Persistence of Hypercoagulable State after Resection of Intra-Abdominal Malignancies

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BACKGROUND: The hypercoagulable state associated with cancer imparts considerable risk for venous thromboembolism. Surgical resection of malignancies should theoretically reverse tumor-induced hypercoagulability. However, coagulation changes in cancer patients post resection have not been described thoroughly. Conventional coagulation tests are unable to detect hypercoagulable states. In contrast, rotational thromboelastography (ROTEM) can detect hypo- or hypercoagulable conditions. We hypothesized that the cancer-induced hypercoagulable state would improve after surgical resection.

METHODS: After informed consent, blood samples of patients undergoing surgical resection for curative intent were analyzed with serial ROTEM.

RESULTS: Thirty-five patients (mean ± SD age 66 ± 17 years; 67% male) had cancers involving the pancreas (n = 12 [34%]), esophagus (n = 10 [29%]), stomach (n = 7 [20%]), bile ducts (n = 3 [9%]), and duodenum (n = 3 [9%]). Preoperative ROTEM identified 14 (40%) who were hypercoagulable. After surgical resection, patients became progressively hypercoagulable with more rapid clot formation time (low clot formation time, high alpha) and higher maximum clot firmness. By week one, 86% (n = 30) had abnormal ROTEM values, including 17 of 21 (81%) who had normal coagulation profiles preoperatively. Most (n = 30 [86%]) remained hypercoagulable at 3 to 4 weeks.

CONCLUSIONS: Rotational thromboelastography identifies baseline hypercoagulability in more than one third of patients with intra-abdominal malignancies. This is among the first studies to demonstrate progressive hypercoagulability that persists for at least 1 month after resection. These data support postdischarge thromboprophylaxis regimens in high-risk cancer patients. (J Am Coll Surg 2013;216:e580–590. © 2013 by the American College of Surgeons)

The pathogenesis of venous thromboembolism (VTE) is explained by the classic triad attributed to Rudolf Virchow: stasis, endothelial injury, and hypercoagulability.1 The association between hypercoagulability and cancer has been recognized for more than a century and a half. In the 1860s, Trousseau first made the observation of migratory thrombosis in a series of patients with occult visceral malignancies.2 Today, it is well appreciated that VTEs are commonly associated with cancer; 10% to 20% present with symptomatic events and 50% will be discovered on autopsy.3,5 There are many risk factors for VTE in cancer, including patient characteristics (eg, advanced age, presence of comorbidities, and prothrombotic gene mutations), tumor-specific influences (eg, primary site, histology, and stage), and chemotherapy, which increases the risk of VTE as much as 47%.3,6-8 In addition, surgery is an important contributing factor to hypercoagulable states after general and orthopaedic procedures.9-11 Traditional coagulation tests (eg, prothrombin time and partial thromboplastin time) are not generally helpful in the diagnosis of hypercoagulability, but viscoelastic hemostatic assays (VHA), such as the thromboelastogram (TEG) and, more recently, rotation thromboelastometry (ROTEM), have the advantage of providing global assessments of hemostatic function and clotting mechanisms. Viscoelastic hemostatic assays have been used to detect venous thromboembolism (VTE) is explained by the classic triad attributed to Rudolf Virchow: stasis, endothelial injury, and hypercoagulability. The association between hypercoagulability and cancer has been recognized for more than a century and a half. In the 1860s, Trousseau first made the observation of migratory thrombosis in a series of patients with occult visceral malignancies. Today, it is well appreciated that VTEs are commonly associated with cancer; 10% to 20% present with symptomatic events and 50% will be discovered on autopsy. There are many risk factors for VTE in cancer, including patient characteristics (eg, advanced age, presence of comorbidities, and prothrombotic gene mutations), tumor-specific influences (eg, primary site, histology, and stage), and chemotherapy, which increases the risk of VTE as much as 47%. In addition, surgery is an important contributing factor to hypercoagulable states after general and orthopaedic procedures. Traditional coagulation tests (eg, prothrombin time and partial thromboplastin time) are not generally helpful in the diagnosis of hypercoagulability, but viscoelastic hemostatic assays (VHA), such as the thromboelastogram (TEG) and, more recently, rotation thromboelastometry (ROTEM), have the advantage of providing global assessments of hemostatic function and clotting mechanisms. Viscoelastic hemostatic assays have been used to detect...
Abbreviations and Acronyms

CFT = clot formation time  
DVT = deep vein thrombosis  
MCF = maximum clot firmness  
ROTEM = rotation thromboelastometry  
RR = relative risk  
TEG = thromboelastogram  
VHA = viscoelastic hemostatic assay  
VTE = venous thromboembolism

hypercoagulable conditions in trauma,12 after surgery,10,13 and in patients with various malignancies.14-17 However, there is a paucity of literature describing longitudinal coagulation changes in cancer patients.14,18

The purpose of this study was to use ROTEM to prospectively evaluate the coagulation status of patients undergoing operative resection of intra-abdominal malignancies for curative intent. We hypothesized that the majority of patients would be hypercoagulable preoperatively and the hypercoagulable state would reverse after tumor resection.

METHODS

This prospective observational study took place at the University of Miami/Jackson Memorial Hospital and Sylvester Comprehensive Cancer Center. Patients under the care of a surgical oncologist and 2 hepatobiliary surgeons were screened during a 1-year period from February 2011 to March 2012. Patients were evaluated in preoperative clinics for those undergoing potentially curative resection of intra-abdominal tumors. Patients with malignant tumors of the upper gastrointestinal tract (ie, esophagus, stomach, and duodenum) and hepatobiliary system (ie, pancreas and bile ducts) were included in the study. Exclusion criteria were those with benign disease; unresectability at the time of operation; and liver, retroperitoneal, or gastrointestinal stromal tumors. The protocol was approved by the Institutional Review Boards of the University of Miami and the clinical trials office of Jackson Memorial Hospital.

After informed consent, peripheral blood samples were drawn either preoperatively in the operative holding area or intraoperatively after induction of anesthesia (before operative incision). Additional samples were drawn on postoperative day 1, at 1 week, and on postdischarge follow-up (3 to 4 weeks postoperatively). For those with arterial access, standard 3-cm, 20-gauge radial arterial catheters were used to obtain samples. The remainder were obtained by venipuncture with 22-gauge butterfly needles. Each 6-mL sample was drawn after 3 to 5 mL blood was evacuated as waste, and subsequently transferred into two 2.7-mL vacuum-sealed tubes (BD Vacutainer) containing 3.2% sodium citrate.

Samples were analyzed with ROTEM (Rotem Inc), which has been described in detail elsewhere.19 Rotation thromboelastometry tests (eg, EXTEM, INTEM, and FIBTEM) were performed according to manufacturer’s instructions using standardized equipment and test reagents. Blood was recalified with 20 μL 0.2 mol/L calcium chloride (star-TEM reagent; Rotem Inc) and coagulation was activated by tissue factor from rabbit brain (EXTEM) or with partial thromboplastin phospholipids made from rabbit brain and ellagic acid (INTEM). In the FIBTEM test, the contribution of platelets to whole blood coagulation is inhibited by the platelet-neutralizing reagent cytochalasin D.

Only ROTEM parameters with standard US reference ranges were used for the study; additional experimental parameters provided by the device were not examined. The clot time represents the time from the start of measurement until initiation of clotting, clot formation time (CFT) is the time from initiation of clotting until a clot firmness of 20 mm is detected, alpha-angle reflects the rapidity of clot formation, and maximum clot firmness (MCF) represents the quality of the clot. Overall, CFT and alpha characterize the clot kinetics and MCF signifies clot strength. Hypercoagulability is reflected by a rapid clot time/CFT (low value), high MCF, and/or a high alpha-angle. Patients were considered hypercoagulable if 1 or more of the 9 ROTEM parameters evaluated (ie, clot time, CFT, MCF in EXTEM or INTEM, or MCF in FIBTEM) were outside the established reference range.

Only patients with complete follow-up ROTEM data (preoperatively, postoperative day 1, week 1, and weeks 3 to 4) were included. Demographics (ie, age and sex), operative details (ie, preoperative diagnosis and procedure), outcomes (ie, mortality, development of VTE, and surgical complications), and tumor data (ie, organ involved, histologic type, and size) were collected. Pathology reports were reviewed to determine tumor grade, marginal status, and presence of lymphovascular or perineural invasion. Tumors were staged based on the TNM classification used by the American Joint Committee on Cancer.

Using PASW statistical software version 19.0 (SPSS, Inc), categorical data (ie, sex, presence of hypercoagulability, and tumor characteristics) were compared using chi-square test or Fisher’s exact test. Longitudinal changes in coagulation markers were assessed with repeated measures ANOVA with post-hoc comparisons done with the Bonferroni correction for normally distributed
variables. Friedman test and Wilcoxon signed ranks test were used for nonparametric data. Values are expressed as mean ± SD, median (interquartile range), or number (percentage) as appropriate. Significance was assessed at p < 0.05.

RESULTS

Demographics

Thirty-five patients met inclusion criteria during the 13-month period. Demographic data for the study cohort are shown in Table 1. Mean age was 68 ± 10 years (range 43 to 86 years), and 60% of patients were male. Tumors most commonly affected the pancreas, esophagus, and stomach. The most common histologic type of tumor was adenocarcinoma, which was found in 80%. On final pathologic examination, nearly half of patients had positive lymph nodes, a high proportion (63%) had poorly differentiated tumors, and 43% had stage III or IV disease (Table 1).

The majority of patients (n = 23 [66%]) received a combination of sequential compression devices and pharmacologic thromboprophylaxis for the duration of hospitalization. The most common drugs used were dalteparin 5,000 U daily (n = 13), heparin 5,000 U 3 times a day (n = 6), and enoxaparin 40 mg daily (n = 4). Postdischarge prophylaxis was not used.

There was 1 pulmonary embolism on postoperative day 1 in a patient with metastatic renal cell carcinoma to the pancreas that underwent a distal pancreatectomy and splenectomy. At the time, the patient was receiving heparin 5,000 U 3 times daily. There was another possible pulmonary embolism on postoperative day 2 in a patient with pancreatic adenocarcinoma s/p pylorisparing Whipple. The patient had high clinical suspicion with development of new-onset atrial flutter, negative bilateral lower extremity Duplex ultrasound, and a questionable CT angiography. Other postoperative complications included pancreatic fistula (n = 4), disease recurrence (n = 3), cervical fistula (n = 2), and stricture (n = 2). There were no mortalities. Mean clinical follow-up time after surgery was 129 ± 94 days, with the longest being 14 months.

Longitudinal coagulation changes

Table 2 shows the longitudinal coagulation changes in patients undergoing surgical resection. Other than an increased MCF in the final common pathway, there were no other differences observed between preoperative variables and those on postoperative day 1. However, at 1 week, there was a significant difference in multiple variables, including rapid clot kinetics (lower rapid CFT, higher alpha) in both the extrinsic and intrinsic pathways and enhanced clot strength (higher MCF) in all 3 coagulation pathways. Taken together, these variables represent a relative hypercoagulable state at 1 week. At postdischarge follow-up (weeks 3 to 4), the trend toward hypercoagulability remained (Table 2, Fig. 1).

Specific rotation thromboelastometry abnormalities

The number and location of abnormal ROTEM variables is shown in Table 3. Preoperative hypercoagulability was detected in 40% (n = 14) of patients. Over time, more
patients demonstrated coagulation abnormalities, with up to 86% experiencing hypercoagulability at weeks 3 to 4 (Fig. 2). When hypercoagulability was defined as having multiple abnormalities on ROTEM, more patients were hypercoagulable at week 1 and weeks 3 to 4 than preoperatively, regardless of the cutoff used (all, p < 0.001). For example, only 6% of patients had ≥5 ROTEM abnormalities preoperatively, 43% did at 1 month (Table 3, Fig. 2). Stratified by tumor type, 100% of patients with pancreatic (n = 12), bile duct (n = 3), and duodenal (n = 3) tumors were hypercoagulable at weeks 3 to 4, as were 70% (n = 7) of esophageal and 71% (n = 5) of gastric tumors (data not shown).

Figure 3 shows the distribution of coagulation abnormalities over time. Preoperatively, the extrinsic pathway was the most commonly affected isolated pathway (17%), followed by all 3 (11%). Over time, although the extrinsic pathway remained commonly affected, the majority of patients experienced aberrancies in multiple pathways. Seventy-one percent at 1 week and 60% at 1 month had multiple pathway abnormalities. At both of these follow-up times, most patients had all 3 coagulation pathways affected (Table 3, Fig. 2).

**DISCUSSION**

The current study is among the first to use ROTEM to investigate postoperative coagulation changes in patients after resection of upper gastrointestinal or pancreatobiliary malignancies. The data showed that, before surgery, 40% were hypercoagulable. After surgical resection, an even higher proportion became hypercoagulable, reflected by more rapid clot formation time (low CFT, high alpha) and higher MCF. By week 1, 86% (n = 30) had abnormal ROTEM values, including 17 of 21 (81%) who had normal coagulation profiles preoperatively. Most (n = 30 [86%]) remained hypercoagulable at 3 to 4 weeks. These results support the conclusion that surgical resection does not immediately reverse tumor-induced hypercoagulability and support the use of postdischarge thromboprophylaxis regimens.

Since TEG was introduced by Hartert in 1948,20 it has proven useful for providing a comprehensive assessment of the coagulation system. Recently, the ROTEM has been developed that overcomes limitations of TEG, such as sensitivity to vibration and mechanical shocks. These VHAs have the ability to detect hypocoagulability and have been used extensively to predict massive transfusion and guide goal-directed therapy in trauma, cardiac, and transplantation surgery.21-25

The capability of VHA to identify hypercoagulability has also been exploited. Schreiber and colleagues12 concluded that TEG was more sensitive than routine coagulation assays for identifying hypercoagulability in trauma. More recently, ROTEM demonstrated relative hypercoagulability in patients with clinically significant deep vein thrombosis (DVT) vs healthy controls.26 Burke and colleagues27 demonstrated that patients undergoing simultaneous kidney/pancreas transplantation for type 1 diabetes/end-stage renal disease were more hypercoagulable on TEG (lower K, higher maximum amplitude, alpha and TEG index) than those receiving isolated kidney transplants. In a heterogeneous population of patients undergoing major elective noncardiac surgery, altered TEG within 2 hours of surgery was predictive of postoperative myocardial infarction.28 In a recent meta-analysis by Dai and colleagues,13 TEG was found to be useful for predicting postoperative DVT, although there was a widely

<table>
<thead>
<tr>
<th>Table 2. Longitudinal Coagulation Changes after Surgical Resection</th>
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<tbody>
<tr>
<td><strong>Intrinsic pathway (INTEM), mean ± SD</strong></td>
</tr>
<tr>
<td>Clotting time, s</td>
</tr>
<tr>
<td>CFT, s</td>
</tr>
<tr>
<td>Alpha, degrees</td>
</tr>
<tr>
<td>MCF, mm</td>
</tr>
<tr>
<td><strong>Extrinsic pathway (EXTEM)</strong></td>
</tr>
<tr>
<td>Clotting time, s, mean ± SD</td>
</tr>
<tr>
<td>CFT, s, median (IQR)</td>
</tr>
<tr>
<td>Alpha, degrees, mean ± SD</td>
</tr>
<tr>
<td>MCF, mm, mean ± SD</td>
</tr>
<tr>
<td><strong>Final common pathway (FIBTEM)</strong></td>
</tr>
<tr>
<td>MCF, mm, median (IQR)</td>
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</table>

*p < 0.01; denotes Bonferroni comparison with preoperative variables.  
*p < 0.05; denotes Bonferroni comparison with preoperative variables.  
CFT, clot formation time; IQR, interquartile range; MCF, maximum clot firmness.
variable predictive value (odds ratio = 1.5 to 27.7) and no consensus on the exact definition of hypercoagulability.

Regardless of how it is measured, surgery itself is an important contributing factor to hypercoagulability. Wilson and colleagues described longitudinal changes in TEG after orthopaedic surgery for proximal femur fractures. Thromboelastogram coagulation index was elevated on postoperative day 1 and remained elevated for 6 weeks, despite use of low-molecular-weight heparin. Gibbs and colleagues showed time-related changes in coagulants (e.g., fibrinogen, factor VIII, von Willebrand factor, and α-1-antitrypsin) and marked decreases in anticoagulants (e.g., protein C, antithrombin III, and α-2-macroglobulin) in patients undergoing elective abdominal aortic surgery. Mahla and colleagues performed daily TEG in patients undergoing major abdominal surgery (including 16 of 20 with cancer), and demonstrated decreased R time (comparable to ROTEM clotting time) and increased maximum amplitude (comparable to ROTEM MCF) immediately after surgery. Although the R eventually normalized, maximum amplitude remained elevated on postoperative day 7. Our data, exclusively in patients with intra-abdominal malignancies, are consistent with these findings and suggest that hypercoagulability (decreased CFT, increased alpha/MCF) persists for at least 1 month after surgical resection.

Isolated measurements of coagulation status by VHA have also been used in the cancer population. In the 1970s, Caprini and colleagues and Haid advocated using TEG as a screening test for cancer, citing accuracies between 80% and 98%. Subsequently, TEG has been used to detect hypercoagulability in patients with cancers of the colon, breast, and gynecologic organs compared with healthy controls. Recently, Papa and colleagues used ROTEM to detect hypercoagulability in patients with solid digestive tract cancers. Although they found no difference in standard ROTEM variables (i.e., clotting time, CFT, and MCF), they reported differences in maximum velocity and area under the curve, which are derived from the ROTEM curve. Akay and colleagues used ROTEM in a heterogenous population of cancers (i.e., gastrointestinal, respiratory, and miscellaneous) and demonstrated accelerated clot formation (shortened CFT) and increased clot strength (increased MCF) relative to healthy controls.

Despite the evidence of hypercoagulability in cancer patients, there have been few studies investigating longitudinal coagulation changes after resection. In a small animal study, injection of tumor cells produced a hypercoagulable TEG index within 4 days, which remained elevated at 1 month postinjection. In 1984, Greenstein and colleagues investigated coagulation changes after curative resection in rats. Four weeks after implantation of squamous cell carcinoma in the flank, the cancer was excised in 1 group, with the remainder undergoing sham operation. The excision group was similar to healthy controls at 2 weeks via TEG, and those with residual tumor demonstrated hypercoagulability. In the human population, Byrne and colleagues demonstrated elevated procoagulants for 7 days (thrombin:antithrombin complex), 21 days (prothrombin fragment 1+2), 3 months (D-dimer), and 6 months (factor VIII) after surgery. Likewise, there was a considerable decrease in the anticoagulants antithrombin III and protein C/S, which returned to baseline by day 14.

To our knowledge, there has only been one other longitudinal investigation of coagulation status with VHA solely in cancer patients. De Pietri and colleagues performed daily

Figure 1. Longitudinal changes in INTEM (A) and EXTEM (B) variables after resection of intra-abdominal malignancies. Decreases in clot formation time (CFT) and increases in maximum clot formation (MCF) and alpha reflect relative hypercoagulability over time.
investigated hemostatic changes in 59 patients undergoing surgery for liver (n = 38) or pancreatic (n = 18) tumors. Blood was examined postinduction, at the end of surgery, and on postoperative days 1, 3, 5, and 10. They reported TEG values within the normal range preoperatively. Postoperatively, TEG values remained consistently normal in liver patients, despite a prolonged partial thromboplastin time/international normalized ratio, reduced platelets, and low fibrinogen. In the pancreas group, both the TEG and traditional coagulation tests trended toward hypocoagulability. Despite the discrepancies between the results of TEG and standard laboratory tests, they supported use of TEG as a valuable tool for the evaluation of postoperative hypercoagulable changes. Our data show the opposite; patients with intra-abdominal malignancies become progressively more hypercoagulable after surgical resection and the majority (86%) remain so at 1 month. The incongruities between their study and this one cannot be easily explained. Although we did not include patients with liver tumors, 34% of our population had pancreatic tumors, all of whom were hypercoagulable at 1-month follow-up. In our overall cohort of patients, 86% were hypercoagulable at 1 week and 3 to 4 weeks. Other disparities might be due to different severity of disease, population-based disparities, length of follow-up (10 days vs 1 month), or use of different VHA (TEG vs ROTEM).

Our data support current knowledge about risk factors for VTE. Stein and colleagues reported that hospitalized cancer patients had twice the incidence of VTE compared with similar patients without cancer. The highest incidence was with cancers of the pancreas (RR = 4.3), brain (RR = 3.5), and lymphatic/myeloproliferative (RR = 2.9). In a study of >1 million patients in the University HealthSystem Consortium discharge database, age 65 years or older, female sex, black race, use of chemotherapy, comorbidities, and primary site of cancer (pancreatic odds ratio = 2.5) were risk factors on multivariate analysis. In the large prospective observational RISTOS study, history of VTE, prolonged anesthesia time or bed rest, advanced stage disease, and age 60 years or older were identified as risk factors postoperatively. Venous thromboembolisms were identified in 2.1%, with 40% of events occurring 21 days or more postoperatively. Merkow and colleagues demonstrated highest VTE rates in esophagogastric (4.2%) and hepatopancreaticobiliary (3.6%) cancers, with 18% and 33% of these events occurring after hospital discharge, respectively. In the current study, there were 2 pulmonary emboli (6% VTE rate), both occurring during hospitalization in the acute postoperative period.

Due to the high rates of postoperative VTE in cancer patients, the concept of extended-duration (postdischarge) anticoagulation has been examined in 3 randomized control trials. In 2002, the ENOXICAN II investigators demonstrated a 12% VTE incidence in those receiving enoxaparin for 1 week vs 4.8% in those

### Table 3. Distribution of Rotation Thromboelastometry Abnormalities

<table>
<thead>
<tr>
<th>Hypercoagulable ROTEM values</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Week 1</th>
<th>Weeks 3 to 4</th>
</tr>
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<tbody>
<tr>
<td>n%</td>
<td>n%</td>
<td>n%</td>
<td>n%</td>
<td>n%</td>
</tr>
<tr>
<td>1+ Abnormalities</td>
<td>14 40</td>
<td>21* 60</td>
<td>30† 86</td>
<td>30† 86</td>
</tr>
<tr>
<td>2+ Abnormalities</td>
<td>6 17</td>
<td>9 26</td>
<td>25† 71</td>
<td>21† 60</td>
</tr>
<tr>
<td>3+ Abnormalities</td>
<td>4 11</td>
<td>3 9</td>
<td>21† 60</td>
<td>18† 51</td>
</tr>
<tr>
<td>4+ Abnormalities</td>
<td>3 9</td>
<td>1 3</td>
<td>15† 43</td>
<td>17† 49</td>
</tr>
<tr>
<td>5+ Abnormalities</td>
<td>2 6</td>
<td>1 3</td>
<td>12† 34</td>
<td>15† 43</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Location of ROTEM abnormalities</th>
<th>Isolated pathway</th>
<th>Extrinsic pathway</th>
<th>Fibrin pathway</th>
<th>Multiple pathways</th>
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</thead>
<tbody>
<tr>
<td>Intrinsic pathway</td>
<td>1 3</td>
<td>3 9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Extrinsic pathway</td>
<td>6 17</td>
<td>5 14</td>
<td>1 3</td>
<td>6 17</td>
</tr>
<tr>
<td>Fibrin pathway</td>
<td>1 3</td>
<td>4 11</td>
<td>4 11</td>
<td>3 9</td>
</tr>
<tr>
<td>Extrinsic + fibrin</td>
<td>2 6</td>
<td>6 17</td>
<td>4 11</td>
<td>5 14</td>
</tr>
<tr>
<td>Extrinsic + intrinsic</td>
<td>—</td>
<td>—</td>
<td>1 3</td>
<td>—</td>
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<tr>
<td>Intrinsic + fibrin</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>All 3 pathways</td>
<td>4 11</td>
<td>3 9</td>
<td>20 57</td>
<td>16 46</td>
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</table>

*p < 0.05; denotes comparison with preoperative variables.

*p < 0.01; denotes comparison with preoperative variables.

ROTEM, rotation thromboelastometry.
with 1 month of therapy (60% RR reduction). Rasmussen and the FAME investigators found similar results, with a relative risk reduction of 55% (VTE rate 16.3% vs 7.3%). However, the study investigated those undergoing major abdominal surgery with only 58% being for cancer. Most recently, Kakkar and colleagues reported results with extended use of bemiparin in the CANBESURE study. There was no difference found in primary efficacy outcomes (ie, VTE and all-cause mortality), but the incidence of proximal DVT (0.4% vs 3.3%) was less in the extended-duration group. A limitation in the application of the CANBESURE (Cancer, Bemiparin and Surgery Evaluation) results to our population is the exclusion of patients undergoing surgery for cancer of the biliary tract and pancreas.

Despite the evidence supporting postdischarge VTE prophylaxis, controversy remains and adherence with recommendations is poor. A systematic review demonstrated that mortality was only investigated in one study, and there were no mortality differences between extended-duration and standard regimens. Although none of the trials reported analyzable data for symptomatic DVT, and only one study had follow-up >80%, the difference in asymptomatic DVT rates between extended-duration and standard regimens was statistically significant (RR = 0.21). In addition, it has been shown that although 82% of patients receive in-hospital thromboprophylaxis, only 31% receive it after discharge. In our study, all patients received some sort of in-hospital thromboprophylaxis (sequential compression devices + chemical thromboprophylaxis or sequential compression devices + early aggressive ambulation for those admitted to the hospital floor), with the majority receiving the former. At this time, postdischarge extended thromboprophylaxis is not used routinely at our institution.

Current thromboprophylaxis guidelines include those published by the American Society of Clinical Oncology, the National Comprehensive Cancer Center Network, and the American College of Chest Physicians. For those undergoing major surgical interventions for malignant disease, all guidelines recommend thromboprophylaxis with unfractionated heparin or low-molecular-weight heparin for the duration of their hospitalization. The current recommendations for extended-duration thromboprophylaxis are shown in Table 4. Prolonged prophylaxis (up to 4 weeks) is recommended by all guidelines for high-risk cancer patients undergoing major surgery, with the level of evidence ranging from lower level (based on uniform consensus) to strong recommendation (based on moderate-quality evidence). Of note, the most recent American College of Chest Physicians guidelines have upgraded the level of evidence from 2A (8th edition) to 1B (9th edition).

Due to the variable definition of high risk, the treating physician is left to decide what is best for each individual patient. One must weigh the benefit of reducing the risk of VTE with the risk of adverse bleeding events and cost to the patient. The ROTEM can offer the advantage of identifying those who might benefit most from extended-duration thromboprophylaxis. Depending on the definition of hypercoagulability, somewhere between 34% and 86% of cancer patients in the current study were hypercoagulable at 1 week. More importantly, 43%
to 86% of patients remained hypercoagulable at 3 to 4 weeks. Therefore, extended duration thromboprophylaxis might be justified beyond the current recommendations.

Our findings must be interpreted in context with a few limitations. First, this was a descriptive observational study of patients undergoing surgical resection of intra-abdominal malignancies. No clinical decisions were based on the results of the ROTEM. Second, we did not include a normal healthy control group or cohort undergoing surgery for other reasons, and instead chose to investigate longitudinal changes over time in cancer patients alone. This was done because numerous studies have already demonstrated that cancer patients are more hypercoagulable on TEG/ROTEM than healthy controls. Third, only 40% of patients were hypercoagulable before surgery, and 86% became hypercoagulable after surgery. Although the presence of cancer seems to play a role, the tissue trauma imparted by major surgery also appears to contribute considerably to the overall hypercoagulable state. We do not believe this affects the interpretation of the results, as there is likely a complex interplay between tumor biology, genetics, and operative tissue trauma. Whatever the cause, cancer patients remain or develop hypercoagulability after surgery, which is sustained until at least 1 month postoperatively. Lastly, the functional clinical correlate for hypercoagulability is VTE; this study is not powered to detect these differences. Large-scale, multicenter studies are needed to determine whether a hypercoagulable state detected by ROTEM correlates with development of adverse events.

CONCLUSIONS

This study is one of the first to use ROTEM to report serial coagulation changes in patients after resection of upper gastrointestinal or pancreatobiliary malignancies. The data showed significant changes in clot kinetics and strength, representing relative hypercoagulability at 1 week and postdischarge follow-up. Over time, more patients demonstrated coagulation abnormalities, with up to 86% experiencing hypercoagulability at 1 month. Our findings, in context with current literature, suggest that extended-duration thromboprophylaxis is warranted in this population and can be justified for longer than the currently recommended 4 weeks postoperatively. ROTEM can be a valuable tool for identifying which patients are high risk for which prophylaxis is recommended.

Author Contributions

Study conception and design: Thorson, Van Haren, Ryan, Proctor
Acquisition of data: Thorson, Van Haren, Ryan, Curia
Analysis and interpretation of data: Thorson, Sleeman, Levi, Livingstone, Proctor
Drafting of manuscript: Thorson, Proctor
Critical revision: Thorson, Van Haren, Ryan, Curia, Sleeman, Levi, Livingstone, Proctor

Acknowledgment: We recognize the efforts of several volunteers/staff, including Gerardo A Guarch, MD, Jose M Barrera, MD, and Alexander Busko, BS, who assisted with patient

Table 4. Guidelines for Postoperative Extended-Duration Thromboprophylaxis

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Chest Physicians, Guyatt, 201244</td>
<td>Grade 1B: strong recommendation, moderate-quality evidence47</td>
</tr>
<tr>
<td>For high VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, we recommend extended-duration thromboprophylaxis (4 weeks) with LMWH over limited-duration prophylaxis.</td>
<td></td>
</tr>
<tr>
<td>American College of Chest Physicians, Geerts, 200845</td>
<td>Grade 2A: weak recommendation, high-quality evidence47</td>
</tr>
<tr>
<td>For selected high-risk general surgery patients, including some of those who have undergone major cancer surgery or have previously had VTE, we suggest that continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days be considered.</td>
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</tr>
<tr>
<td>National Comprehensive Cancer Center Network, Streiff, 201046</td>
<td>Category 2A: the recommendation is based on lower-level evidence and there is uniform National Comprehensive Cancer Center Network consensus</td>
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<td>Extended VTE prophylaxis (up to 4 weeks postoperation) should be considered for all high-risk cancer patients undergoing major surgery.</td>
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<td>American Society of Clinical Oncology, Lyman, 200747</td>
<td>Study quality evaluated by method of Moher and colleagues48; no specific quality score given for recommendation</td>
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<tr>
<td>Prolonged prophylaxis should be considered in patients undergoing major abdominal or pelvic surgery for cancer with high-risk features, such as residual malignant disease after operation, obese patients, and those with a history of VTE.</td>
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LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.
enrollment and blood processing, and Ronald Manning, RN, BSN, MSPH who serves as our research coordinator. We would also like to thank the surgical oncology, hepatobiliary, and preoperative staff for their cooperation with the study; without their continued support, this study would not have been possible.

REFERENCES

Discussion

DR LD BRITT (Norfolk, VA): The hypercoagulable state seen in patients with malignancy has been well documented in the literature. However, it’s not known how long this condition persists after the malignancy is treated or resected. If the prothrombotic state is specifically related to the tumor itself, and not a nonspecific result of a pathophysiologic change seen in cancer patients, it would be reasonable to suggest that the hypocoagulability associated with cancer would resolve either immediately or shortly after definitive resection of the malignancy. My colleagues from Miami propose in this study that the cancer-induced hypercoagulable state would resolve, but, as they stated, just the opposite happened.

Measuring viscoelastic changes of a blood sample by thromboelastography (TEG), is neither unique nor new. The first demonstration, as Dr Livingstone highlighted, of thromboelastographic visualization of fibrin polymerization was actually 3 years before I was born, in 1948. Fortunately, the techniques have been increasingly refined. With the multiple facets of altered coagulation that exist, the advantage of TEG or rotational thromboelastometry (ROTEM) over conventional coagulation tests is well documented. There is no reason to rely on incomplete characterization of coagulation abnormalities. I have several questions for the authors.

First, what was the rationale for ROTEM vs use of TEG? Is there a substantive difference?

Second, with ROTEM able to detect both hypo- and hypercoagulable states, how is the management specifically modified or therapy directed based on the ROTEM findings?

Third, contrary to the authors’ hypothesis, the patients studied were significantly more hypercoagulable, as they stated, postoperatively and remained so for 3 to 4 weeks of follow-up. Based on their data, the authors suggest that the hypercoagulable state associated with cancer patients does not resolve in the immediate postoperative period.

The authors’ study demonstrated an actual increase, so, unfortunately, the authors did not establish that the increase in the hypercoagulable state was directly attributed to the presence or absence of malignancy. The authors’ findings could suggest that the increase seen in the patients is more likely related to their postoperative condition and recent major intra-abdominal surgery than the presence or absence of malignancy. So my question would be, why did the authors not compare the coagulation changes seen postoperatively in patients undergoing major abdominal surgery for the benign pathology, let us say, as compared with those for malignancy?

And finally, with the above-outlined concerns that I just outlined and the inability to specifically identify the actual mechanism for this sustained hypercoagulable state, is there sufficient evidence to warrant a change in the current standards of thromboprophylaxis?

DR F CHARLES BRUNICARDI (Los Angeles, CA): The authors have shown, in 35 patients, before and after major surgical resection of upper gastrointestinal, pancreatic, and biliary malignancies, that the use of rotational thromboelastometry demonstrated a progressive hypercoagulability persisting up to 1 month post-resection. This is a remarkable and surprising finding. The authors conclude that the data support the continued use of thromboprophylaxis protocols in these high-risk patients during their hospitalization and after discharge. I have 3 questions.

First, how do you explain the finding of hypercoagulability despite 60% of the patients being on chemical thromboprophylaxis?

Next, how do you explain the differences between your findings and those of the De Pietri study, where he was using the TEG, which showed hypocoagulability after pancreatic resections?