Prolonged interval in prophylactic heparin flushing for maintenance of subcutaneous implanted port care in patients with cancer

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The long-term use of subcutaneous implanted ports for chemotherapy in cancer patients has been associated with the occurrence of thrombosis and infection. In this study, we compared the safety and efficacy of administration of 1000 U of heparin flushes in prolonged interval (every 6 weeks) with standard dose and schedule (500 U every 4 weeks) for port-related infections and thrombosis during periods of non-use. Data were collected retrospectively from patients treated for various cancer types (matched as 2:1 for age, gender, stage of the disease). Patients who had diseases that could cause thrombosis or bleeding in their past medical history, or were taking oral anticoagulants, or had contraindications for heparin usage were excluded. After completing their chemotherapy, 59 patients received prolonged interval, while 30 patients received standard schedule. All patients were followed for at least 1 year. No clinically documented port-related infection or thrombosis has been found in both groups. Also, none of the devices was removed during this time. Prophylactic flushing of central venous ports with 1000 U of heparin in every 6 weeks might be a safe, easy, cheaper, comfortable and effective alternative to standard dose and schedule for preventing thrombosis and infections.

Keywords: catheters, indwelling, catheterization, central venous, neoplasms, heparin, venous thrombosis

INTRODUCTION

Central venous catheters (CVCs) and ports have become the cornerstone of therapy in general medicine and oncology. They have considerably changed the nature of chemotherapy administration, improved the quality of life of patients and facilitated transfusions, parenteral nutrition and blood sampling (O’Grady et al. 2002, Verso & Agnelli 2003, Dillon et al. 2004). The ideal CVC should be inserted and cared easily, should have low infection and trombogenic risk and should be used in long term (Barbati & Lucugnano 1997; O’Grady et al. 2002).

Several problems are associated with the long-term use of CVCs and subcutaneous implanted ports for chemotherapy in cancer patients. The most common and serious complications, aside from their insertional complications [catheter misplacement or breakage, pneumothorax and...
hemotherax, air embolism and injury to adjacent anatomic structures [Mansfield et al. 1994; Taber & Bergamini 1997; Verso & Agnelli 2003; Pazdur et al. 2005]), are thrombosis and infection. Previous studies demonstrated that catheter-related infection and thrombotic events have resulted in catheter removal in 20–35% of patients [Wiener et al. 1992; Fan 1998].

In clinical studies, it has been shown that within days of insertion, almost all CVCs are coated with a fibrin sheath and this fibrin deposition within catheters causes thrombosis. Thrombosis is a major risk factor for infection of CVCs and leads to catheter-related infection [Verso & Agnelli 2003; Dillon et al. 2004]. Consequently, many attempts are tested by using heparin or other solutions to prevent fibrin and/or thrombus formation. A meta-analysis of randomized controlled trials in CVC patients showed a benefit of heparin in the prevention of venous thromboembolic complications and of catheter colonization [Wickham et al. 1992]. Several studies have been performed on the prophylactic use of unfractionated heparin, low-molecular-weight heparin, warfarin and thrombolytic agents to reduce thrombosis and infection [Bern et al. 1990; Fraschini et al. 1991; Monreal et al. 1996; Boraks et al. 1998; Randolph et al. 1998; Ray et al. 1999; Solomon et al. 2001; Massicotte et al. 2003; Mismetti et al. 2003; Dillon et al. 2004; Karthaus et al. 2006].

To our knowledge, there is no widely accepted prophylactic heparin dosing regimen. Standard duration between CVC cares is generally accepted as 4 weeks for long-term prophylaxis and 500 U of heparin is preferred in some practices [Pazdur et al. 2005; Central Venous Access Device Guideline Panel 2006]. Individual trials of prophylaxis in patients with prophylaxis in CVCs are contradictory [Monreal et al. 1996; Randolph et al. 1998]. In our practice, we also use the regimen of 1000 U of heparin in every 6 weeks for the prophylaxis of CVCs during periods of non-use.

The purpose of this study was to compare the safety and efficacy of administration of increased dose (1000 U) of heparin flushes in prolonged interval (every 6 weeks) versus standard dose and schedule (500 U every 4 weeks) for reducing the incidence of port-related infections and thrombosis during periods of non-use.

**MATERIALS AND METHODS**

The study was designed as a retrospective trial in patients with diagnosis of cancer who have been inserted CVCs and ports for their chemotherapy treatment.

Patients had received chemotherapy for various malignancies, including gastrointestinal system cancer, head and neck cancer, breast cancer and renal carcinoma, had no other diseases in their past medical history that could cause thrombosis or bleeding and had CVCs [Table 1]. Also patients taking oral anticoagulants or patients having contraindications for heparin usage were not included into the study. Patients were matched as two cases to one control subject for age, gender, stage of the disease. Data collection occurred during a 32-month period from February 2003 to October 2005.

During their active chemotherapy, all patients received 500 U of heparin flushes. After completing their chemotherapy, 59 patients received 1000 U of heparin flushes in 3 ml of normal saline in every 6 weeks [group 1], while 30 patients were administered 500 U of heparin in 3.5 ml of normal saline in every 4 weeks [group 2].

All patients were followed regularly for clinical signs of thrombosis and central venous port-related infections for at least 3 months. Patients received regular port care by the same group of trained oncology nurses according to clinic’s standard regulations. Patients’ data routinely were documented on standardized data collection forms.

### RESULTS

Eighty-nine patients were enrolled into the study, 59 patients [group 1] received 1000 U of heparin and 30 patients [group 2] received 500 U of heparin. There were a male predominance [n: 50] and the majority of patients had gastrointestinal system carcinoma. The characteristics of patients are shown in Table 2.

The mean duration of chemotherapy treatment was 7.6 months for the first group [range: 3–12 months] and 3 months [range: 2–12 months] for the second group. In group 1, there were no patients with renal cancer and, in group 2, there were no patients with breast cancer.

Aside from the complications of CVC placement, no clinically documented port-related infection or thrombosis has been found among these two groups. Also, none of the devices were removed during this time. None of the

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**Table 1. Classification of median port duration during chemotherapy according to patients’ cancer type**

<table>
<thead>
<tr>
<th>Patients’ cancer type</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal system cancer</td>
<td>8.9</td>
<td>7.75</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>7.6</td>
<td>3</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>Renal cancer</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Other cancer</td>
<td>9.3</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1. Classification of median port duration during chemotherapy according to patients’ cancer type

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patients in both groups reported any kind of bleeding in this study.

**DISCUSSION**

The incidence of clinically symptomatic catheter-related infection and thrombosis was totally zero in this study. There were no differences between flushing of catheters with 1000 U of heparin in every 6 weeks versus flushing with 500 U of heparin in every 4 weeks. The likely reasons for these results might be related to strict port care by the trained nurses [Karamanoglu et al. 2003] and close follow-up of patients by the doctors. These trained staff played a significant role in reducing catheter-related complications. Patients were given clear and specific instructions about what they should do and what symptoms they should report. The ability to minimize and accurately recognize catheter-related problems requires adequate education of nurses and physicians because their inexperience has been documented to be the factor that is most frequently related to catheter complications. The development of standards of care and expertise in staff are important components to successfully prevent catheter-related complications. Research in the field of nursing care is needed to provide support for nursing practice, as tradition commonly provides the rationale for current practice [Wickham et al. 1992, Scott 1998].

Increasing the dose of heparin and the interval between central venous port cares was preferred by patients as every return visit to infusional therapy clinics is a stress factor for patients. Longer interval duration between visits increases the quality of life of both patients and families. It decreases the cost both to patient and families and to the healthcare system (for transportation, equipment that is used in port care, more efficient usage of time for educated oncology nurses, less working days that will be missed by patients and family members, etc.). Also when the number of hospital visits for CVC management and maintenance decreases, patients, families and staff save time.

Standard duration between CVC cares is generally accepted as 4 weeks for long-term prophylaxis and 500 U of heparin is preferred for prophylaxis in some practices [Pazdur et al. 2005; Central Venous Access Device Guideline Panel 2006]. Randolph et al. [1998] reported a meta-analysis of 14 randomized controlled trials evaluating prophylactic doses of heparin or heparin bonding. They found a significantly decreased risk of thrombosis, colonization of the catheter and an associated reduction in catheter-related bacteraemia with prophylactic heparin administration. Also, a randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of dalteparin in preventing catheter-related complications in cancer patients [Karthaus et al. 2006]. In contrast to previous results, this study did not show a benefit in terms of reduction of CVC-related complications in the dalteparin group as compared with placebo.

Another study in cancer patients compared a monthly installation of heparin with urokinase administration in implanted ports [Fraschini et al. 1991]. Patients in the urokinase group had lower rates of infection and catheter occlusion compared with those in the heparin group. In contrast, Dillon et al. compared the efficacy of an every-2-week (14-day) instillation of urokinase versus heparin for reducing the incidence of catheter-related infections and occlusions in central venous devices in children with malignancies. No differences in the number of total occlusive events and in the rates of infection were noted between urokinase or heparin treatment groups.

The finding of these studies is consistent with that a significant proportion of CVCs are affected by thrombotic events and infection. Several studies have been performed to prevent these complications by the prophylactic use of unfractionated heparin, low-molecular-weight heparin, warfarin and thrombolytic agents [Bern et al. 1990; Monreal et al. 1996; Boraks et al. 1998; Ray et al. 1999; Solomon et al. 2001; Massicotte et al. 2003; Mismetti et al. 2003]. Conflicting results and differences in complications have been observed. Additional studies are needed to define the efficacy and safety of pharmacological prophylaxis in cancer patients with CVCs.

The major limitations of our study are that patients are enrolled into the study retrospectively and the number of control patients is limited. Patients were matched as two cases to one control subject. For the detection of infection, no microbiologically documented data were collected, so colonization of catheters, if existed, might have been

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**Table 2. Patients’ characteristics**

<table>
<thead>
<tr>
<th>Underlying condition (%)</th>
<th>Total</th>
<th>Group 1 (n = 59)</th>
<th>Group 2 (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal cancer</td>
<td>77</td>
<td>46</td>
<td>31</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>11</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Renal cancer</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

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missed. Also, thrombosis within catheters without clinical symptoms might be skipped because of the lack of routine use of ultrasound imaging of CVCs and ports in this group of patients.

In summary, prophylactic flushing of central venous ports with 1000 U of heparin in every 6 weeks might be a safer, easier, cheaper, comfortable and effective alternative to standard 4-weekly administration for preventing thrombosis and infections. Also effectiveness of this strategy might suggest that there is no need for routine use of prophylactic thrombolytic agents or anticoagulants other than heparin for prevention of clinically important complications seen in cancer patients with central venous ports. Prospective, randomized and confirmatory studies with higher number of patients and longer follow-up will determine the complication rate and efficacy of 1000 U of heparin in every 6-week administration more effectively.

REFERENCES


