Coagulation, angiogenesis and cancer

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Prevention of catheter-related venous thrombosis with nadroparin in patients receiving chemotherapy for hematological malignancies, a randomized placebo controlled study

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Chapter 9

Abstract

Background
Hemato-oncology patients treated with intensive chemotherapy usually require the placement of a central venous catheter (CVC). CVCs are frequently complicated by catheter-related central venous thrombosis (CVT), which has been associated with an increased risk of pulmonary embolism and catheter-related infection.

Objectives
To determine the efficacy and safety of thromboprophylaxis with s.c. low-molecular-weight heparin (nadroparin) administered once daily in a randomized placebo-controlled, double-blind trial in patients with hematologic malignancies.

Patients and methods
Consecutive patients with hematologic malignancies requiring intensive chemotherapy including autologous stem cell transplantation were eligible. The patients were randomized to receive nadroparin 2850 anti factor Xa units once daily or placebo s.c. for 3 weeks. Venography was performed on day 21 after CVC insertion. Secondary outcomes were bleeding and catheter-related infection.

Results
In total, 113 patients were randomized to nadroparin or placebo, and 87 patients (77%) underwent venography. In total, 11 venographically proven catheter-related CVTs were diagnosed. The frequency of catheter-related CVT was not significantly different between study groups, namely four catheter-related CVTs in the placebo group (9%; 95% CI: 0.002–0.16) vs. seven catheter-related CVTs in the nadroparin group (17%; 95% CI: 0.06–0.28). In addition, no difference in the incidence of catheter-related infection or bleeding was observed between the groups.

Conclusions
This study showed that the actual risk for catheter-related CVT in patients with hematologic malignancies is lower than suggested in earlier studies in cancer patients. Although prophylactic administration of nadroparin appeared to be safe in this group of patients with a high risk of bleeding, it cannot be recommended for the prevention of catheter-related CVT or catheter-related infection in patients with hematologic malignancies.
Introduction

In the last three decades substantial progress has been made in the treatment of patients with hematological malignancies. In particular, high dose chemotherapy including autologous stem cell transplantation and better supportive care has improved the prognosis of these patients. Nowadays, most patients undergo a central venous catheter (CVC) placement before intensive chemotherapy for the frequently combined administration of cytotoxic agents, blood products, antibiotics and parenteral nutrition. However, these CVCs are often complicated by catheter-related central venous thrombosis (CVT) and infection. Previous studies have shown that the incidence of venographically proven catheter-related CVT in cancer patients treated with high dose chemotherapy, varies considerable and ranges between 27% and 66%\(^1\).\(^2\). Importantly, although the majority of these cases are asymptomatic, prospective studies have shown that 15% of catheter-related CVT are accompanied by (silent) pulmonary embolism\(^1\).\(^3\). In addition, catheter-related CVT and in particular asymptomatic catheter-related CVT increase the risk of catheter-related infections\(^4\) and subsequent catheter-related sepsis\(^5\). Besides the high risk of fatal outcome of catheter-related sepsis in neutropenic patients, infected catheters have to be often replaced since administration of parental nutrition, intravenous medication and blood products remain indicated.

It is a matter of debate whether thromboprophylaxis is indicated in cancer patients with CVC, and if so, which type of drug or regimen can be recommended. Several studies have evaluated the efficacy of low dose warfarin or heparin prophylaxis in a variety of cancer patients with CVCs\(^6\)-\(^14\), but do not allow any firm conclusion regarding the clinical effectiveness. Most of the studies were hampered by an open study design, small sample size or used different study outcome definitions. A few placebo-controlled trials in cancer patients with venographically proven catheter-related CVT have recently been performed, although these studies have excluded most patients with hematological malignancies, because of the high risk of bleeding\(^10\)-\(^14\).\(^16\).

We therefore performed a prospective, placebo-controlled, double-blind randomized trial to assess the effect of low molecular weight heparin (LMWH) on the incidence of catheter-related CVT and catheter-related infection in a group of patients with hematological malignancies receiving high-dose chemotherapy including autologous stem cell transplantation. In addition, the bleeding risk of the prophylactic dose of LMWH was evaluated.

Patients and Methods

Patients

Consecutive patients with hematological malignancies who were going to receive a CVC for high-dose chemotherapy including autologous stem cell transplantation were eligible
for the study. Patients were excluded in case of: age below 17 years, allergy for i.v. contrast medium, previous catheter-related CVT, current use or indication for anticoagulant treatment, acute promyelocytic leukemia, previous CVC, evident hemorrhagic diathesis or renal failure (creatinine > 200 μmol/L).

**Study design**
This study was designed as a single-center, prospective, randomized, placebo controlled, double blind trial, to evaluated the efficacy and safety of LMWH 2850 antifactor (anti FXa) units once daily (nadroparin, Fraxiparin, Sanofi-Synthelabo) for the prevention of catheter-related CVT in patients with hematological malignancies. Patients were randomized to receive either once daily nadroparin or placebo injections s.c. The study medication was started 2 h before insertion of the CVC and was continued for three weeks or until the day of CVC removal, whichever came first. The CVC was inserted according to a standard protocol under sterile conditions. The study was performed at the Department of Haematology of the Academic Medical Center in Amsterdam, The Netherlands. The study protocol was approved by the local ethics committee, and all participating patients gave written informed consent. The study drug was obtained commercially, and there was financial support for the study.

**Outcomes**
The primary outcome was venographically proven catheter-related CVT. Catheter-related CVT was defined as either occlusive or non-occlusive thrombosis of the vein in which the CVC was placed or a contiguous vein. Patients with clinically suspected catheter-related CVT prior to venography were investigated by duplex ultrasonography first. A positive ultrasound was also considered to be diagnostic for catheter-related CVT. A normal ultrasound had to be followed by venography. The ultrasound criteria for thrombosis were: non-compressibility of a venous segment; and a visible intraluminal thrombus or an abnormal flow pattern (absent flow or absence of phasic flow pattern) indicating outflow obstruction. A normal ultrasound finding had to be followed by venography. In all other patients, venography was scheduled for day 21 after CVC insertion or earlier in case of premature removal of the CVC. Venography was performed according to standard procedures using a distal vein in the ipsilateral hand or arm to inject the contrast medium. All venograms were independently adjudicated by an expertise radiologist using a priori found criteria without knowledge of treatment allocation. Occlusive catheter-related CVT was defined as complete stasis of contrast with filling of collateral veins. In the case of occlusive catheter-related CVT, the catheter was removed and therapeutic anticoagulation was started and continued for three months. Non-occlusion catheter-related CVT was defined as an intravascular filling defect with normal flow to the superior or inferior cava vein. Non-occlusive catheter-related CVT was not treated, but patients were carefully followed-up.
Secondary outcomes of this study were the frequency of bleeding, the incidence of catheter colonization, catheter-related infection and catheter-related sepsis. Bleeding was classified as major, clinically relevant non-major or minor bleeding. Major bleeding was defined as overt bleeding with a fall in hemoglobin of 2 g/dL or more, or leading to a transfusion of 2 or more units of packed red blood cells, or bleeding in a critical organ such as intracranial, retroperitoneal or pericardial, or contributing to death. Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding and include skin hematoma if the size is larger than 100 cm², epistaxis lasting more than 5 minutes or repetitive (i.e. two or more episodes within 24 hours) or leading to an intervention (packing, electro coagulation), macroscopic hematuria if spontaneous or lasting for more than 24 hours after instrumentation (e.g. catheter placement or surgery), or any other bleeding type that was considered to have clinical consequences for the patient. All other bleeding episodes not meeting the criteria for clinically relevant bleeding were classified as minor bleeding. Since prolonged exposure to heparins may be associated with heparin-induced thrombocytopenia (HIT) all patients underwent antibody screening on day 14. HIT was only diagnosed if there was a clinical suspicion and positive antibodies against the heparin-platelet factor 4. Antibody screening for HIT was performed with the previously described PF4-heparin enzyme-linked immunosorbent assay (ELISA)\textsuperscript{18,19}. CVC-related infections were distinguished as ‘systemic CVC-related infection’, ‘Insertion site infection’ and ‘CVC colonisation’ according to well established definitions\textsuperscript{20}. Systemic CVC-related infection was defined as presence of fever (body temperature >38.5°C) or hypothermia (body temperature <36°C) with one or more positive peripheral drawn blood cultures (for Staphylococcus epidermidis at least two positive cultures are required) in combination with either a positive blood culture drawn from the catheter, or tip colonisation (15 colony-forming units; CFU) with the same organism, or with a purulent insertion point with the same organism in culture as the blood cultures. Insertion site infection was defined as a purulent insertion point with or without localized findings such as pain, erythema or tenderness without fever. CVC colonization was defined as at least more than 15 CFU found on the catheter tip through the rolling method without systemic signs of infection.

**Statistical analysis**

The study was powered to find a reduction in catheter-related CVT of minimally 50% with an anticipated incidence rate of 60% in those receiving placebo. It was therefore estimated that 50 patients per group were required. Baseline characteristics for continuous variables were expressed, depending on the distribution of the data, as mean (SD) or median (range). Differences in baseline characteristics between the two groups were analyzed using the chi-squared test. The primary outcome was venographically proven catheter related CVT and was dichotomously scored. Differences between the two treatment groups were analyzed using the chi-squared test. Statistically significance was established.
at p<0.05. All analyses were performed using SPSS (SPSS Benelux B.V., Gorinchem, The Netherlands).

Results

Patient population
A total of 202 consecutive patients were eligible. Forty-five patients were excluded for the following reasons; three (3%) patients had an allergy to contrast medium; 16 (18%) patients had an indication for anticoagulation; eight (9%) patients had a previous CVC in the same vein; one (1%) patient had an evident hemorrhagic diatheses; three (2%) patients had renal failure and 14 (16%) patients could not be included because of logistic problems. Of the remaining 157 eligible patients, 44 (28%) patients refused consent. Therefore, a total of 113 patients were eventually randomized to nadroparin or placebo (Table 1). The study-treatment groups were well balanced with regard to gender, CVC location, and type of hematological malignancies. The majority of patients included had acute myeloid leukemia or multiple myeloma.

Catheter-related CVT and catheter-related infection
Of the 113 randomized patients, 15 patients (27%) in the nadroparin group and 11 patients (19%) in the placebo group did not undergo venography, because of prior catheter removal because of suspected serious infections (five patients in each group), logistic problems including catheter removal during weekends (six patients in the nadroparin group and four patients in the placebo group) or withdrawal of informed consent (four patients in the nadroparin group and two patients in the placebo group). Eighty-seven patients (77%) underwent venography which was adequate in all (Table 2 and 3). Eleven catheter-related CVT were diagnosed, seven (17%) in the nadroparin group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nadroparin (n=56)</th>
<th>Placebo (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean +/- SD)</td>
<td>58 +/- 10</td>
<td>55 +/- 13</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>27 (48%)</td>
<td>24 (42%)</td>
</tr>
<tr>
<td>Hematological tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute myeloid leukemia/ MDS RAEB*</td>
<td>23 (41%)</td>
<td>17 (30%)</td>
</tr>
<tr>
<td>acute lymphoblastic leukemia</td>
<td>2 (4%)</td>
<td>10 (18%)</td>
</tr>
<tr>
<td>multiple myeloma</td>
<td>14 (25%)</td>
<td>16 (28%)</td>
</tr>
<tr>
<td>(non) Hodgkin lymphoma- relapsed</td>
<td>17 (30%)</td>
<td>14 (24%)</td>
</tr>
<tr>
<td>Central venous catheter location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>subclavian vein, left</td>
<td>15 (27%)</td>
<td>20 (35%)</td>
</tr>
<tr>
<td>subclavian vein, right</td>
<td>32 (57%)</td>
<td>28 (49%)</td>
</tr>
<tr>
<td>jugular vein, left</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>jugular vein, right</td>
<td>9 (16%)</td>
<td>8 (14%)</td>
</tr>
</tbody>
</table>

Table 1. Baseline characteristics of the two study groups. * MDS RAEB; myelodysplastic syndromes refractory anemia and excess blasts.
Prevention of catheter-related venous thrombosis

vs. four (9%) in the placebo group (p=0.49). Only one patient (in the placebo group) had a symptomatic catheter-related CVT which was confirmed by venography. The median number of days between CVC insertion and venography was 20 (quartile 25-75%, 18-21 days) in the nadroparin group vs. 19 days (quartile 25-75%, 17-20 days) in the placebo group.

Nineteen patients (17%) were diagnosed with systemic catheter-related infection (nine patients in the nadroparin group versus 10 patients in the placebo group; p=0.35). The microorganisms involved in systemic catheter-related infection were 18 cases of coagulase-negative \textit{Staphylococcus} infections (eight cases in nadroparin group and 10 cases in the placebo group) and one with \textit{Klebsiella pneumonia} (in the nadroparin group). None of the patients had a localized infection of the insertion site. Two patients (4%) in the placebo group had CFUs found on the catheter tip with coagulase-negative \textit{Staphylococcus} in both cases. Catheter-related CVT and catheter-related infection coincided in two out of seven patients in the nadroparin group and two out of four patients in the placebo group.

\textbf{Safety}

There were no cases of major bleeding (Table 4). Clinically relevant non-major bleeding occurred at a similar rate in the nadroparin and placebo group (two patients (4%) in both groups).
Minor bleeding was experienced by five patients (9%) in the nadroparin group vs two patients (4%) in the placebo group. Two patients had positive serology for antibodies against platelet FIV-heparin complexes but had no clinical suspicion of HIT. One of these two patients developed thrombosis but had no persistent thrombocytopenia and was uneventfully treated with nadroparin at a therapeutic dose.

**Discussion**

In this study, no beneficial effect of prophylactic nadroparin on the incidence of catheter-related CVT was demonstrated (9%; 95% CI: 0.002 to 0.16; in the placebo versus 17%; 95% CI: 0.06 to 0.28; in the nadroparin group). In addition, no significant difference in catheter-related infection or bleeding was observed between the groups.

Previous studies in cancer patients have reported a wide range of catheter-related CVT rate with incidences up to 66%21. Lower incidence rates of catheter-related CVT have been reported in more recent studies 10,12,14 as compared to the initial observations 7,13,21,22. The frequency of catheter-related CVT in our study is very comparable to what was found in three recent studies which demonstrated a venographically proven thrombosis rate between 3.4% and 18%10,14. Moreover, two of these studies did not find any effect of LMWH thromboprophylaxis on the incidence rate of catheter-related CVT whereas a non-statistically significant reduction in the rate of thrombosis was found in the third study of Verso et al 14. As the proportion of patients with a hematologic malignancy varied - 9%12, 10%10 and 16%14 - in these studies, the reduced incidence of catheter-related CVT cannot be explained by the fact that more hematologic patients were included than in the older studies. Also no difference in the treatment period was found between the studies that could explain the difference in thrombosis. Other factors, such as catheter type, standardized catheter care, and improved supportive care, may be responsible for the lower rate of catheter-related CVT in the more recent studies.

Some aspects of our study require comment. Firstly, the study has a limited sample size relative to the low incidence of catheter-related CVT. However, as thrombosis rates in our study appeared to be even slightly higher in the nadroparin-treated group (17%) as compared to the control group (9%), it is unlikely that a potential effect of nadroparin was missed, although this cannot be excluded. Secondly, approximately one-quarter of the randomized patients were not analyzed by venography for various reasons. Although

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Nadroparin (n=56)</th>
<th>Placebo (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>major bleeding</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>clinically relevant non major bleeding</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>minor bleeding</td>
<td>5 (9%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Frequency of positive HIT* serology</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
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</tbody>
</table>
this is a considerable proportion, the number of missed venographies was similar in both groups. Furthermore the study groups (with and without venography) were comparable with respect to baseline and prognostic variables. Therefore, the internal validity of the study remains high. Thirdly, although our study is a single center study we included a representative group of patients with hematological malignancies requiring high dose chemotherapy and hence we believe that our findings can be extrapolated to these types of patients.

In conclusion, this study showed that the actual risk for catheter-related CVT in patients with hematological malignancies is lower (approximately 13%) than suggested in earlier studies in cancer patients. Although prophylactic administration of nadroparin appeared to be safe in this group of patients with a high risk of bleeding, it cannot be recommended for the prevention of catheter-related CVT or catheter-related infection in patients with hematological malignancies.

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Chapter 9

References


