bjh research paper

Incidence of thrombotic complications in patients with haematological malignancies with central venous catheters: a prospective multicentre study

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Received 1 February 2005; accepted for publication 11 April 2005

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Summary

This prospective, observational and multicentre study assessed the incidence of, and risk factors for, symptomatic venous thrombotic complications after central venous catheter (CVC) positioning in patients with haematological malignancies. A total of 458 consecutive CVC insertions were registered in 416 patients (81·2% of whom had severe thrombocytopenia). Over the observation period (3 months or up to catheter removal), the incidence of events was: CVC-related deep vein thrombosis (DVT), 1·5%; lower limb DVT, 0·4%; pulmonary embolism (PE), 1·3%; fatal PE, 0·6%; CVC-related superficial thrombophlebitis, 3·9%; CVC-occlusion/malfunction of thrombotic origin, 6·1%; major arterial events, 1·1%. Severe bleeding and CVC-related infections were observed in 3·5% and 4·6% of cases respectively. A composite end point (any venous thromboembolism or superficial thrombophlebitis or CVC occlusion/malfunction) was defined in order to consider venous thrombotic events with a significant impact on clinical practice. With this criterion, the overall incidence was 12·0% (2·54 cases/1000 catheter days). No factor helped to predict venous thrombotic complications: only thrombocytopenia was associated with a weak trend for a reduced risk (odds ratio 0·52; 95% confidence interval 0·26–1·07). No severe bleeding was observed in those patients who received antithrombotic prophylaxis. This study shows that the impact on clinical practice of symptomatic CVC-related thrombotic complications is not negligible in patients with haematological malignancies.

Keywords: central venous catheter, haematological malignancies, thrombosis, thrombocytopenia, antithrombotic prophylaxis.

The use of a central venous catheter (CVC) to facilitate the delivery of medications and of nutritional support has become increasingly frequent in a number of acute and chronic clinical conditions. However, benefits from CVC can be offset by complications associated with their use, such as thrombosis and infections, which may threaten the patient and/or impair CVC functioning (Verso & Agnelli, 2003). Many studies have addressed the incidence, associated risk factors and role of antithrombotic prophylaxis in patients with solid tumours, but only few data are available on haematological patients who often have severe thrombocytopenia (Cortelezzi *et al*, 2003; Couban *et al*, 2005). The latter might decrease the risk of thrombosis, but, on the contrary, increase bleeding and perhaps contraindicate the use of antithrombotic prophylaxis.

  doi:10.1111/j.1365-2141.2005.05529.x

The primary aim of this prospective, multicentre and observational study was to assess the incidence of, and risk factors for, symptomatic thrombotic complications after CVC positioning in patients with haematological malignancies.

Patients and methods

Elegible patients

Consecutive patients with haematological malignancies aged more than 18 years who underwent CVC positioning were eliglible for the study. Patients were prospectively followed-up from CVC insertion for 3 months or up to CVC removal, whichever came first. All types of CVCs were allowed, including tunnelized and non-tunnelized, centrally inserted, totally implanted and peripherally inserted devices, with both single and double lumen.

Design of the study

This study was performed between May 2002 and June 2003 in eight Italian Haematology Units. Each unit was allowed to use its own protocol for CVC care, defined and adopted prior to starting the study. The use of antithrombotic prophylaxis was left to the investigators' choice. Each CVC-positioning was considered as a single case for the study, so that a patient who had completed the scheduled observation period was registered as a new case for the study if another CVC was inserted. The study protocol was approved by Institutional Review Boards and participating patients gave written informed consent.

Events registered during the follow-up period were: deep vein thrombosis (DVT) of the upper limbs, DVT of lower limbs, pulmonary embolism (PE), CVC-related superficial thrombophlebitis, CVC occlusion/malfunction of thrombotic origin, atherothrombotic events (myocardial infarction, stroke and peripheral thromboembolism), bloodstream infections and CVC-related bloodstream infections, severe bleeding and death. Clinically suspected DVT and PE had to be confirmed by objective criteria (compression ultrasonography or venography, lung scan or computed tomography scan). CVC-related superficial thrombophlebitis was defined as the occurrence of signs/symptoms of inflammation along a superficial vein. CVC-occlusion/malfunction was defined as persistent pain during infusion or impossibility for sampling and/or infusion occurring after at least 24 h of initial adequate CVC function that was not reversible after at least two flushes with saline. In case of failure, low-dose urokinase was used. Malfunction/occlusion was attributed to thrombosis when other possible causes (i.e. kinking or rupture) were excluded. In order to consider thrombotic events with an impact on daily clinical practice, all DVTs or PE, superficial thrombophlebitis and CVC occlusion/malfunction attributable to thrombosis were included in a composite end point (one event considered for each case). As commonly accepted criteria for major bleeding, which include blood transfusion requirement, might be misleading in these patients, because of the type of disease and the frequent need for transfusions independently of haemorrhagic episodes, severe bleeding was defined as causing hospitalization, prolongation of hospital stay, or if it was life-threatening or fatal. Infections were classified and registered as bloodstream infections or CVC-related bloodstream infections as previously reported (Cortelezzi *et al*, 2003). All deaths were reviewed by an independent adjudication committee that evaluated a possible relationship with thromboembolic complications.

A dedicated electronic database was developed and used to collect the patients' main characteristics, including the disease under treatment, previous history of thrombosis and pertinent laboratory data. Detailed information on CVC positioning (type of CVC, order of CVC insertion–first, second and more than second, side and site of insertion, tip position and possible positioning-related complications) were also collected. During the follow-up, the reasons for using CVC (infusion, sampling and apheresis), duration of daily use and deviations from planned procedures of CVC care were recorded. Chemotherapy, anti-infective or anti-thrombotic drugs, transfusions, total parenteral nutrition, infusion of peripheral stem cells, both through CVC and/or other routes of administration, were also recorded. Daily dosages >5000 UI of unfractionated heparin, low molecular weight heparins or antiplatelet drugs were considered antithrombotic prophylaxis, whereas flushing of CVC with unfractionated heparin at doses of <5000 IU/d was not. Information on the occurrence, duration and severity of thrombocytopenia (platelet count $<50 \times 10^9$/l or $<10 \times 10^9$/l) and/or neutropenia ($<0{\cdot}5 \times 10^9$/l and $<0{\cdot}1 \times 10^9$/l) were recorded.

Statistical analysis

The sample size was computed according to the primary study objective that is merely descriptive. A total of 450 implanted catheters was calculated as necessary to provide a reliable estimate of the incidence of symptomatic thrombotic events (composite end point), by hypothesizing an event rate of 10%, with 95% confidence intervals (CI) of the estimate equal to the event rate ±2·5%. Assuming a ratio of catheters per patient equal to 1·1 during the period of survey, a sample size of 410 patients was computed. Descriptive statistics refer to all included cases. For continuous variables, the mean, standard deviation, median, minimum value and maximum value were calculated. For each discrete variable the number of cases in each category with missing or non-missing values, in relation to all cases with non-missing values of that variable, was calculated. The relationship of the composite study end point with covariates was investigated by means of univariate and multivariate logistic regressions with generalized estimating equation (GEE) approach and exchangeable correlation matrix in order to take into account clustered data (two or more catheters implanted in the same patient). The number and type of covariates included into the multivariate model were

selected according to the usual rule of thumb (no more than one covariate for 10 events) and based to prior knowledge about their clinical relevance, regardless of univariate and subset selection findings (epidemiological approach). Covariates included in the multivariate logistic regression were: type of CVC, use of antithrombotic prophylaxis, occurrence of thrombocytopenia ($<50 \times 10^9$/l) and catheter-related infection. Univariate analyses were performed to relate the aforementioned composite end point with the same covariates considered for the multivariate analysis, plus age group (≤50, 51–64, ≥65 years), gender, prior thrombosis, order of CVC insertion, high-dose chemotherapy, apheresis, stem-cell infusion, total parenteral nutrition and occurrence of bloodstream infection. Odds ratios (ORs) and 95% CI were reported with two-tailed probability (*P*) values. Statistical calculations were carried out using SAS version 8·2. A two-tailed *P*-value of 0·05 was used to define statistical significant results.

Results

Study population

A total of 458 cases of CVC positioning in 416 patients were entered in the study. Baseline demographic and haematological characteristics, underlying diseases and phases of treatment of the patients are shown in Table I. Previous thrombotic events were reported in 47 (10·3%) and mediastinal bulk in 25 (5·5%) of the cases. Thrombocytopenia ($<50 \times 10^9$/l) was present in 81·2% of cases, with a mean overall duration of 19·2 (±15·5) d, severe thrombocytopenia ($<10 \times 10^9$/l) in 53·2% of cases, with a mean overall duration of 5·6 (±6·8) d. Neutropenia ($<0{\cdot}5 \times 10^9$/l or $<0{\cdot}1 \times 10^9$/l) occurred in 69·2% and 59·8% of cases, lasting for a mean of 15·4 (±13·1) and 9·7 (±9·1) d respectively.

Table I. Patient characteristics at baseline, underlying haematological disease, and phase of treatment.

Patient characteristics (median, ranges)	
Age (years)	53 (18–87)
Gender (M/F) (*n*)	231/227
Weight (kg)	68 (40–126)
Neutrophils ($\times 10^9$/l)	2.5 (0–94.4)
Platelets ($\times 10^9$/l)	137.0 (0.1–894.0)
Haemoglobin (g/dl)	11.0 (5.0–17.0)
Disease *n* (%)	
Acute lymphatic leukaemia	47 (10.3)
Acute myeloid leukaemia	130 (28.4)
Chronic myeloid leukaemia	7 (1.5)
Multiple myeloma	86 (18.8)
Non-Hodgkin's lymphoma	107 (23.4)
Hodgkin's disease	18 (3.9)
Other	63 (13.7)
Phase of treatment, *n* (%)	
Induction	117 (25.6)
Consolidation	51 (11.1)
Salvage	73 (15.9)
Autologous-SCT	81 (17.7)
Allogeneic-SCT	35 (7.6)
Miscellaneous	101 (22.1)

SCT, stem-cell transplantation.

CVC positioning and use

Non-tunneled CVCs were the most frequently used type of catheters (65·9 %), peripherally inserted central catheters (PICCs) and port devices being used in a smaller number of cases (2·8% and 1·7 %) and tunneled in the remaining ones (29·6%). In 189 cases (41·3%) a CVC had been already positioned and removed at least once in the same patient.

Jugular and subclavian veins were the site of access in 49·1% and 43·0% of the insertions respectively; the right side was used in 79·7% of cases. In 54·5% of cases the catheter tip was positioned at the level of the cava vein, in 34·9% at the atrio-cava junction. The order of CVC positioning was: first in 58·7%, second in 19·2% and more than second in 22·1%. CVC was used for drug infusion in 96·7%, for sampling in 91·0%, for transfusions in 81·6%, for total parenteral nutrition in 40·6%, and for apheresis in 15·6% of cases. Mean (±SD) duration of CVC daily use (single or multiple periods for each case) was 25·7 (±17·0) d. Complications in CVC positioning were reported in 44 cases (9·6%), the most frequent being haematomas at the insertion site (17 cases, 3·7%). Central venous catheter malfunction at positioning in 10 cases and arterial puncture in eight cases (four of them inducing local haematoma) necessitated the need for revision. In one patient CVC insertion was complicated by pneumothorax.

Antithrombotic prophylaxis and other treatments

Antithrombotic prophylaxis was used in 65 cases (14·2%): low molecular weight heparin in 53 cases (11·6%); unfractionated heparin, antiplatelet agents and oral anticoagulants in six, five and one cases respectively. In 22 cases (4·8%) prophylaxis was given to patients who had previously suffered thrombotic events. Antibiotic prophylaxis was used in the great majority of patients included in the study to prevent bacterial, micotic or viral infections. Patients received high-dose or conventional dose chemotherapy in 179 (39·1%) and 195 (42·6%) cases, respectively, or both in 21 (4·6%) cases. Chemotherapy was administered through CVC in 98·7% of cases. Blood transfusions were required in 383 cases (83·6%), whilst 185 (40·4%) cases underwent total parenteral nutrition through the CVC. Peripheral stem cells were infused in 132 cases (28·8%), 112 of them (24·4%) through the CVC.

Infection and bleeding

The incidence of bloodstream infections and CVC-related bloodstream infections in the study population was 15·1% and

4·6% respectively. Severe bleeding events occurred in 16 cases (3·5%); in three patients bleeding (cerebral) was fatal. Sites and types of bleeding episodes were the followings: intracranial (seven cases), CVC insertion site (five), haematoma (two), intraperitoneal and multiorgan because of disseminated intravascular coagulation in one patient each. Two of the 16 patients with severe bleeding were receiving antithrombotic prophylaxis, but none of those who died of intracerebral bleeding was receiving antithrombotic prophylaxis.

Thrombotic complications

The incidence of thrombotic events is reported in Table II. CVC-related upper limb DVT was followed by CVC removal in four of seven cases; malfunction/occlusion of thrombotic origin was observed in 28 cases and was followed by CVC removal in 11 of them. Seven cases of PE (three fatal) were observed, one (non fatal) being concomitant with CVC-related DVT.

Composite end point

Figure 1 shows the incidences of events, obtained by adding progressively the clinically relevant complications. Column C represents a composite end point combining all the CVC-related venous thrombotic complications, and this end point

Table II. Incidence of thrombotic events.

Events	Percentage	*Number of events/1000 catheter-days*
CVC-related DVT	1·5 (0)	0·32
Lower limb DVT	0·4 (0)	0·09
Total PE/fatal PE	1·3 (0)/0·6 (0)	0·28/0·14
Superficial thrombophlebitis	3·9 (0·2)	0·83
CVC-malfunction/occlusion of thrombotic origin	6·1 (1·1)	1·29
Atherothrombotic events	1·1 (0·4)	0·23

CVC, central venous catheter; DVT, deep vein thrombosis; PE, pulmonary embolism. The percentage of events in patients receiving antithrombotic prophylaxis are shown in parentheses.

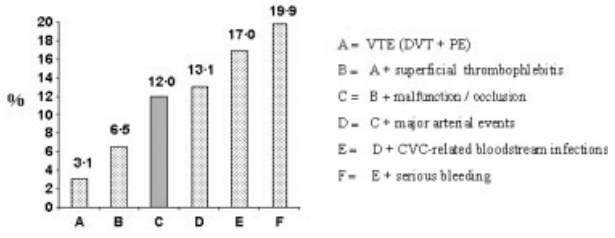

Fig 1. Composite incidence (%) of clinically relevant complications. Column *C* represents the clinical end point considered for univariate and multivariate analyses.

Table III. Relationship between variables and thrombotic complications: univariate analyses (for type of catheter, 'other' denotes peripherally inserted central catheter or port).

Variable	Effect	Odds ratio	95% CI
Age	51–64 vs. ≤50 years	0·70	0·38–1·28
	≥65 vs. ≤50 years	0·82	0·34–1·94
Gender	Male vs. female	0·86	0·49–1·51
Previous thrombosis	Yes vs. no	1·59	0·70–3·59
Type of catheter	Non-tunnelled vs. tunnelled	1·49	0·74–3·01
	Other vs. tunnelled	0·47	0·06–3·98
Order of CVC positioning	II vs. I	1·49	0·74–3·00
	>II vs. I	1·38	0·71–2·72
High-dose chemotherapy	Yes vs. no	0·94	0·54–1·63
Apheresis	Yes vs. no	1·23	0·60–2·52
Stem-cell infusion	Yes vs. no	0·85	0·44–1·62
Total parenteral nutrition	Yes vs. no	0·98	0·57–1·71
Antithrombotic prophylaxis	Yes vs. no	0·71	0·30–1·70
Thrombocytopenia	Yes vs. no	0·57	0·30–1·10
BSI	Yes vs. no	1·16	0·55–2·48
Catheter-related BSI	Yes vs. no	0·76	0·17–3·37

BSI, blood stream infection; CI, confidence intervals; CVC, central venous catheter.

Table IV. Relationship between variables and thrombotic complications: multivariate logistic regression analysis (for type of catheter, 'other' denotes peripherally inserted central catheter or port).

Variable	Effect	Odds ratio	95% CI
Type of catheter	Non-tunnelled vs. tunnelled	1·65	0·79–3·43
	Other vs. tunnelled	0·45	0·05–4·43
Antithrombotic prophylaxis	Yes vs. no	0·69	0·28–1·70
Thrombocytopenia	Yes vs. no	0·52	0·26–1·07
Catheter-related BSI	Yes vs. no	0·80	0·18–3·69

BSI, blood stream infection; CI, confidence intervals.

was considered for univariate (Table III) and multivariate analyses (Table IV). None of the variables selected for statistical analysis was significantly related to the occurrence of venous thrombotic complications. However, thrombocytopenic patients tended to have a lower risk of thrombotic events, close to statistical significance (OR 0·52; 95% CI 0·26–1·07 – multivariate analysis). In Fig 2 the time distribution of venous thrombotic events (column C, Fig 1) is reported. The great majority of events occurred within the first 20 d after catheter insertion.

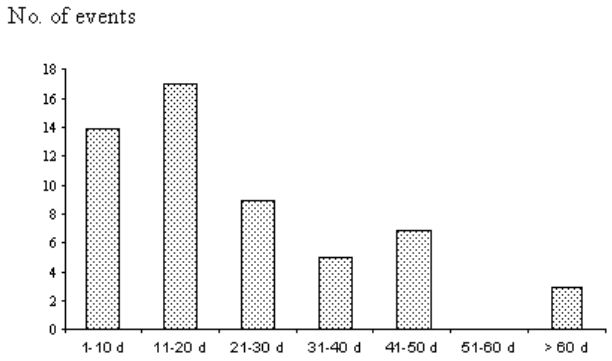

Fig 2. Time-distribution of venous thrombotic complications included in the composite end point (d = days).

Follow-up

The mean observation period was 47·2 ± 35·2 d. In 156 cases (34·1%) the planned observation period of 3 months was achieved. In 177 cases (38·6%) CVC was removed because it was no longer used before the end of the planned observation period. CVC removal for thrombotic or infectious complications occurred in 47 cases (10·2%, in 16 cases because of thrombotic events, in 31 because of infection). Four patients were lost to follow-up (0·9%). Interruption of the study occurred in 22 cases (4·8%) and it was related to other reasons (i.e. removal of the CVC caused by accidental events, or local side effects at the insertion site). Fifty-two patients (11·3%) died during the scheduled observation period: in three cases death was caused by an acute thrombotic complication (objectively documented fatal PE). In the remaining patients, death was because of disease progression and/or other disease-related complications.

Discussion

In adult patients with malignancy the reported incidence of clinically overt CVC-related venous thrombosis ranges from 0·3% to 28·3% (0·02–0·92 events/1000 catheter days) (Bona, 1999; Verso & Agnelli, 2003). In a recent meta-analysis (Klerk *et al*, 2003) the incidence of thrombosis varied between 0% and 20% when symptomatic thrombosis was considered, and between 27% and 90% when thrombosis was objectively diagnosed. The majority of objectively detected thrombi were clinically silent (Lokich & Becker, 1983; Bern *et al*, 1990; Balestrieri *et al*, 1995; Monreal *et al*, 1996; De Cicco *et al*, 1997; Franck *et al*, 2000; Glaser *et al*, 2001) and non-occlusive (Martin *et al*, 1999). CVC-related thrombosis was evaluated mainly in patients with solid tumours, but fewer data are available in patients with haematological malignancy (Couban *et al*, 2005). Data on CVC-related complications in haematological patients had been obtained mainly from retrospective studies of small sample size, whereas in this prospective observational, multicentre study the incidence of clinically overt thrombotic complications was evaluated in a large cohort of consecutive haematological patients with CVC.

We arbitrarily chose a cumulative end point of clinically significant thrombotic events (including DVT, superficial thrombophlebitis, and occlusion/malfunction), because these symptomatic events have a remarkable impact on the daily clinical practice in haematological patients. Our choice to look only for symptomatic events was driven by the consideration that the clinical relevance of asymptomatic CVC-related thrombosis is still debated and regular screening with objective tests is generally not recommended.

In this study an incidence of 12% of thrombotic events, as previously defined, was recorded; 3·2% were major events such as DVT and/or PE. However, in our experience, even a minor event, such as a CVC occlusion, had a significant impact on the clinical management of these patients. The relatively low incidence of major thrombotic events in our registry may be explained by the fact that patients were enrolled in haematological units with teams experienced in CVC positioning and care. Each haematology unit had written procedures (collected and reviewed before the start of enrolment) that were strictly followed during the observation period. In 64·2% of the cases, CVCs were positioned in the surgical room under sterile conditions and CVC insertion was controlled radiologically in 84·9% of patients. The CVCs with higher thrombotic (PICCs) (Cortelezzi *et al*, 2003) and haemorrhagic risks (totally implantable) (Johansson *et al*, 2004) were used in a very small proportion of patients (4·5%). The majority of venous thrombotic events (72·7%) occurred within 1 month from CVC-positioning, with a median interval of 19 d after CVC placement, a timing consistent with previous findings (van Rooden *et al*, 2003).

In this study, no predictive factors seemed to influence the occurrence of venous thrombotic complications, at variance with other findings suggesting a role for type of catheter, high-dose chemotherapy, apheresis (Haire *et al*, 1990, 1991; Conlan *et al*, 1991; Sletnes *et al*, 1996), or infections (Raad, 1998). However, it should be noted that only a minority of patients used the CVCs at higher thrombogenic potential. Thrombocytopenia was associated with a trend for reduced risk of thrombotic complications. However, >10% of severely thrombocytopenic patients had an episode of venous thrombosis, and three of six cases of pulmonary embolism occurred in thrombocytopenic patients.

The use of routine antithrombotic prophylaxis to prevent CVC-related thrombosis is still debated (Klerk *et al*, 2003; Geerts *et al*, 2004). Although some studies carried out in patients with tumours have shown a benefit of prophylaxis with low molecular weight heparin or fixed low-dose warfarin (Bern *et al*, 1990; Monreal *et al*, 1996; Boraks *et al*, 1998), other studies did not confirm these results (Heaton *et al*, 2002; Reitchard *et al*, 2002; Massicotte *et al*, 2003; Couban *et al*, 2005; Verso *et al*, 2005), so that no definite recommendations are currently available (Verso & Agnelli, 2003). Haematological patients may differ from patients with solid tumours because

they present more frequently with severe thrombocytopenia. This may decrease the risk of thrombosis but may increase that of bleeding. In this study 14·2% of patients received antithrombotic prophylaxis, mainly low molecular weight heparin. The decision of using antithrombotic drugs was left to the attending physician. Antithrombotic prophylaxis was not associated with an increased incidence of severe bleeding. However, it should be kept in mind that this study was not planned to give an answer on the efficacy and safety of antithrombotic prophylaxis in haematological patients with CVC.

In conclusion, our survey provides information on the incidence of clinically overt thrombotic complications in patients with haematological malignancies with a CVC, showing that they remain a clinical problem. Future studies may utilize the cumulative clinical end point developed in this prospective registry in order to test the efficacy of drugs or of other tools meant to reduce the incidence of clinically relevant CVC-related thrombotic complications in haematological patients.

Acknowledgements

We are indebted to Carlo Bianchini for his scientific advice; to Mario Marzanatti for development of the electronic database and data management; to Patrizia Ronchetti and Dina Casiraghi for their secretarial assistance; to the nursing staff of the participating Centres for their co-operation; and to the patients included in the study for their trust and support.

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Appendix

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