Venous thromboembolism: deep venous thrombosis and pulmonary embolism in a neurosurgical population

Clinical article

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Object. Venous thromboembolism (VTE), a combination of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and death in neurosurgical patients. This study evaluates 1) the risk of developing lower-extremity DVT following a neurosurgical procedure; 2) the timing of initiation of pharmacological DVT prophylaxis upon the occurrence of VTE; and 3) the relationship between DVT and PE as related to VTE prophylaxis in neurosurgical patients.

Methods. The records of all neurosurgical patients between January 2006 and December 2008 (2638 total) were reviewed for clinical documentation of VTE. As part of a quality improvement initiative, a subgroup of 1638 patients was studied during the implementation of pharmacological prophylaxis. A high-risk group of 555 neurosurgical patients in the intensive care unit underwent surveillance venous lower-extremity duplex ultrasonography studies twice weekly. All patients throughout the review received mechanical DVT prophylaxis. Pharmacological DVT prophylaxis, consisting of 5000 U of subcutaneous heparin twice daily (initially started within 48 hours of a neurosurgical procedure and subsequently within 24 hours of a procedure) was implemented in combination with mechanical prophylaxis. The DVT and PE rates were calculated for each group.

Results. In the surveillance group (555 patients), 84% of the DVTs occurred within 1 week and 92% within 2 weeks of a neurosurgical procedure. There was a linear correlation between the duration of surgery and DVT development. The use of subcutaneous heparin reduced the rate of DVT from 16% to 9% when medication was given at either 24 or 48 hours postoperatively, without any increase in hemorrhagic complications. In the overall group (2638 patients), there were 94 patients who exhibited clinical signs of a possible PE and therefore underwent spiral CT; 22 of these patients (0.8%) had radiological confirmation of PE. There was no correlation between the use of pharmacological prophylaxis at either time point and the occurrence of PE, despite a 43% reduction in the lower-extremity DVT rate with pharmacological intervention.

Conclusions. The majority of DVTs occurred within the first week after a neurosurgical procedure. There was a linear correlation between the duration of surgery and DVT occurrence. Use of early subcutaneous heparin (at either 24 or 48 hours) was associated with a 43% reduction of developing a lower-extremity DVT, without an increase in surgical site hemorrhage. There was no association of pharmacological prophylaxis with overall PE occurrence.

(Key Words: • deep venous thrombosis • pulmonary embolism • venous thromboembolism • heparin)

Venous thromboembolism refers to both DVT and PE. Deep venous thromboses of the lower extremities are believed to be the source of as many as 90% of PEs.7 Risk factors for developing DVT in the neurosurgical patient population include the presence of either benign or malignant tumors, spinal cord injury, head trauma, hemorrhagic or ischemic stroke, duration of surgery, and decreased mobility or limb movement.4,12 The reported incidence of DVT in untreated neurosurgical patients varies between 18% and 50%.1,12 Deep venous thrombosis prophylaxis may represent the single most significant intervention for lowering morbidity and death in the neurosurgical population.7 Mechanical devices for DVT prophylaxis are considered to be a standard of care.11 As opposed to pharmacological prophylaxis, mechanical devices may minimize hemorrhagic complications but may not sufficiently reduce the VTE rates. The adverse rates of surgical site hemorrhage complication with pharmacological prophylaxis compared with the rates of VTE postprocedure are not well studied and the optimal method of prophylaxis in neurosurgical patients (mechanical, pharmacological, or both) remains controversial.12

Deep venous thrombosis is an important cause of morbidity in neurosurgical patients because of the ensuing risk of thrombophlebitis as well as the potential for
Venous thromboembolism in a neurosurgery population

venous embolization to the lung. It is the occurrence of an actual PE that is associated with the greatest risk of preventable death. The rate of PE in untreated neurological patients ranges from 0.5%–5% in one study to 0%–25% in another study. An autopsy study of neurological patients revealed a PE rate of 8%–25% with a mortality rate of 5%–60%. Clinical studies of patients with brain tumors demonstrated a PE rate of approximately 8.4%. The overall incidence of PE in the literature is reported to approximate 0.4% with a mortality rate of nearly 60%.

Many quality assurance measurements and hospital rating dashboards include VTE rates. The accuracy of VTE events based on hospital discharge data has recently been called into question. The sensitivity of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for PE is approximately 74% and for DVT the sensitivity is approximately 67%. Additionally, neurological specific rates are poorly defined in the literature. In this study we describe the overall VTE rate in a neurological population. Furthermore, we describe our experience with a subgroup of this neurological patient population at our institution following a systemwide quality improvement project to reduce the rates of VTE in postsurgical patients by using pharmacological prophylaxis postoperatively in combination with mechanical prophylaxis. The overall VTE, DVT, PE, and surgical site hemorrhage rates in our study populations were reviewed and relationships between DVT, PE, and pharmacological prophylaxis were analyzed.

Methods

Study Population

After receiving approval from our Institutional Research Review Board, we searched the complete electronic medical records for all patients who underwent a neurological procedure and were admitted to our center between January 2006 and December 2008. Patient demographic information along with admitting/discharge diagnosis, type of surgery, and duration of surgery were recorded. Patients admitted between January 2006 and December 2007 were evaluated in the context of a quality improvement project studying the overall incidence of VTE. In this implementation group, patients admitted to our neurosciences intensive care unit were defined as a “high-risk” group and underwent surveillance lower-extremity venous ultrasonography (duplex) studies performed twice weekly. Patients admitted to the floor service, who were considered at increased risk of developing DVT, were also screened. Any patient who developed clinical symptoms or signs of DVT such as calf swelling, tenderness, warmth, and/or acute edema of the lower extremities underwent an immediate diagnostic duplex study for possible DVT.

All lower-extremity duplex ultrasonography studies were reviewed by vascular surgeons at our institution and the data were analyzed for DVT. Patients with symptoms or signs of PE, including unexplained tachycardia, sudden onset of shortness of breath, or abnormal unexplained arterial blood gas gradients underwent an urgent emergency spiral chest CT scan to rule out PE.

Statistical Analysis

The analysis of the data, including descriptive statistics, was performed using statistical software (SPSS version 13.0). An ANOVA was used to compare mean values. Means between different outcome groups at corresponding time points were compared using the unpaired t-test. Differences were considered statistically significant with probability values <0.05. Values were expressed as mean ± SEM unless otherwise indicated.

Results

Records of 2638 neurological patients who were admitted to our institution between January 2006 and December 2008 were reviewed for occurrence of VTE (DVT and/or PE). Patient demographic information along with diagnosis, type of surgery, age, length of stay, and sex were reviewed and recorded (Tables 1 and 2). Records of 1638 neurological patients admitted between January 2006 and December 2007 were specifically identified as part of the systemwide quality improvement initiative. Thirty-four percent (555 patients) had undergone at least 1 lower-extremity duplex ultrasonography venous study. This group included the patients who had undergone either a lower-extremity venous duplex study during their neurosciences intensive care unit stay or who were considered to have a high risk of developing DVT while they were on the neurological floor service. The vast majority of the lower-extremity venous duplex screening studies were found to be positive (84%) within the first week of admission with an additional 8% by the end of the second week (Fig. 1).

The duration of surgery was rounded to the nearest hour. The relationship between operative time and positive venous lower-extremity duplex study was plotted (Fig. 2). There was a linear relationship between the duration of surgery and DVT development ($r^2 = 0.64; p < 0.05$). This correlation was independent of the pathology, type of surgery, and postoperative examination.

Subcutaneous Heparin and DVT

The risk of developing DVT following a neurological procedure while using only mechanical DVT prophylaxis was calculated as 16%. The risk of developing DVT using mechanical and pharmacological prophylaxis was reduced to 9% with implementation of a regimen of subcutaneous heparin at 5000 U twice daily. This was a 43% reduction in the rate with the addition of pharmacological prophylaxis (Fig. 3). Initially patients received subcutaneous heparin within 48 hours but this regimen was subsequently advanced to within 24 hours of surgery because of the systemwide initiative and anecdotal concerns of high rates of VTE with delays in the initiation of therapy to the 48-hour window. There was no significant difference in the rate of surgical site or other hemorrhagic complications between the 24-hour group and the 48-hour group as compared with the control group (no pharmacological prophylaxis; Fig. 4).

Pulmonary Embolism

Between January 2006 and December 2008 we iden-
tified 94 (4%) of 2638 patients who exhibited possible clinical manifestations of PE leading to a diagnostic radiological study. Twenty-two (0.8%) of these 2638 patients had a positive radiological study. We did find a positive correlation between the duration of surgery and the risk of developing PE, which was independent of heparin use (p < 0.05; Fig. 5). Six patients with a radiological study confirmed positive for PE did not receive prior lower-extremity duplex ultrasonography (from a total of 34 without a prior lower-extremity duplex study); 9 of 38 patients with a prior negative lower-extremity duplex study had a confirmed positive PE; and just 7 of 22 patients with a prior positive lower-extremity duplex study had a confirmed PE (Fig. 6). Interestingly, 12 of the 22 patients with PE had undergone central line placement. Of these 12, 6 had upper-extremity duplex studies and 3 were positive for an upper extremity DVT. Furthermore, the use of subcutaneous heparin, at either 24 or 48 hours after surgery, did not appear to reduce the rate of PE (Fig. 4).

Discussion

Deep Vein Thrombosis

Venous thromboembolism includes DVT and PE. Neurosurgical patients have an increased risk of developing VTE due to limb paralysis, stroke, and immobility as well as hypercoagulable states induced by certain neoplasms, such as astrocytoma. The high rate of VTE in neurosurgical patients was related to malignant neoplasms (18%), trauma (12%), congestive heart failure (10%), central venous catheters (9%), neurological disease (7%), and superficial vein thrombosis (5%) in 1 series, and VTE in neurosurgical patients was associated with brain tumors (28%–43%), craniotomy (25%), and head injury (20%) in a second series.12,14

The use of mechanical prophylaxis—including early ambulation, intermittent pneumatic compression, and sequential compression devices—has been shown to decrease DVT formation. An array of pharmacological agents for VTE prophylaxis has also been used, including unfractionated continuous intravenous heparin, low-dose unfractionated heparin (5000 U every 8–12 hours), low-molecular-weight heparins (such as enoxaparin), warfarin, aspirin, other heparinoids, and thrombin inhibitors (danaparoid, hirudin, fondaparinux, ximelagatran). The efficacy of subcutaneous heparin in a mixed population of surgical patients has been well documented, with a 45% relative risk reduction in VTE based on one meta-analysis.15 Our results show a similar risk reduction of 43% following the use of subcutaneous heparin at either 24 or 48 hours after surgery in our neurosurgical patients. Importantly, this risk reduction was not associated with any increased occurrence of complicating hemorrhage at either time point.

The risk of developing DVT in neurosurgical patients is variably estimated at between 22% and 45%. The addition of mechanical prophylaxis reduces the risk of DVT by approximately 10%–20%. We found a similar DVT risk reduction of 16% (for mechanical prophylaxis only) in our study population. This result was validated using routine surveillance of the lower-extremity venous duplex studies. Significantly, surveillance of high-risk patients is important because 50%–60% of patients with DVT may not have clinical manifestations such as a swollen, tender, warm calf or a positive Homan sign.

The timing and choice of VTE prophylaxis for patients undergoing a neurosurgical procedure remains controversial. The use of low-dose heparin (5000 U twice daily) started before surgery has been shown to reduce the risk of DVT by two-thirds and PE by one-half. Furthermore, a meta-analysis of randomized controlled trials on the efficacy and safety of prophylactic heparin in neurosurgery revealed a 45% relative risk reduction of VTE. The bleeding risk with early use of subcutaneous heparin was found to be low. This risk was confirmed in a small blinded study in which subcutaneous heparin was administered 2 hours before surgery and continued for 7 days at a rate of 5000 U of subcutaneous heparin twice daily. In addition, Wen and Hall performed an analysis of the literature and found that the rate of postoperative hematoma was approximately 1.2% when using unfractionated heparin compared with a control (1.6%). This finding is similar to our results in which the rate of hemorrhage

### Table 1: Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Received Heparin</th>
<th>No Heparin</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>male patients</td>
<td>803</td>
<td>500</td>
<td>1303</td>
</tr>
<tr>
<td>female patients</td>
<td>858</td>
<td>477</td>
<td>1335</td>
</tr>
<tr>
<td>mean age in yrs (range)</td>
<td>54 (0–95)</td>
<td>40 (0–99)</td>
<td>49 (0–99)</td>
</tr>
<tr>
<td>mean length of stay in days (range)</td>
<td>7.4 (0–115)</td>
<td>4.7 (0–126)</td>
<td>6.4 (0–126)</td>
</tr>
</tbody>
</table>

### Table 2: Distribution of neurosurgical cases

<table>
<thead>
<tr>
<th>Type of Case</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>simple spine†</td>
<td>23</td>
</tr>
<tr>
<td>complex spine‡</td>
<td>13</td>
</tr>
<tr>
<td>tumor spine</td>
<td>3</td>
</tr>
<tr>
<td>cranial§</td>
<td></td>
</tr>
<tr>
<td>tumor</td>
<td>20</td>
</tr>
<tr>
<td>vascular</td>
<td>4</td>
</tr>
<tr>
<td>trauma</td>
<td>8</td>
</tr>
<tr>
<td>other</td>
<td>20</td>
</tr>
<tr>
<td>miscellaneous¶</td>
<td>9</td>
</tr>
</tbody>
</table>

*Cases that were evaluated for lower-extremity DVT by duplex ultrasonography (555 total).
† Spine cases that lasted < 5 hours (mean 3.1 hrs); these included anterior and posterior cervical cases as well as multilevel lumbar surgeries.
‡ Cases that extended beyond 5 hours (mean 6.8 hrs); these included scoliosis surgery as well as major spine surgery.
§ Cranial cases included tumor, vascular, and trauma. Cranial cases that could not be categorized into the above categories, such as Chiari malformation decompression and deep brain stimulation, were considered “other.”
¶ Vagus nerve stimulator and peripheral nerve cases.
Venous thromboembolism in a neurosurgery population

following the administration of subcutaneous heparin ranged from 0.5% to 2.3% (data not shown).

The use of enoxaparin (low-molecular-weight heparin) in neurosurgical patients has produced conflicting data. A study in which enoxaparin was administered preoperatively at a dose of 30 mg and every 12 hours after until day of discharge was terminated early because of an increased incidence of intracerebral hemorrhage in the enoxaparin group. However, there was no increase in bleeding when enoxaparin was begun within 24 hours of surgery with a significant reduction in DVT from 32% to 17%. These findings suggest that the use of both unfractionated and low-molecular-weight heparin appears to be safe when used within 24 hours after the conclusion of neurological surgery. Of note, the prevention of VTE following acute ischemic stroke with enoxaparin (PREVAIL) study demonstrated a 43% relative risk reduction as compared with 5000 U of subcutaneous heparin given twice daily. Overall absolute symptomatic event rates were low in this study with a PE rate of just 0.5%. Major and symptomatic hemorrhage rates were also low (<1%) although slightly higher with enoxaparin.

The reduction in DVT after the use of pharmacological prophylaxis was observed after initiating subcutaneous heparin at either 24 or 48 hours after surgery without an increase in postoperative hematoma. In addition, 84% of the DVT was found within 1 week of surgery. This result begs the question as to whether high-risk patients have a predilection for developing DVT regardless of the timing of administration of pharmacological prophylaxis.

Fig. 1. Graph showing results of surveillance lower-extremity (LE) duplex ultrasonography performed on 555 high-risk neurosurgical patients twice weekly (Mondays and Thursdays). The first and second surveillances occurred within 1 week of surgery and the third surveillance occurred within 2 weeks of surgery.

Fig. 2. Graph comparing operative time estimated to within 1 hour of surgery (x axis) and percentage of positive lower-extremity DVT (y axis) based on positive duplex ultrasonography of the lower extremity in 555 high-risk patients.
Perhaps there is a subset of neurosurgical patients who have DVT present on admission. Therefore, one might argue for screening lower-extremity venous duplex ultrasonography studies even prior to surgical intervention.

**Pulmonary Embolism**

Symptoms of PE include shortness of breath, pleuritic chest pain, and tachycardia. The use of spiral CT is superior to a ventilation/perfusion scan for detection of PE. In our study, we preferentially used spiral CT to rule out PE in 94 (4%) of 2638 patients who exhibited signs or symptoms of PE. Of those patients, 22 (0.8%) of 2638 had a positive PE on the spiral CT with a mortality rate of 18%. This rate is similar to that observed in the aforementioned PREVAIL study and prior neurosurgical series have suggested a PE risk of approximately 1.5%–5% in neurosurgical patients with an associated mortality rate of approximately 9%–50%. Close to 25% of all patients with PE will die suddenly and the 1-week survival rate of the remaining patients is approximately 71%.

Prophylaxis against DVTs is believed to be the best way to prevent subsequent VTE to the lungs. Pharmacological DVT prophylaxis for reducing PE rates in neurosurgical patients is not well established. In our study, the rate of PE was not significantly altered with the addition of subcutaneous heparin. This could be due to a lack of statistical power to detect differences in our population as the overall incidence of PE (0.8%) was low.

The relationship between PE and lower-extremity DVT in neurosurgical patients is also not well established. In our study, of 22 patients with radiologically confirmed PE, 7 had a positive lower-extremity venous duplex study for DVT but an additional 9 patients had a negative lower-extremity venous duplex study. Thus, we could not demonstrate a good correlation between lower-extremity DVT and PE in our patient population. Lower-extremity venous duplex studies are not as sensitive for occult DVT as the gold standard of lower-extremity venography. However, in our study population, we speculate another reason for a dissociation between lower-extremity DVT and PE could be related to a higher than expected rate of embolism to the lungs from upper-extremity DVTs. Upper-extremity DVTs are also observed in patients with cancer, insertion of central lines, immobility, and lower-extremity DVT.

Of interest, in our study, of 22 patients who had radiologically confirmed PE, 12 had preexisting central lines, and 4 of these 12 patients had an upper-extremity venous duplex study with 3 positive for DVT.

The relationship between duration of surgery and PE suggests a potential group at high-risk for complications. In addition, there is a relationship between the duration of surgery and risk of developing PE. Cases that extend 6 hours or longer were almost 4 times more likely to develop PE in our study.

**Conclusions**

The reduction of VTE in all postsurgical patients is a major quality and safety target and continues to be a major complication following all surgical as well as neurosurgical procedures. Understanding the incidence of DVT and
Venous thromboembolism in a neurosurgery population

Fig. 6. Flow chart of patients who exhibited signs and symptoms of PE. All patients underwent spiral CT to rule out PE. Of the 94 patients who underwent the PE protocol, 60 had lower-extremity duplex ultrasonography. Of those patients that had lower-extremity duplex studies, 22 were positive lower-extremity duplex studies with 7 developing PE. An additional 9 patients had PE with a negative lower-extremity duplex study. There were 6 patients who developed PE but never had lower-extremity duplex ultrasonography performed during their hospital stay. UE = upper extremity.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Origitano, Khaldi, Schneck. Acquisition of data: Khaldi, Helo. Analysis and interpretation of data: Origitano, Khaldi, Helo. Drafting the article: Origitano, Khaldi, Helo. Critically revising the article: Origitano, Khaldi, Helo. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Khaldi, Helo. Study supervision: Origitano.

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