulmonary embolism.

Many CVC characteristics have been associated with an increased risk of CVC-related thrombosis. The type of CVC may be an important factor in the development of CVC-related thrombosis. CVCs composed of silicon or polyurethane are less often associated with local thrombosis than CVCs made of polyethylene (35;54;36). In addition, the risk of thrombosis tends to increase with the number of CVC lumina (5;55). The role of the puncture-site of CVC insertion is still much debated. In two randomized trials (level 1) in intensive care unit patients insertion via the subclavian route had a low risk of thrombosis as compared to a femoral route (0% vs. 25%, respectively 6%) (56;57). A similar observation was found in a cohort (level 2) study in patients with subclavian vein CVC as compared with jugular CVCs (11% vs. 42%) (24). In both studies patients were routinely screened by ultrasound for CVC-related thrombosis. However, the methodology of comparing femoral with subclavian vein thrombosis associated with CVCs can be debated as the technique and accuracy of ultrasound in asymptomatic upper and lower DVT differ. In a recent cohort study (level 2) in children, the subclavian route had an increased risk of thrombosis as compared with the jugular route as assessed by a combination of routine venography and routine ultrasound (58). In cohort studies, a left insertion side has been reported to increase the risk of thrombosis (37;53;58) and with a CVC tip position into the subclavian or innominate vein, thrombosis was more often observed in comparison to a superior caval vein or right atrial tip location (39). Additional factors in cohort studies that have been reported to increase the risk of thrombosis are a percutaneous insertion procedure, prior CVC at the same puncture site and a prolonged stay of the CVC for over 2 weeks (58;59).

Summary

In summary, CVC-related thrombosis is a multicausal disease. Prothrombotic factors (e.g. FVL) and the underlying disease (cancer) may play an important role in the development of CVC-related thrombosis. Some important CVC characteristics increase the risk of thrombosis, such as the type and material of the CVC, vascular trauma and the duration of stay of the CVC.

Complications

Catheter related thrombosis may be associated with several complications including PE, infection of the thrombus, CVC dysfunction and subsequent loss of intravenous access and post-thrombotic syndrome or recurrent thrombosis.

Pulmonary embolism

The reported incidence of PE as a complication of catheter-related thrombosis varies. In only one study, all patients with proven thrombosis systematically underwent screening for PE (ventilation-perfusion scan) and a 15% cumulative incidence was reported (60). In other studies incidences of PE, using merely clinical endpoints, varied greatly. Whereas incidences of symptomatic PE up to 17% have been reported, others did not observe any PE (61;62). PE associated with CVC-related thrombosis has been reported to be the cause of death (7;60).

Screening for PE if a diagnosis of CVC-related thrombosis is established is usually not mandatory, as in most patients anticoagulant treatment is initiated, eventually with a removal of the CVC. A firm evidence regarding clinical outcome needs however to be established prospectively.

Infection

The CVC-related thrombosis and CVC-related infection have been reported to be associated (24;41;63;64). The pathogenesis of catheter-related infection seems to depend on the development of thrombosis of the catheter. Several thrombo-proteins were shown to increase the risk of subsequent infection (65;66). Results from a postmortem study in 72 patients with a CVC at death revealed that in all patients with catheter-related sepsis

($n = 7$) mural thrombosis after a CVC was present, out of a total number of 31 patients with thrombosis (63). In a study in 265 critically ill patients the risk of infection and sepsis was 2.6-fold increased in patients with catheter-related thrombosis (24). In 43 patients undergoing intensive chemotherapy, 13 patients had objectified subclinical thrombosis of whom 12 developed infection (41).

In addition, CVC-related infection may also increase the risk of subsequent clinically manifest thrombosis. In one study CVC-related infection increased the risk of thrombosis (24%) markedly in comparison with those without infection (3%) (relative risk 17.6) (64).

In the presence of CVC-related infection, it may be useful to screen patients for thrombosis with ultrasound, even in the absence of other clinical overt signs and symptoms. Whether such a strategy is clinically beneficial, improves clinical outcome, and is cost-effective should be further investigated.

Early CVC removal and dysfunction

The CVC dysfunction because of clot formation may occur due to obstruction within the CVC lumina, or occlusion due to an enveloping sheath obstructing the CVC luminal tip. Clot formation of the CVC has been identified as the principal cause of catheter dysfunction in prospective follow-up studies. In a study in 85 CVCs placed for hemodialysis, 16 (19%) clot formation occurred leading to catheter malfunctioning requiring removal of the catheter in all cases (67). In another study in 92 CVCs inserted for hemodialysis, 11 CVCs had to be removed because of catheter complications (68). In six (55%) of these cases, occlusion because of clot was the major reason for removal of the catheter. In a study of 949 CVC placed for ambulatory chemotherapy in cancer patients, 152 (18%) of the catheters had to be removed because of complications (69). In this study infection of the CVC was the leading cause of removal of the CVC, 47 (31%) out of 152 CVCs, but also 38 (25%), had to be removed due to catheter-related thrombosis or dysfunction due to clot. In a large study based on the Strategic HealthCare Programs National Database, catheter complications that occurred in 45 333 CVCs used in an outpatient setting in a 17-month period between 1999 and 2000 were evaluated (70). In 1871 catheters, dysfunction occurred and in 511 (27%) cases dysfunction occurred as a consequence of clot formation. In this study different types of central catheters were shown to carry a different complication rate but thrombosis was the most commonly reported cause of catheter dysfunction for peripherally and centrally inserted CVC with implantable ports.

Post-thrombotic syndrome and recurrent DVT

The incidence of the post-thrombotic syndrome, characterized by venous hypertension, swelling of the extremity and pain (10), has been studied in patients without a CVC who experienced an episode of DVT. In such patients, an incidence of up to 80% of the post-thrombotic syndrome has been reported (71). However, data on post-thrombotic syndrome occurring as a sequela of CVC-related thrombosis are scarce and show contradictory results. Hingorani *et al.* reported a cumulative incidence of 4%, whereas Hicken found a much higher cumulative incidence of 50% (62;72). In a prospective study of a large group of 405 children with various diseases who all developed thrombosis of the upper or lower extremity, 244 (60%) had a CVC (73). Of these 405 children, 40% had thrombosis of the lower and 60% had thrombosis of the upper extremity. Post-thrombotic syndrome was found to occur in 50 (12%) of the 405 children. Of the 50 children who developed a post-thrombotic syndrome, 23 had a CVC. In this study a CVC was not an indicator for post-thrombotic syndrome (OR 0.59; 95% CI 0.28-0.94).

There are no reliable data concerning recurrent DVT after an episode of proven CVC-related thrombosis.

Summary

In summary PE is an understudied and probably underdiagnosed complication of catheter-related thrombosis and together with infection of the thrombus a serious life-threatening complication. In clinical practice, an established diagnosis of infection may render it worthwhile to screen for thrombosis with ultrasound. Besides, luminal clot is the most commonly reported cause of catheter malfunctioning and removal of the catheter. The post-thrombotic syndrome causes severe morbidity, however, whether a CVC is an important risk factor is unclear.

Prevention

In several studies among different patient populations the effectiveness of anticoagulant prophylaxis was evaluated. Basically, three groups of patients were distinguished: (i) patients with hematological or solid tumor malignancies; (ii) non-cancer patients (usually

patients with parenteral nutrition); and (iii) critically ill patients. For the purpose of this review three types of studies, according to level of evidence, are discussed subsequently (Table 3): (i) Randomized-controlled studies with routine diagnostic imaging (venography or ultrasound) to define CVC-related thrombosis as an endpoint. Interpretation of data was blindly assessed. (Level 1); (ii) Randomized-controlled studies (double-blind) with clinically manifest thrombosis (or associated complications) as the primary endpoint (Level 2); and (iii) Observational studies which evaluated routine implementation of anticoagulant prophylaxis in a cohort of consecutive patients compared with historical controls without (Level 3).

Adult and pediatric populations are discussed separately.

RCT with routine diagnostic imaging

Three randomized-controlled trials (RCTs) in which routine diagnostic imaging was used were performed in adult cancer patients, and two in pediatric populations (74-78) and five RCT in patients receiving parenteral nutrition (34;79-82).

Cancer patients

In cancer patients with subclavian CVCs, Bern *et al.* (74) studied the benefit of a randomly allocated fixed low dose warfarin (1 mg once daily orally) compared with controls without. Among patients on warfarin a substantially lower frequency of CVC-related thrombosis, as demonstrated by venogram, was observed (9.5% vs. 42% in controls). Monreal *et al.* (75) observed a similar benefit from a low molecular weight heparin (Dalteparin 2500 IU subcutaneously) in cancer patients with subclavian inserted Port-a-Caths. In patients on Dalteparin a 6% rate in thrombosis was observed by routine venogram, as compared with 62% in patient without. In a recent study in 128 hemato-oncology patients a benefit from continuously administered unfractionated heparin (UFH) ($100 \text{ IU kg}^{-1} \text{ day}^{-1}$) was observed (76). In the heparin group a 1.5% of patients were diagnosed with thrombosis by routine ultrasound, in the control group 12.6%. There were three events of severe bleeding in the heparin group, as compared with two in the control group ($P = \text{NS}$). Combining the results of Monreal *et al.* and Abdelkefi *et al.* revealed a clear benefit from heparin as compared with placebo in adult cancer patients (RR 0.11; 95% CI 0.03-0.45).

In a study of 158 children with hematological malignancies no substantial benefit was obtained with a LMWH as prophylaxis (77). A total of 14% (11 of 78) of patients on LMWH and 13% (10 of 80) in control patients got thrombosis. In critically ill children, the effect of a heparin bonded catheter has been evaluated to reduce the risk of thrombosis (78). A significant reduction in thrombosis from 8 of 103 (8%) to 0 of 97 was observed (78).

Non-cancer patients/parenteral nutrition

In patients who received parenteral nutrition, only the benefit of UFH in various dosages added to the infusate has been assessed (Table 3). The statistical power of these studies was however limited, because of the small number of patients of each study. Combining the results of these studies, a trend in risk reduction of thrombosis by adding UFH to the infusate was calculated (RR 0.6; 95% CI 0.34-1.06).

RCT with clinical endpoints

Cancer patients

In RCTs with clinically manifest thrombosis as a primary endpoint no clear benefit from anticoagulant prophylaxis was noticed in all three available studies (83-85) (Table 3). Remarkably, the absolute risk of clinically manifest thrombosis in the control group without anticoagulant prophylaxis was low in all these studies (4%), which might explain the lack of statistical power of these studies. The reason for the discrepancy with observational studies with incidences of up to 13% (Table 3) is unclear, but may be caused by selection of patients or referral criteria for diagnostic imaging.

There have been no studies in non-cancer patients or critically ill patients or pediatric patients in this category of studies.

Observational studies

Cancer patients

In cancer patients two cohort studies were performed which evaluated the effect of LMWH (two regimens) or a fixed low dose warfarin on CVC-related thrombosis (Table 3) (86;87). In a study among hematology patients a fixed low dose warfarin (1 mg orally) revealed

a 5% clinically manifest thrombosis, as compared with 13% in historical controls without (86). In another study with retrospective controls, a 7- (2850 IU) and 10-day (5700 IU) course of a LMWH in hematology patients was analyzed. Overall, there was no difference in the cumulative incidence of clinically manifest thrombosis between the groups who received nadroparin (7% and 8% respectively) and those without (6%) (87). However, in this study most thrombotic events occurred after stopping prophylaxis while the CVC remained in place. It is unknown whether a prolonged course would have been effective.

Combining the results of RCT and cohorts-studies, neither an effect of warfarin or heparin was calculated, with regard to the risk of clinically CVC-related thrombosis (warfarin: RR 0.72, 95% CI 0.27-1.9; heparin 0.92, 95% CI 0.57-1.49).

In order to reduce CVC the risk of intraluminal clot formation or dysfunction flushing or locking CVCs with UFH is performed routinely in many clinics. Whether such strategy is more beneficial as compared with saline is unsure. Currently there are no reliable data addressing this theme with clearly defined endpoints including routine assessment by contrast linogram, ultrasound/venography, response-rate to subsequent thrombolysis and safety.

Summary

In summary, the risk of thrombosis may be reduced by applying routine anticoagulant prophylaxis in patients with CVCs in cancer patients. However, a clear benefit was only demonstrated in cancer patients who underwent mandatory diagnostic imaging, including risk reduction of subclinical events. It is therefore debatable whether routine implementation of prophylaxis for CVCs is warranted. Besides, the safety of anticoagulant prophylaxis, a matter of serious concern especially with regard to patients with cancer, has not been studied well. In a recent survey, it was reported that a major reason for clinicians not to comply with consensus guidelines was the risk of bleeding due to thrombocytopenia, which presumably outweighed the risk of thrombosis, particularly in patients with cancer (88-90). In this view, individualized strategies upon allocation of risk assessment in certain vulnerable patients with CVCs and a high risk of thrombosis - such as those with (chemotherapy induced) thrombocytopenia - might be potentially useful to guide decisions on anticoagulant prophylaxis.

In non-cancer patients or critically ill patients no clear benefit from anticoagulant prophylaxis was observed. Available data consisted of small studies. With the improvement of CVC material no definite recommendations in these groups of patients can be made, until a large interventions study becomes available.

In critically ill children one study showed a risk reduction of CVC thrombosis using heparin bonded CVCs. These CVCs might be a safe alternative to systemic prophylactic anticoagulation, and this needs to be evaluated in other populations in need for short term catheterization.

Treatment

For the treatment of CVC-related thrombosis, various options are available. Anticoagulant treatment, removal or replacement of the CVC, or thrombolytic therapy may be used after a diagnosis of thrombosis is established. In this review randomized-controlled intervention-trials evaluating the recurrence rate of thrombosis and complications, and safety of therapy are considered most convincingly (level 1), cohort studies as level 2, case series as level 3.

Currently, no randomized trials have appeared in the literature. In one cohort study, 112 cancer patients with catheter-related thrombosis, a diversity of therapeutic interventions (several anticoagulation strategies with or without CVC removal) were shown not to result in major differences in clinical outcome (61). Treatment consisted of anticoagulation ($n = 39$), anticoagulation with CVC removal or replacement ($n = 22$), CVC removal or replacement ($n = 32$), other therapy ($n = 7$) or no therapy ($n = 8$). In no patients recurrent DVT or secondary complications or death of unknown cause occurred within 2 weeks of diagnosis, while in four patients with CVC replacement only symptoms of edema were persistent. In a prospective case-series of 46 outpatients with upper extremity DVT, in whom 16 (35%) had a central-vein catheter, showed that LMWH (Dalteparin 200 aXa IU kg^{-1}) for a minimum of 5 days together with oral anticoagulants was shown to be safe and effective (91) Evaluation after 12 weeks showed one recurrent DVT (2%), no secondary complications of DVT and one major bleeding event (2%). However, seven patients died, all presumably to underlying disease. Another study evaluated 36 patients with proven DVT of the upper extremity, mostly related to CVCs, up to 1 year after the diagnosis. With LMWH followed by oral anticoagulants (6 months), no recurrent DVT or secondary complications were noted. Nine patients died, presumably due to underlying disease (25%) (92).

A number of non-randomized studies of thrombolytic therapy in catheter related thrombosis have been carried out (93-96). In a retrospective analysis of 95 patients with an upper-extremity thrombosis of whom 62 patients were treated with anticoagulants and 33 with systemic thrombolysis, it was shown that in 21% of the patients, bleeding complications were observed after thrombolysis compared with no complications in the group of anticoagulants only (97). Besides, in the long term no clinical differences with regard to recurrent DVT and post-thrombotic syndrome were observed between thrombolysis and anticoagulation.

For the treatment of fibrin sheaths or luminal occlusion which can lead to CVC dysfunction, the first choice of therapy is local thrombolytic therapy with low dose tissue plasminogen activator (98;99) or urokinase (100,101). After 2-h treatment with 2 mg per 2 mL recombinant tissue plasminogen activator (Alteplase), function was restored to 74% in the alteplase arm and 17% in the placebo arm ($P < 0.0001$ compared with placebo) (98). After another dose (2 mg per 2 mL), function was restored in 90% of patients. There were no serious study-drug-related adverse events, no intracranial hemorrhage, no major hemorrhage, and no embolic events (98). Similar results were confirmed in a large randomized trial in over 1000 patients (99).

Summary

In summary, the treatment of catheter-related thrombosis is controversial. There are no randomized designed studies on the best treatment of catheter-related thrombosis, but in most cohort studies anticoagulant therapy is given. The necessity to remove the catheter depends on the underlying diagnosis and need for vascular access. There is a definite need for well designed studies evaluating the optimal treatment in CVC-related thrombosis. Because of the high rate of complications during systemic thrombolysis, this therapy should be reserved to life-threatening or extremity-threatening venous thrombosis.

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