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Acquired inpatient risk factors for venous thromboembolism after thermal injury

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Abstract

Objective—Acquired, in-hospital risk factors which contribute to venous thromboembolism (VTE) risk after thermal injury remain unknown. We performed a retrospective, matched case-control study to examine associations between acquired, in-hospital risk factors and development of VTE.

Methods—We identified thermally injured patients who were diagnosed with VTE over an 8.5 year period at our institution. VTE patients were matched 2:1 with non-VTE controls based on age, total body surface area burned (TBSA), and presence of inhalation injury. Retrospective chart review identified recognized VTE risk factors such as infectious complications, operative procedures, or central venous access. For each VTE patient and their matched controls, data analysis was limited to the time period before VTE developed. This allowed examination of differences in the pre-VTE hospital course between patients with and without VTE.

Results—Nineteen patients with VTE were matched 2:1 with non-VTE controls. No significant differences were present between groups for age, gender, TBSA, inhalation injury, body mass index, ventilator days, ICU or hospital length of stay. Patients with VTE had significantly more operations (3.7 vs. 1.9, $p=0.038$), were more likely to have pneumonia (73.7% vs. 43.2%, $p=0.031$), or have central venous line insertion (84.2% vs. 51.4%, $p=0.016$) in the pre-VTE period. No significant differences were present for positive blood cultures, urinary tract infections, or burn wound infection between groups.

Conclusions—Our study demonstrates that number of operations, pneumonia, and central venous access are significantly associated with VTE after thermal injury. These in-hospital risk factors should be incorporated into future risk assessment models.

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Keywords

Deep venous thrombosis; pulmonary embolus; venous thromboembolism; DVT; PE; VTE; burn injury; thermal injury; risk factor

INTRODUCTION

Thermally injured patients have multiple risk factors for venous thromboembolism (VTE) ¹⁻⁹. Two studies which performed screening duplex ultrasound at regular time periods have been performed ^{8, 10}. These studies documented that deep vein thromboses (DVT) were present in 6%–23% of thermally injured patients with prolonged hospital admission. In 1968, Foley and colleagues published a case series of 233 autopsies performed on burn patients. Less than 1% of patients had pulmonary embolus (PE) as the proximate cause of death. However, 25% of patients had autopsy evidence of subclinical and non-fatal PE ¹¹.

Ferguson and colleagues recently surveyed ACS-verified burn centers regarding VTE prophylaxis. Of 71 centers surveyed, 24% did not routinely use VTE prophylaxis. Of those who used prophylaxis, 22% reported using sequential compression devices alone and 78% reported using some form of pharmacologic prophylaxis ¹².

Multiple authors believe that VTE represents a threat to patients with thermal injury. Wibbenmeyer and colleagues conclude that “given the prevalence of VTE in our thermally injured patients, prophylaxis of these patients seems justified” ⁸. Similarly, Wahl and colleagues “support the recommendation that DVT prophylaxis should be routine” ¹⁰.

Our previous work with the National Burn Repository (NBR) identified risk factors present at admission for thermal injury which are predictors of venous thromboembolism (VTE). These include total body surface area burned (TBSA) and presence of inhalation injury ¹³. However, VTE risk factors which occur during hospitalization for thermal injury remain unknown. Additionally, although multiple authors recommend prophylaxis for higher-risk patients, no objective tool is currently available to stratify thermally injured patients for VTE risk based on both admission and in-hospital risk factors.

Here, we present the results of a retrospective, matched case-control study performed using our institution’s internal database of thermally injured patients. The specific aim of this project was to examine associations between acquired, in-hospital risk factors and development of VTE.

METHODS

This study was approved by our institution’s Institutional Review Board.

Since 2002, we have prospectively maintained a database of all patients with thermal injury admitted to our ACS-verified burn center. The database contains a unique identifier linked to demographic information. Major complications, including DVT and/or PE, are tracked as outcomes of interest. Screening duplex ultrasound is not routinely performed at our institution.

The database was used to identify all thermally injured patients who were diagnosed with DVT and/or PE between January 2002 and June 2010. Patients with VTE were individually matched with two non-VTE control patients based on age, TBSA, and presence/absence of inhalation injury. For age and TBSA, an initial attempt was made to match ± 4 years and $\pm$

4% TBSA. If two suitable matches were not found, a second attempt was made to match ± 8 years and $\pm 8\%$ TBSA.

Retrospective chart review was conducted for all patients. Demographic variables included age, TBSA burned, percent of partial thickness burns, percent of full thickness burns, and body mass index (BMI) at admission.

Daily progress notes, procedure notes, and operative reports were hand-reviewed to identify presence and location of central venous access. Time to central line placement was tracked as a separate independent variable. Chart review identified total number of ICU days, ventilator days, hospital days, and number and timing of operative procedures. Review of pharmacy records identified number of days of prophylactic-dose chemoprophylaxis (either twice or three-times daily unfractionated heparin or daily low-molecular weight heparin) which were prescribed. Our institution does not routinely follow anti-Xa levels in patients who receive low-molecular weight heparin.

Microbiology data was reviewed to identify infectious complications. Pneumonia was identified through review of bronchoscopic-alveolar lavage (BAL) culture data. Patients with 10,000 organisms/ml grown on a BAL specimen were considered to have pneumonia. The clinical diagnosis of sepsis is difficult to confirm using retrospective chart review. Blood cultures which grew microorganisms were used as a proxy for sepsis. Urinary tract infection (UTI) was defined as 10,000 organisms/ml grown from a urine specimen. Wound infection was defined as quantitative cultures 10^5 colony-forming units/gram of tissue. Time to infection was tracked as a separate independent variable.

Objective imaging tests, such as extremity duplex ultrasound and/or pulmonary embolism protocol CT scan, which could potentially diagnose DVT or PE were reviewed by hand. Location of DVT and whether the DVT was central-line associated were tracked as additional independent variables. The dependent variables of interest included objectively diagnosed DVT or PE as well as time-to-DVT and time-to-PE.

For each group of three patients (one with VTE and two matched controls without VTE), data analysis was limited to the time period before VTE developed. This time-limited analysis is presented throughout the Results section. For example, if a VTE in patient #1 occurred on hospital day 15, then the two matched patient's risk factors were tracked to day 15. Risk factors which were acquired after hospital day 15 in any of the three patients were dropped from the analysis. This allowed examination of differences in the pre-VTE hospital course between patients with and without VTE.

Bivariate statistics were generated. The STATA 11 statistical package (College Station, Texas) was used to perform all matching and statistical analyses.

RESULTS

Our database contained 21 patients with thermal injury who had DVT or PE. Two elderly patients with TBSA $>70\%$ and DVT could not be matched with any controls and were excluded from the analysis. Of the remaining 19 patients with VTE, eight were matched 2:1 for inhalation injury, age ± 4 years and TBSA $\pm 4\%$ with non-VTE controls. Ten patients with VTE were matched 2:1 for inhalation injury, age ± 8 years and TBSA $\pm 8\%$ with non-VTE controls. One patient with VTE was matched 1:1 for inhalation injury, age ± 8 years and TBSA $\pm 8\%$ with a non-VTE control. A second suitable control could not be found for this patient even when age and TBSA matching criteria were extended to age ± 12 years and TBSA $\pm 12\%$. Thus, retrospective chart review was performed for 19 patients with VTE and 37 matched control patients without VTE.

No significant differences were present between groups for age, gender, TBSA, inhalation injury, BMI, ICU or hospital length of stay, or ventilator days (Table 1).

Of the 19 patients with VTE complications, 15 patients had DVT, three patients had PE, and one patient had both DVT and PE. The locations of clot identified in the 16 patients with DVT were: six in the calf veins, three in the femoral or popliteal veins, two in the internal jugular vein, and five in the brachial or axillary veins. Six patients with DVT (37.5%) had central venous access at that site during hospitalization. Four of five (80%) upper extremity DVT were central line-associated.

Among inpatients with VTE, the median time to event was hospital day 14. One patient was diagnosed with a DVT after discharge. This patient had a personal history of DVT and known hypercoagulable state and was on warfarin at baseline. The patient was admitted for overnight observation for a partial-thickness, 6% TBSA burn and had a DVT diagnosed 92 days after burn injury. No other patient in this series had a personal or family history of VTE or known hypercoagulable state prior to admission. No patient received warfarin as VTE prophylaxis.

In the pre-VTE period, risk factor analysis showed that patients with VTE had significantly more operations (3.7 vs. 1.9, $p=0.038$) and were significantly more likely to have central venous line insertion (84% vs. 51%, $p=0.016$).

Among infectious complications, pneumonia was the only significant predictor of VTE. In the pre-VTE period, patients with VTE were significantly more likely to have pneumonia (73.7% vs. 43.2%, $p=0.031$). No significant differences were present for positive blood cultures (25.0% vs. 21.1%, $p=0.73$), UTI (21.0% vs. 21.6%, $p=0.96$), or burn wound infection (15.8% vs. 16.2%, $p=0.97$) between VTE and non-VTE groups in the pre-VTE period (Table 2).

Patients with VTE were significantly more likely to receive chemoprophylaxis (93% vs. 74% of pre-VTE days, $p=0.029$) when compared to controls.

DISCUSSION

We have performed a retrospective matched case-control study to examine acquired, in-hospital risk factors for VTE after thermal injury. We have demonstrated that three factors, including total number of operations, pneumonia, and central venous access, were significantly increased in the pre-VTE period among those patients who developed VTE. Previous risk models¹³ incorporated only risk factors present at admission into a weighted risk score model. This study complements our previous work by identifying additional risk factors suitable for inclusion in future risk models.

Our analysis indicates that patients with central venous access in the pre-VTE period were significantly more likely to have a VTE event. Of note, 80% of upper-extremity DVT were central line associated. Current American College of Chest Physicians guidelines for management of central line associated DVT recommend that 1) the catheter not be removed if it is functional and 2) therapeutic anti-coagulation be initiated for at least three months, even if the catheter is removed¹⁹. As the minimum recommended anti-coagulation regimen is similar, we did not distinguish between central-line associated and non-central line associated DVT in this analysis.

We have previously created and validated a VTE risk stratification tool for thermally injured patients¹³. The model incorporated risk factors which were either known or could be derived at the time of admission. We were unable to include acquired, in-hospital risk

factors due to a lack of a time-to-complication variable in the NBR. Each year, complete data for at least 5,000 thermally injured patients is uploaded to the NBR. A time-to-complication and time-to-procedure variable would allow researchers to identify complications (such as pneumonia, sepsis, or burn wound infection) or procedures which occurred prior to VTE diagnosis; these events could then be considered as VTE risk factors. If time-to-complication and time-to-procedure variables were introduced, one year of data would likely be sufficient to validate a new risk stratification model which incorporates both at-admission and acquired in-hospital risk factors for VTE. This remains an important direction for future research.

There are no randomized trials which examine VTE prevention in burn patients using chemoprophylaxis. There is a paucity of data on what type, if any, of chemoprophylaxis should be provided to burned patients or the efficacy and safety profiles of different chemoprophylaxis doses. Enoxaparin, a commonly used low-molecular weight heparin, is metabolized in the liver and subsequently cleared by the kidney. Enoxaparin clearance should be increased due to the hyperdynamic state which occurs 48 hours after burn injury¹⁴. A recent study from Lin and colleagues examined pharmacokinetics of enoxaparin after burn injury. Standard doses of enoxaparin (30mg subcutaneously twice daily) failed to produce detectable anti-Xa levels in 79% of patients. Among patients who reached appropriate anti-Xa levels, the median required enoxaparin dose was 50mg subcutaneously twice daily. A linear relationship was shown between TBSA and enoxaparin dose required for appropriate anti-Xa levels¹⁵. Patients in our series received standard doses of either unfractionated or low-molecular weight heparin. Based on the results provided by Lin and colleagues, our finding that patients with VTE were significantly more likely to receive standard doses of chemoprophylaxis (93.1% vs. 74.2% of pre-VTE days, $p=0.029$) is difficult to interpret. This finding may represent a type I error.

Our study has several limitations, many of which have been discussed in our previous work on VTE after burn or electrical injury^{5, 13, 16, 17}. We matched for baseline risk factors, including TBSA, inhalation injury, and age, to minimize variability between our two patient cohorts. Despite this, we are still hampered by small sample size. As a result, we were only able to examine acquired, in-hospital risk factors which occur frequently. Previous work in general surgery patients has demonstrated that personal history of DVT and pregnancy are each significant independent predictors of VTE¹⁸. Only one patient in our series had a personal history of DVT and none were actively pregnant. Thus, we cannot comment on the relative importance of these risk factors among burn patients.

Additionally, our previous work using the NBR identified TBSA as an important driver of VTE risk. The current study identified number of operations in the pre-VTE period as an important acquired in-hospital risk factor. A high degree of colinearity is likely present between TBSA and total number of operations. Future weighted risk models will need to examine the relative contributions toward VTE risk made by TBSA and number of operations using multivariable regression techniques.

Conclusions

Our retrospective matched case-control study demonstrates that number of operations, pneumonia, and central venous access are significantly associated with VTE after thermal injury. These in-hospital risk factors should be incorporated into future risk assessment models.

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Table 1

Demographic data in patients with VTE and matched controls. Patients were matched based on age, TBSA, and inhalation injury. Equivalence of these variables between patients with and without VTE indicates adequacy of the matching process.

	Patients with VTE (n=19)	Patients without VTE (n=37)	p value
Age, mean	47	47	0.99
Female gender	32%	24%	0.56
Body mass index	29.3	28.9	0.83
TBSA, mean	31%	30%	0.78
Partial thickness burn, mean	17%	19%	0.72
Full thickness burn, mean	14%	11%	0.49
Inhalation injury	37%	38%	0.94
ICU days, mean	22	14	0.11
Ventilator days, mean	12	8	0.25
Hospital days, mean	40	27	0.09

Table 2

Bivariate statistics examining acquisition of risk factors in the pre-VTE period.

	Patients with VTE (n=19)	Patients without VTE (n=37)	p value
Pneumonia	74%	43%	0.031
Number of operations	3.7	1.9	0.038
Central venous line	84%	51%	0.016
Positive blood cultures	25%	21%	0.73
Urinary tract infection	21%	22%	0.96
Burn wound infection	16%	16%	0.97