Systemic Effects of Subcutaneous Heparin Use in Otolaryngology Patients

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Abstract

Objectives. To describe a population of otolaryngology patients who developed systemic anticoagulation from pharmacologic deep vein thrombosis prophylaxis using subcutaneous low-dose unfractionated heparin and describe associated adverse events and identify risk factors for this occurrence.

Study Design. Retrospective case series with chart review.

Setting. Single-institution, academic tertiary care center.

Subjects and Methods. Patients who developed prolonged partial thromboplastin times from routine administration of subcutaneous low-dose unfractionated heparin postoperatively were retrospectively identified during a 16-month period. Data regarding demographics, disease characteristics, laboratory values, associated complications, and risk factors were collected and analyzed.

Results. Five patients, all with head and neck cancer, postoperatively developed prolonged partial thromboplastin time levels with prophylactic subcutaneous low-dose unfractionated heparin. All had body mass index ≤20 kg/m² and received 5000 units of subcutaneous low-dose unfractionated heparin 3 times daily. Four had impaired renal function. Adverse events included 5 postoperative wound hematomas, an emergent reintubation, and a case of persistent mucosal bleeding. These bleeding complications accounted for 25% of all bleeding complications in otolaryngology patients during the same period.

Conclusion. Unanticipated systemic effects of subcutaneous low-dose unfractionated heparin can cause significant morbidity in surgically treated patients with head and neck cancer. From this case series, risk factors appear to include subcutaneous low-dose unfractionated heparin 3 times daily dose frequency, low body mass index, and renal dysfunction. For this at-risk patient population, a protocol is needed to minimize both deep vein thromboses and complications of prophylactic therapy.

Keywords
subcutaneous, heparin, bleeding, deep venous thrombosis, pharmacologic prophylaxis

While otolaryngology patients have a low risk for deep venous thrombosis (DVT) or pulmonary embolism (PE) postoperatively, the subpopulation of patients undergoing surgery for head and neck cancer has been recognized as having a higher risk, which likely ranges from 0.6% to 8%.1–7 When venous thromboembolism (VTE) events occur after head and neck cancer surgery, there are additional significant risks, including mortality, postoperative complications, increased length of hospitalization, and increased hospital-related costs.7 Pharmacologic prophylaxis needs to be evaluated based on the balance between the benefit of preventing VTE and the associated complications of therapy. Numerous clinical trials and meta-analyses have shown a benefit to the routine use of pharmacologic thromboprophylaxis following major surgical procedures, with a reduction in VTE by at least 60% in general surgery patients.8 There are only sporadic studies that evaluate the bleeding risks of this therapy, however, and even more limited data specific to the otolaryngology patient. Consequences of postoperative bleeding in otolaryngology patients can be significant.

Although not including a section for otolaryngology patients or those undergoing surgery for head and neck cancer, the clinical practice guidelines for the prevention of VTE published in 2008 from the American College of Chest Physicians include their strongest recommendations for (1) every hospital to develop a protocol for addressing the prevention of VTE and (2) general surgery patients

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undergoing major surgery for cancer to receive thromboprophylaxis with low molecular weight heparin (LMWH), low-dose unfractionated heparin (LDUH) 3 times daily (TID), or fondaparinux.8 As a result, our hospital instituted a computerized physician order entry (CPOE) form for VTE prophylaxis for a nonobese (<100 kg) medical or surgical patient (excluding trauma, orthopedic surgery, and neurosurgery) to be treated with 5000 units (U) of subcutaneous (SQ)–LDUH dosed TID as the recommended dosage. With the updated clinical practice guidelines for VTE prevention published in 2012 not specifying a preference for 2 or 3 times daily dosing for SQ-LDUH in these patients, the order set now also includes the twice-daily dosing (BID) option.9

The Department of Otolaryngology–Head and Neck Surgery at Washington University School of Medicine has a robust Patient Safety/Quality Improvement (PSQI) reporting system. Postoperative bleeding is one of the adverse events that are carefully tracked. Analysis of patients who developed postoperative bleeding complications began to show a trend of patients developing prolonged partial thromboplastin times (PTT) as a likely cause of the postoperative bleed. These events started to occur after the standard treatment for patients who required pharmacologic VTE prophylaxis became SQ-LDUH on a TID dosing schedule. The otolaryngology service became particularly aware of this possibility following a sentinel case of recurrent neck hematoma in which no identifiable source of venous or arterial bleeding was found, but a PTT was checked and found to be markedly elevated (patient 2 in the tables).

The objectives of this study are to (1) describe a population of otolaryngology patients who developed systemic anticoagulation from pharmacologic DVT prophylaxis using subcutaneous SQ-LDUH, (2) describe associated adverse events, and (3) identify risk factors for this occurrence.

**Methods**

This study was approved by the Institutional Review Board at Washington University School of Medicine. A retrospective analysis of prospectively collected cases was performed of all otolaryngology patients who had an adverse event reported into the PSQI database of the Department of Otolaryngology–Head and Neck Surgery at Washington University School of Medicine (RL Solutions, Toronto, Ontario, Canada) from December 1, 2011, to April 1, 2013. Patients with postoperative bleeding were identified using this database, and data from the electronic medical record were collected and analyzed. Data collected included patient demographics, diagnoses, comorbidities, body weight, body mass index (BMI), glomerulofiltration rate (GFR), laboratory values, pharmacologic thromboprophylaxis dosing, number of doses of SQ-LDUH received, and adverse events. Standard statistical analysis was performed to determine the median for quantifiable data.

**Results**

A total of 5 patients, all undergoing surgery for head and neck cancer, developed prolonged PTT while on thromboprophylactic doses of LDUH. Details regarding these patients are summarized in Table 1. Three patients were men, and 2 were women. Patient age ranged from 66 to 86 years, with a median age of 76 years. All patients had a normal baseline PTT obtained within 30 days of the operative date. No patients received antiplatelet or anticoagulation medication within 7 days prior to surgery. Prolonged PTT values ranged from 52.8 to 127.0 seconds, with a median of 90.0 seconds. The PTT normalized in all patients after stopping the SQ-LDUH. All patients were treated with SQ-LDUH 5000 U TID, the first dose of which was typically given following the patient’s arrival to his or her postoperative location. Patients did not routinely receive preoperative pharmacologic thromboprophylaxis.

Four of the 5 patients (80%) developed bleeding complications in the setting of a prolonged PTT. Three of these patients developed a surgical site hematoma, 2 of whom required operative drainage and 1 of whom required urgent reintubation and bedside drainage. Both patients who underwent operative drainage had recurrence of the hematoma requiring another operative drainage, making a total of 5 postoperative hematomas that required additional treatment. Another patient developed mucosal bleeding at dental

Table 1. Patient Details.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, y</th>
<th>Primary Tumor Site</th>
<th>TNM Stage</th>
<th>SQ Heparin Dose, U</th>
<th>No. of Doses Prior to Detection of Prolonged PTT</th>
<th>Baseline PTT, s</th>
<th>PTT Peak, s</th>
<th>Adverse Events and Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>Oral cavity</td>
<td>T2N0M0</td>
<td>5000 TID</td>
<td>9</td>
<td>33.9</td>
<td>52.8</td>
<td>Neck hematoma requiring surgical evacuation (twice)</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>Supraglottis</td>
<td>T2N1M0</td>
<td>5000 TID</td>
<td>18</td>
<td>31.6</td>
<td>104.2</td>
<td>Neck hematoma requiring surgical evacuation (twice)</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>Oral cavity</td>
<td>T0N3M0</td>
<td>5000 TID</td>
<td>17</td>
<td>33.0</td>
<td>57.7</td>
<td>Neck hematoma requiring bedside drainage and reintubation</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>Scalp</td>
<td>T4aN0M0</td>
<td>5000 TID</td>
<td>32</td>
<td>32.9</td>
<td>90.0</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>Supraglottis</td>
<td>T4aN0M0</td>
<td>5000 TID</td>
<td>20</td>
<td>29.3</td>
<td>127.0</td>
<td>Mucosal bleeding at surgical site</td>
</tr>
</tbody>
</table>

Abbreviations: PTT, partial thromboplastin time; SQ, subcutaneous; TID, 3 times daily; TNM, tumor node metastases.
During the period of this study, 3279 surgical procedures were performed on adult otolaryngology patients at our hospital. A total of 16 patients (0.49%) were reported during this period to develop VTE. A total of 16 otolaryngology patients (0.49%) were identified to have postoperative bleeding complications. Ten of the 16 patients (62%) who developed postoperative bleeding complications were patients with head and neck cancer. Of the 16 patients identified with bleeding complications, 1 patient was on a heparin drip, 1 patient received 5000 units SQ-LDUH BID, 12 patients received 5000 units SQ-LDUH TID, and 2 patients were outpatients who received no pharmacologic thromboprophylaxis. For the 13 patients with bleeding complications who were being treated with SQ-LDUH at the time of developing the complication, 4 had a prolonged PTT, 7 had a normal PTT, and the PTT was not obtained for 2 patients. Thromboprophylaxis was stopped for 24 hours, and the dose of SQ-LDUH was decreased to 5000 U SQ BID after the PTT normalized. This was the only patient who had no adverse events. Data for potential risk factors for systemic complications in otolaryngology patients during this period.

One patient was found incidentally to have a PTT of 90 seconds after 32 doses of SQ-LDUH. Although PTT levels are not routinely checked in postoperative patients with head and neck cancer, due to the heightened awareness of the systemic effects of SQ-LDUH during this period, a PTT level was prophylactically checked on this patient. Thromboprophylaxis was stopped for 24 hours, and the dose of SQ-LDUH was decreased to 5000 U SQ BID after the PTT normalized. This was the only patient who had no adverse events. Data for potential risk factors for systemic anticoagulation effects from SQ-LDUH are summarized in Table 2. Patient BMI ranged from 15.9 to 20.2 kg/m², with a median of 17.0 kg/m². Four of the 5 patients had a low GFR, with the range being 25 to 54 mL/min. The fifth patient had a GFR of 63 mL/min, which is on the low end of normal. The median GFR was 52 mL/min. One patient had a low albumin level, and no patients had a low total protein level. No patients had abnormal liver function.

### Discussion

At our institution, changing the frequency of SQ-LDUH dosing from BID to TID for pharmacologic VTE prophylaxis in otolaryngology patients was influenced by the clinical practice guidelines for the prevention of VTE published in 2008. During a 16-month period following the implementation of this recommendation, we identified 5 patients who developed prolonged PTT levels after administration of SQ-LDUH 5000 U TID for VTE prophylaxis. Four of these patients developed associated bleeding complications, which accounted for 25% of all otolaryngology patients with postoperative bleeding complications during the studied period. While these 5 patients represent a minority of the otolaryngology patients treated with pharmacologic VTE prophylaxis during that period, the incidence of systemic anticoagulation effects from SQ-LDUH is likely underestimated. There may have been other patients who had more than the standard prophylaxis effect who were at risk of bleeding but not identified since PTT levels were not standardly performed postoperatively on all patients receiving thromboprophylaxis. All patients described in this study had surgery for head and neck cancer. This finding is likely related to the fact that most otolaryngology patients who receive pharmacologic prophylaxis for VTE in our department are patients undergoing surgery for head and neck cancer.

The rate of VTE in our study was 0.49%, which is relatively infrequent in comparison to joint replacement surgery (3%) and gynecologic surgery (1%-6.5%). With such low rates of VTE in this patient population, it is particularly important to be aware of potential adverse effects of prophylactic subcutaneous heparin. The risk/benefit ratio of preventing VTE and the potential for bleeding complications warrant careful consideration.

Previous studies have reported an increased risk for bleeding complications for patients being treated with pharmacologic prophylaxis for VTE. Leonardi et al performed a systematic review of 33 randomized clinical trials to determine if there was an increased risk for bleeding complications with the use of pharmacologic prophylaxis for VTE after undergoing general surgical procedures. The risk for hematoma was 5.7% for patients receiving prophylaxis vs 0.8% for those patients receiving placebo. The hematoma risk and rate of reoperation were slightly lower for patients who received BID vs TID dosing of SQ-LDUH. The authors commented that the need for transfusions related to bleeding complications from thromboprophylaxis was not included in their data analysis due to the difficulty with interpreting this variable in the setting of recent surgery (surgical blood loss, fluid shifts, and preoperative anemia). For similar reasons,
we did not include transfusion data in our analysis. For patients with head and neck cancer, Clayburgh et al13 studied 100 patients prospectively to determine the incidence of VTE in this patient population. Although only 14% of these patients received some form of postoperative anticoagulation therapy, the risk of bleeding complications was higher in patients who received this therapy. Gabriel et al13 studied 1018 patients after undergoing head and neck surgery, and patients who received pharmacologic prophylaxis (55% of the patients) had a significantly higher risk for postoperative hematoma or bleeding (1.9% vs 0.2%). The PTT levels were not reported in either of these studies.

Fiebig et al14 reported a sentinel case of a medical patient who developed a spontaneous retroperitoneal hematoma secondary to a significantly prolonged PTT from receiving SQ-LDUH 5000 U TID. This case led these investigators to further study patients receiving SQ-LDUH for prolonged PTTs, and they identified 15 more patients, all asymptomatic, with a peak PTT $\geq 1.5$ above baseline with the use of SQ-LDUH at TID dosing. All 16 patients in this study, in addition to the TID dosing schedule, had at least one other attribute: Asian ethnicity, low body weight, impaired renal function, low albumin, or low total protein level. Matsubara et al15 studied 280 patients after undergoing cesarean section treated with SQ-LDUH 5000 U BID and found that 7.1% had an elevated PTT $\geq 45$ seconds and 0.7% had a PTT $\geq 60$ seconds. Postoperative PTT level was correlated inversely with postpartum weight. Hudcova and Talmon16 reported a case of surgical site hemorrhage from SQ-LDUH 5000 U BID in a human immunodeficiency virus (HIV)-positive patient. The authors speculated that the augmented effect of the SQ-LDUH was related to liver dysfunction, as the reticuloendothelial system is responsible for clearance of SQ-LDUH.17 The half-life of LDUH would be expected to be prolonged in patients with liver dysfunction.

From analyzing these previously described proposed risk factors in our patients, only TID dosing, low BMI ($\leq 20$ kg/m$^2$), and impaired renal function were associated with systemic anticoagulation effects from SQ-LDUH. As reported in previous studies, a low BMI appears to increase the likelihood of bleeding complications from prophylactic dosing of LDUH.14,15 Ultimately, while patients with high BMI require higher doses of LDUH for thromboprophylaxis, patients with a low BMI may require lower doses of LDUH, although this relationship requires further investigation. Poor renal function was not an expected finding given that SQ-LDUH is predominantly metabolized by the liver. There is a small amount of undegraded LDUH that gets excreted in the urine, however. Furthermore, when serum concentrations of LDUH are elevated, metabolism of heparin occurs through the renal system.18,19 It is possible that LDUH gradually accumulated and contributed to the risk for developing systemic anticoagulation from SQ-LDUH, even for patients with a mild to moderate decrease in GFR. Perhaps renal-associated poor platelet function contributed to the bleeding complications in these patients. Only 1 patient had a low platelet count (patient 5 in the tables; platelet counts not shown) of 101 K/cumm, but this patient had only a minimally decreased GFR.

Our institution preferentially uses LDUH for thromboprophylaxis in this patient population. Advantages of using LDUH rather than LMWH include the fact that it is relatively inexpensive, is easier to monitor, is reversible with protamine, and typically does not require dose adjustments for renal disease. Conversely, LDUH requires more injections per day, it has a higher risk of heparin-induced thrombocytopenia, and there is a relatively higher risk of bleeding than with LMWH.

The present study has several limitations. It is retrospective in design with a limited sample size. Furthermore, the data represent a single institution’s experience. The rate of VTE prophylaxis and total number of patients treated with a TID dosing regimen of LDUH could not be determined. Comparisons between different dosing regimens or alternative pharmacologic thromboprophylaxis agents could not be assessed. We could not determine the overall incidence of prolonged PTT from SQ-LDUH since we did not obtain a PTT in all patients undergoing thromboprophylactic therapy, particularly from those patients who did not have a bleeding complication. Not all reported patients with postoperative bleeding had a PTT level measured, so this study might underestimate the percentage of bleeding complications associated with systemic effects from SQ-LDUH. Although our department has a robust PSQI reporting culture and process, it is possible that not all postoperative bleeding complications were reported and thus identified for data analysis. The present study does, however, show the power of a robust PSQI reporting system for adverse events. The first signal for this occurrence was through a thorough review of quality improvement/morbidity and mortality data, with subsequently tracking and trending the data.

Conclusion

The present study demonstrates that pharmacologic prophylaxis for VTE with SQ-LDUH can unexpectedly cause systemic anticoagulation in surgically treated otolaryngology patients. All patients with this occurrence in this study underwent surgery for head and neck cancer. All affected patients were treated with SQ-LDUH 5000 U TID and had a BMI $\leq 20$ kg/m$^2$. Four of the 5 patients also had a low GFR. This combination of factors might represent a subset of patients at particularly increased risk for developing systemic effects and bleeding complications from thromboprophylaxis using SQ-LDUH 3 times daily. On the basis of these observations and the 2012 updated clinical practice guidelines for VTE prevention that do not specify an advantage to TID dosing for these at-risk patients,9 we have implemented BID dosing of SQ-LDUH as an option and now follow PTT levels regularly when the clinical team decides to still use TID dosing. Moving forward, we aim to develop a prospective thromboprophylaxis protocol for this patient population that will minimize both VTE and complications from prophylactic therapy.
Author Contributions
Sarah J. Blank, data analysis, drafting, final approval, responsibility for content of manuscript; David J. Grindler, data analysis, drafting, final approval, responsibility for content of manuscript; Janice Zerega, data analysis, drafting, final approval, responsibility for content of manuscript; Morey Blinder, data analysis, drafting, final approval, responsibility for content of manuscript; Brian Nussenbaum, data analysis, drafting, final approval, responsibility for content of manuscript.

Disclosures
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