Thromboprophylaxis and Major Oncologic Surgery Performed With Epidural Analgesia

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Objective: To evaluate clinical outcomes in patients with cancer undergoing major abdominal surgery who received preoperative indwelling epidural catheters (ECs) and no postoperative thromboprophylaxis.

Design: Retrospective analysis of a prospective database.

Setting: Tertiary referral medical center.

Patients: Between January 1, 2009, and July 31, 2011, 119 patients, with a mean age of 64.5 years (range, 34-95 years), underwent major abdominal oncologic surgery with an indwelling EC.

Main Outcome Measures: Records of all patients were reviewed for age, duration of surgery, hospital length of stay, and clinical outcomes. All patients underwent lower extremity venous duplex ultrasonography prior to hospital discharge.

Results: The average operative time was 338 minutes. Mean (SD) intensive care unit stay was 2.8 (1.4) days (range, 1-7 days). Patients ambulated by postoperative day 1 or 2. Most ECs were removed on postoperative day 4. There were no major complications from the EC. Fifty-two patients (44%) were treated with deep venous thrombosis prophylaxis on postoperative day 4 after removal of the EC. Lower extremity duplex studies showed 8 patients (6.7%) had an acute thrombus. One patient (0.8%) developed an asymptomatic proximal deep venous thrombosis and 7 patients (5.9%) developed distal superficial thrombi. No patient developed a pulmonary embolus.

Conclusions: Thromboembolic complications following major abdominal surgery for cancer may be reduced with the use of ECs. Epidural catheters may directly prevent deep venous thrombosis through sympathetic blockade, resulting in increased blood flow to the lower extremities. This effect may also be attributable to earlier ambulation. These results suggest that patients who have an EC and do not receive concurrent postoperative thromboprophylaxis do not have an increased risk for thromboembolic events.

P A T I E N T S W I T H M A L G N A N C Y undergoing major abdominal or pelvic surgery are at increased risk for developing a thromboembolic event. It has been suggested that up to 40% of general surgery patients will develop a deep venous thrombosis (DVT) without prophylaxis, and the presence of cancer increases this risk 2-fold. In a review of 26 randomized controlled trials evaluating 7639 patients with cancer undergoing surgery, the rate of DVT without prophylaxis was found to be 35.2%; moreover, 12.7% of patients receiving chemical prophylaxis developed a DVT, while the combination of treatment with heparin and mechanical prophylaxis decreased the rate to 5%. Epidural analgesia has demonstrated multiple benefits both intraoperatively and during the postoperative period. Patients receiving continuous epidural analgesia report better pain control when compared with the use of patient-controlled analgesia. Other studies have shown regional anesthesia to be superior to general anesthesia in reducing myocardial infarction, postoperative ileus, and respiratory depression. Additionally, multiple studies have demonstrated decreased rates of DVT after surgery.

Despite its efficacy in decreasing the incidence of DVT, chemical thromboprophylaxis is associated with an increased risk for bleeding, which can lead to wound complications, and infection. The concomitant use of epidural analgesia and chemical thromboprophylaxis poses a rare but serious threat to patients in the development of epidural hematomas, where the incidence has been reported to be as high as 1 in every 3000. The American College of Chest Physicians has stated that for all patients under-
going neuraxial analgesia, appropriate patient selection and caution is strongly recommended when using thromboprophylaxis. Although the benefit of chemical prophylaxis in preventing DVTs in patients with cancer undergoing surgery has been well described, the effects of epidural analgesia without chemical prophylaxis on reducing the rate of DVTs is not known.

In this retrospective review, we evaluated clinical outcomes in patients with cancer undergoing major abdominal or pelvic surgery who received preoperative indwelling epidural catheters (ECs) and no postoperative thromboprophylaxis, with particular attention paid to the rate of DVT.

**METHODS**

Our prospectively maintained database was reviewed to identify all patients who underwent placement of an EC and subsequently underwent major oncologic abdominal or pelvic surgery between January 2009 and June 2011. Permission to conduct this study was obtained from our institutional review board. Patients who had been admitted to the hospital more than 7 days prior to surgery and patients found to have a thrombus in their lower extremities prior to undergoing surgery were excluded from the study.

All patients underwent EC placement by 1 of 2 dedicated anesthesiologists who routinely place ECs at our institution. Most catheters were inserted between T8 and T12. All patients underwent general endotracheal anesthesia after placement of the catheter. Patients did not receive any form of thromboprophylaxis while the EC was indwelling; however, all patients received mechanical prophylaxis through the use of sequential compression devices.

On removal of the EC, some patients were treated with thromboprophylaxis. The decision to initiate thromboprophylaxis was based primarily on the anticipated length of the hospital stay, history of DVT, and lack of patient mobility. All patients underwent bilateral lower extremity duplex ultrasonography either a day prior to or on the day of hospital discharge to detect the presence of venous thrombosis. Patients were seen at weekly intervals the first 30 days following hospital discharge.

Data retrieved by retrospective review of inpatient records included demographics, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), history of hypercoagulable disorders, diagnosis, smoking history, history of venous thromboembolism, operative time, type of operation, intensive care unit length of stay, hospital length of stay, and the date when each patient was deemed fit to ambulate. Details about the EC, including the location of the catheter, the date of removal, and any associated complications, were recorded. Finally, we collected data on whether the patient received any form of thromboprophylaxis after the EC was removed, when such prophylaxis was started, results of each lower extremity duplex ultrasonography, whether therapy was initiated after a duplex demonstrated a lower extremity thrombosis, and any evidence to suggest the presence of a pulmonary embolus.

**RESULTS**

**PATIENT CHARACTERISTICS**

A total of 119 patients (49.6% men, 50.4% women) were included in our study. The average age of our patients was 64.5 years. Average (SD) BMI was 23.9 (4.4), and 15 patients (13%) were classified as obese (BMI > 30). Among other risk factors for DVT, 11 patients (9%) had a prior history of thrombosis, 6 patients (5%) were active smokers, and 1 patient (0.8%) had a history of a hypercoagulable disorder.

**COURSE IN HOSPITAL**

The average (SD) length of stay in the hospital was 14.9 (8.3) days. The average (SD) duration of surgery was 343.6 (159.3) minutes (range, 103-906 minutes). Postoperatively, 42 patients (35%) went to the intensive care unit with an average (SD) stay of 2.8 (1.4) days. Two patients remained intubated following surgery. Of the 42 patients who were observed in the intensive care unit, all had undergone either an esophagectomy, major pancreatic and hepatobiliary resection, or resection of multiple visceral organs during surgery. On average, patients were ambulating by postoperative day 1 or 2 (mean, 1.5 days). Most ECs were removed on postoperative day 4.

**TUMOR CHARACTERISTICS**

The final diagnoses of our patients were as follows: 31 (26%) had a retroperitoneal, pelvic, or abdominal sarcoma; 24 (20%) had a gastric malignancy; 21 (18%) were diagnosed as having colorectal cancer; 14 (12%) had pancreatic cancer; 13 (11%) were diagnosed as having esophageal cancer; 3 (3%) had duodenal cancer; 3 (3%) had a hepatobiliary malignancy; and 10 (8%) had other malignancies. The major intra-abdominal surgical procedures performed are listed in Table 1.

**OUTCOMES**

Six patients (5%) had a complication associated with the EC. No patients developed epidural abscesses or hematomas. Fifty-two patients (44%) were treated with thromboprophylaxis after removal of their EC. On average, patients were treated with DVT prophylaxis on postoperative day (SD) 6 (2.2).

Overall, 8 patients (6.7%) developed venous thrombosis in their lower extremities, as seen on venous duplex ultrasonography (Table 2). All patients were asymptomatic. Of the 8 patients, 7 patients (3.9%) had distal venous thrombosis below the level of the knee. Five of these patients had been given treatment with thromboprophylaxis after removal of the EC prior to the duplex being performed. Only 1 patient (0.8%) was found to have

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Overall, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>En bloc resection sarcoma/visceral organ resection</td>
<td>31 (26)</td>
</tr>
<tr>
<td>Gastroectomy</td>
<td>24 (20)</td>
</tr>
<tr>
<td>Colectomy</td>
<td>21 (18)</td>
</tr>
<tr>
<td>Pancreatectomy</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Esophagectomy</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Small bowel resection</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Hepatectomy</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Combined bowel and genitourinary surgery</td>
<td>10 (8)</td>
</tr>
</tbody>
</table>

Table 1. Surgical Procedures Performed
a DVT at the level of the knee. This patient had no history of DVT and was not treated with thromboprophylaxis after removal of the EC; however, the patient was given anticoagulation therapy after being diagnosed as having a DVT. Patient 1 underwent a gastrectomy and splenectomy for a malignancy at the gastro-esophageal junction. His risk factors for thrombosis included smoking and obesity (BMI = 30). Patients 2, 3, and 4 also underwent gastrectomy for malignancy and had BMIs of greater than 30. Patients 6 and 7 underwent a total gastrectomy and esophagectomy, respectively, but they had no other risk factors for thrombosis. Patient 8 underwent a pancreaticoduodenectomy and had no risk factors for thrombosis. No patients were found to have a DVT at the level of the thigh or pelvis. Additionally, no patients were diagnosed as having pulmonary embolus. All patients were followed up for at least 30 days postoperatively to assess for signs or symptoms of venous thromboembolism.

### Table 2. DVT Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Location</th>
<th>History of DVT</th>
<th>Prophylaxis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Posterior tibial, peroneal, and soleal veins</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Soleal vein</td>
<td>No</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Peroneal and soleal veins</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Popliteal, peroneal, and soleal veins</td>
<td>No</td>
<td>No</td>
<td>Dalteparin sodium then warfarin sodium</td>
</tr>
<tr>
<td>5</td>
<td>Soleal vein</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Intramuscular veins</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>Soleal vein</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>Soleal vein</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviation: DVT, deep venous thrombosis.

This study was performed to determine the need for chemical thromboprophylaxis among 119 patients with epidural analgesia who underwent major oncologic abdominal or pelvic surgery. During a 2-year period, only 1 patient (0.8%) was found to have an above-knee DVT without the use of chemical thromboprophylaxis. No patients demonstrated any signs or symptoms of DVT. Seven patients were found to have calf vein thrombosis and were not recommended to undergo treatment with anticoagulation.

Guidelines from the American College of Chest Physicians and the National Comprehensive Cancer Network recommend extending thromboprophylaxis treatment of patients postdischarge after major abdominal and gynecological surgery for cancer. None of our patients who were given treatment with thromboprophylaxis after removal of the EC had extension of their treatment postdischarge. In addition, patients who developed below-knee DVTs in our study were not treated with anticoagulation therapy. All patients were followed up closely postdischarge and no additional patients developed DVTs. None of the patients developed complications in their lower extremities related to the DVTs including venous insufficiency or propagation of thrombi proximally. Murray et al performed a meta-analysis of 130,000 patients who underwent total hip replacement and reported a 0.2% risk for fatal pulmonary embolism in patients who developed DVT on chemical prophylaxis. None of the patients in this study who had DVTs went on to develop symptoms suggestive of a pulmonary embolus during the postoperative period or during follow-up in the outpatient setting.

To our knowledge, our study is the first to evaluate the risk for DVT in patients with cancer undergoing major abdominal or pelvic surgery with epidural analgesia without the concomitant use of chemical thromboprophylaxis. The rate of DVT among our patient population was similar to the rate seen among comparable patient populations undergoing major oncologic surgery with chemical prophylaxis. Leonardi et al estimated the rate of DVT to be 35.2% among patients with no thromboprophylaxis, 12.7% among patients with only chemical prophylaxis, and 5.0% among patients with both chemical and mechanical prophylaxis.

Multiple studies focusing on orthopedic surgery have demonstrated a lower incidence of DVT among patients undergoing spinal anesthesia compared with patients who underwent general anesthesia and postoperative parental analgesia. In a recent meta-analysis, Rodgers et al analyzed 141 randomized clinical trials comparing epidural analgesia with general anesthesia and calculated a 44% reduction in DVT and subsequent 55% reduction in pulmonary emboli. Daniel et al reported a DVT rate of 4.6% among 219 patients undergoing primary hip arthroplasty treated with a multimodal thromboprophylaxis regimen consisting of hypotensive epidural anesthesia, an antiplatelet agent (generally aspirin), elastic compression stockings, and early mobilization.

The mechanism by which epidural analgesia reduces the incidence of thromboembolic events remains unclear, and the mechanism may be multifactorial. The primary contributors to the prothrombotic state initiated during surgery are a reduction in venous blood flow, neuromuscular blockade, and activation of the sympathetic system. Sympathetic stimulation markedly increases the levels of factor VIII, inhibits fibrinolysis, decreases antithrombin III, and initiates platelet aggregation. Epidural analgesia blunts the sympathetic response, improving lower extremity blood flow. Furthermore, the systemic absorption of local anesthetics acts as an anticoagulant by reducing blood viscosity through minimizing protein, erythrocyte, and platelet aggregation.
Aggregation.\textsuperscript{27,28} In addition, improved pain control and earlier mobilization could possibly decrease the incidence of clot formation.

There are several limitations to our study. First, our study lacked a formal control group, which makes it difficult to determine whether the rate of DVT among our patient population was similar to a comparable group that would have received thromboprophylaxis without an EC. In addition, we did not designate a specific time during which to perform lower extremity duplex ultrasonography, which may have led to an inaccurate estimate of the rate of DVT. Finally, we did not formulate specific guidelines for starting thromboprophylaxis once the EC was removed. As such, it would be difficult to predict the usefulness of thromboprophylaxis once an EC is removed within our patient population.

In conclusion, thromboembolic complications following major abdominal or pelvic surgery for cancer may be reduced with the use of epidural analgesia. Epidural catheters may directly prevent the development of DVT and subsequent pulmonary embolism through sympathetic blockade, resulting in increased blood flow and decreased venous stasis within the lower extremities. This effect may also be attributable to earlier postoperative ambulation. Our results suggest that patients who receive epidural analgesia but not concurrent postoperative thromboprophylaxis may not have an increased risk for thromboembolic events. Conducting larger prospective studies with the appropriate control groups is warranted to determine the efficacy of using epidural analgesia without chemical thromboprophylaxis in preventing thromboembolism.

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REFERENCES