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Venous Thromboembolism in Thermally Injured Patients: Analysis of the National Burn Repository

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INTRODUCTION

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolus (PE), results in significant morbidity and mortality. The majority of PE deaths occur within hours of the embolic phenomenon, often secondary to unrecognized DVT [1, 2]. VTE carries the risk of sudden mortality but also notable morbidity, including the post-thrombotic syndrome and pulmonary hypertension with progression to right heart failure [1]. Venous thromboembolic events pose significant threats to all hospitalized patients, both medical and surgical. Patients in the critical care setting are among those at highest risk due to severity of illness, immobility, central vascular access, and concomitant infections [3].

Patients with thermal injury have multiple, well recognized risk factors to develop VTE. These risks include increased total body surface area (TBSA) burned [4-6], increased length of intensive care unit (ICU) stay [4], central venous access [7], increased age [6], obesity [6], burn wound infection [8], and transfusion over 4 units of packed red blood cells [7]. Despite these risks, there is no consensus regarding the use of VTE prophylaxis. Currently, burn centers are forced to extrapolate data from large, single center case-series of burn patients or other non-burn medical, surgical, and critical care populations when making prophylaxis decisions.

In order to further understand the risk factors and prevalence of VTE in burn patients, we used the American Burn Association's National Burn Repository. Our goals were to examine the incidence and risk factors for venous thromboembolism in thermally injured patients and develop a clinically relevant predictive model to identify those patients at highest risk to develop VTE.

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METHODS

The American Burn Association (ABA) has sponsored the National Burn Repository (NBR) since 1990. This voluntary data set compiles de-identified, HIPAA compliant data from participating burn centers in the United States and Canada. The data is also de-identified with respect to burn center providing care. Trained chart reviewers identify eligible patients and upload data using a standardized computer data collection tool. The database contains comprehensive information on patient demographics and comorbidities, etiology and extent of burn injury, ventilator days, ICU days, hospital length of stay, and patient disposition. Procedural data is coded using ICD-9 procedural codes. A comprehensive summary of complications is also included for each patient. The NBR has previously been described in detail [9, 10].

Patient data from 1995-2007 were utilized for this analysis. Patients who died within 24 hours or were admitted for less than one day were excluded. Patients treated at hospitals reporting no complications were removed from the analysis. Additionally, patients whose burn etiology was coded as skin disease or radiation associated were dropped. Exclusion criteria are demonstrated graphically in Figure 1.

Independent variables included age, gender, ethnicity, TBSA burned, presence of inhalation injury, medical comorbidities, ventilator days, need for ICU admission, and ICU length of stay. Placement of central venous access was identified as an additional independent variable using ICD-9 procedural codes 38.93 (central venous catheterization or peripherally inserted central catheter), 38.95 (central venous catheterization for renal dialysis) or 89.62 (central venous pressure monitoring).

The National Burn Repository records approximately 110 distinct complications. All complication data must be supported by burn morbidity and mortality conference data and confirmed by a member of the burn surgery attending staff. Two specific types of venous thromboembolic disease, specifically DVT and PE, were identified as dependent variables. Additionally, we created a venous thromboembolism (VTE) variable, which encompassed patients with DVT or PE. Death during hospitalization was also identified as a dependent variable.

We generated descriptive statistics to examine overall incidence of VTE. Bivariate statistics were used to identify risk factors associated with VTE. All independent variables were placed into a logistic regression model with VTE as the dependent variable. This logistic regression model identified variables independently associated with VTE when controlling for all other risk factors.

We created a predictive model to identify patients at highest risk to develop VTE. All independent variables which were either known or could be derived at time of admission were included in a multivariate stepwise logistic regression model ($p<0.10$). Model discrimination was examined using the c-statistic, defined as area under the Receiver-Operator Curve (AUROC). The Hosmer-Lemenshow goodness of fit test was used to examine the model's ability to predict VTE in low, intermediate, and high risk patients.

RESULTS

We identified all adult patients (age ≥18) with a burn diagnosis in the National Burn Repository. The data sets provided by the ABA were merged and complete data was available for 54,826 patients. After exclusions (Figure 1), a total of 33,637 thermally injured patients receiving care between 1995 and 2007 who met this study's inclusion criteria remained.

The overall rate of DVT was 0.48%, PE was 0.18%, and VTE was 0.61%. Among those with TBSA >10%, the incidence of DVT was 0.92%, PE was 0.38%, and VTE was 1.22%. For patients admitted to the ICU, the incidence of VTE was 1.2%; this was significantly higher ($p<0.001$) than patients not requiring ICU admission (0.32%). Using bivariate statistics, increased age ($p=0.003$), ≥ 2 medical comorbidities ($p=0.05$), presence of inhalation injury ($p<0.001$), need for ICU admission ($p<0.001$), increased number of ICU days ($p<0.001$), mechanical ventilation over 48 hours ($p<0.001$), increased number of ventilator days ($p<0.001$), increased number of operative procedures ($p<0.001$) and increased TBSA ($p<0.001$) were associated with significantly increased VTE risk. When compared to Caucasians, patients of Hispanic ethnicity ($p=0.003$) were significantly less likely to be diagnosed with VTE (Table 1 and Table 2). There were no sustained temporal trends in the rate of VTE diagnosis (Figure 2).

There was a graduated increased VTE risk with increasing TBSA (Figure 3). Patients with TBSA 40-59% were at highest risk for VTE (2.42%). Patients with TBSA of 60-79% and >80% appeared to be at decreased risk for VTE (1.26% and 0.64%, respectively) when compared with those with TBSA 40-59%. A linear relationship exists between TBSA and death (Figure 4).

When controlling for age, gender, presence of inhalation injury, central venous catheter insertion, and ventilator days, three factors—TBSA burned, ICU days, and number of operations—were independently associated with increased VTE risk. For each additional percent burned, a patient's odds of VTE increased by 1.016 (95% CI 1.004-1.029, $p=0.008$). For each additional ICU day, a patient's odds of VTE increased by 1.015 (95% CI 1.001-1.030, $p=0.036$). For each additional operative procedure, a patient's odds of VTE increased by 1.041 (95% CI 1.011-1.071, $p=0.007$).

We created a predictive model to identify patients at highest risk to develop VTE based on all variables which were known or could be derived at time of admission. We used a stepwise logistic regression model ($p<0.10$) including age, gender, presence of ≥2 medical comorbidities, presence of inhalation injury, TBSA burned, and need for ICU admission. The combination of TBSA and need for ICU admission was strongly predictive of patients who eventually developed VTE (c-statistic=0.82). The Hosmer-Lemeshow goodness of fit test (Figure 5) demonstrates that our model has good discrimination to identify patients at lowest and highest risk of VTE.

When controlling for age, gender, presence of ≥2 medical comorbidities, presence of inhalation injury, TBSA, duration of mechanical ventilation, duration of ICU stay, central venous catheter insertion, and total number of operations in a logistic regression model, VTE was significantly associated with death (OR 3.077, 95% CI 1.536-6.163, $p=0.003$).

DISCUSSION

VTE in burn patients

Using the American Burn Association National Burn Repository, we demonstrated that VTE incidence in burned patients is 0.61%. The observed incidence doubles to 1.2% when patients require ICU admission or when patient's TBSA is greater than 10%. Using logistic regression, three risk factors—increased TBSA burned, length of ICU stay, and number of operations—were independently associated with VTE. Our predictive model at time of admission demonstrated that the combination of need for ICU admission and increased TBSA burned was strongly predictive of those patients who developed VTE (c-statistic=0.82).

The burn literature supports that the incidence of symptomatic DVT in patients not receiving chemoprophylaxis is between 2.1% and 3.0% [6, 11]. In reports where chemoprophylaxis was utilized, the symptomatic DVT rate ranged from 0.3% to 2.4% [4, 5, 8, 12]. The current NBR data demonstrate an overall DVT rate of 0.48%, which increases to 0.92% in patients with TBSA>10%. The NBR does not include data on the use of chemoprophylaxis. Published rates of symptomatic pulmonary embolus in burn patients are between .05% and 1.4% [4-8, 11-13]. These rates are supported by findings from the NBR data. The overall PE rate was 0.18%, which rises to a PE rate of 0.38% in patients with TBSA>10%. Smaller series have demonstrated that up to 33% of embolic events occurring after discharge from the hospital [13].

A large portion of DVT and PE in thermally injured patients remain clinically occult. Large autopsy series have shown that pulmonary embolus directly causes death in less than 1% of burn fatalities. However, 25% of burn fatalities had evidence of small vessel pulmonary emboli at autopsy [14]. In clinical studies reporting screening asymptomatic patients with duplex ultrasound, nearly half of DVT in thermally injured patients remain clinically occult [7]. Using screening ultrasound, the incidence of asymptomatic DVT is between 6% and 23% in small case series [7, 15]. This is similar to rates of asymptomatic DVT seen in other high-risk populations, including those with acute spinal cord injury (21%) [16], ICU patients with femoral catheters (11.3%) [17], and patients after open reduction-internal fixation of ankle fractures (21%) [18]. The clinical significance of asymptomatic DVT remains unclear.

Our logistic regression model identified increased TBSA as a risk factor for VTE. However, as shown in Table 2 and Figure 3, VTE risk appears to peak among patients with TBSA burned of 40-60%. In order to explain this phenomenon, we examined rates of death stratified by TBSA. The NBR demonstrates that a linear relationship exists between TBSA and death, as shown in Figure 4. While we hypothesize that patients with TBSA >60% may have died prior to a VTE event occurrence, this cannot be proven using the NBR data set.

Existing guidelines for VTE prophylaxis in burn patients

The 2008 American College of Chest Physicians (ACCP) guidelines include a specific section with recommendations for burn patients. Their recommendations include routine chemoprophylaxis for burn patients with any additional VTE risk factor, including advanced age, extensive or lower-extremity burns, or central venous catheter [3].

Our data supports that patients with these risk factors are at increased risk to develop VTE, with the exception of central venous catheter (Table 1). Central venous line placement was documented in 11.6% of patients overall and in 18.3% of patients with TBSA>10%. Central venous line was not significantly associated with VTE, in contrast to findings by others [6]. Using the NBR procedural codes, only 12.3% of burn patients admitted to the ICU had central venous access. These procedures may not be regularly coded in this database; this may have affected our analysis of this potential source for VTE complications.

Routine VTE prophylaxis for burn patients is recommended by both the ACCP [3] and multiple institutional authors [6, 7, 15]. Additionally, the Joint Commission recently adopted VTE prophylaxis as a “core measure” of hospital quality [19]. A 2005 survey of ABA verified burn centers demonstrated that 23.9% of centers do not routinely utilize mechanical or chemoprophylaxis against VTE. Of those who provide some form of prophylaxis, 22% use mechanical prophylaxis alone and 78% utilize some form of chemoprophylaxis [20]. Currently, there are no randomized control trials evaluating chemoprophylaxis in burn patients and the bleeding risk associated with chemoprophylaxis remains unknown [21]. Meta-analyses in general surgery patients show that hematoma requiring reoperation occurs in only 1% of patients receiving chemoprophylaxis [22].

Limitations

Our study has several limitations. Although it would have been beneficial for this study, the NBR does not include data on method of VTE diagnosis (duplex ultrasound, PE protocol CT scan, etc) or presence of symptoms. The NBR cannot differentiate what form of ongoing screening or testing was routinely performed on patients at various burn centers, or whether the reported VTE rate represents only symptomatic DVT. No data on hospital day when VTE was diagnosed is available. Thus, we are unable to report how VTE risk varies over time in burn patients. Additionally, patient-level data is not available regarding receipt of mechanical and/or chemoprophylaxis against VTE during hospitalization.

The NBR database cannot demonstrate whether chemoprophylaxis decreases VTE in burn patients. Between 2001 and 2003, several publications recommended routine VTE chemoprophylaxis in burn patients [6, 7, 15]. Others advocated for screening duplex ultrasound in asymptomatic burn patients [7, 15]. Despite these recommendations, our data show no clear, sustained temporal trend in the rate of VTE diagnosis (Figure 2). The NBR dataset includes patient data to 2007. Our current analysis cannot evaluate the effect of more recent mandates [19] or recommendations [3, 23, 24] for VTE prophylaxis on VTE rates. Our data analysis did not show that central venous access was a risk factor for VTE, though procedural codes for central venous catheterization may be under-reported. In the NBR database, only 12.3% of burn patients who were admitted to the ICU had a procedural code for central venous access. The signal-to-noise issue is a recognized issue when using the NBR for scholarly work [25]. To minimize this issue, we have attempted to filter the data and stratify among independent variables which intuitively contribute to VTE risk. However, due to limitations in the data set, we were not able to stratify for all potential "noise" issues (symptomatic vs. asymptomatic VTE, chemoprophylaxis vs. no chemoprophylaxis, etc).

The NBR data set is comprised of data from a wide range of hospitals and patients with variable levels of burn injury severity. This should maximize our study's external validity, or ability to be generalized to all burned patients. However, it is possible that systematic differences exist between hospitals who contribute patient data to the NBR and those hospitals who do not contribute data. Similarly, such systematic differences may exist for severity of burn injury between contributing and non-contributing hospitals. Finally, the NBR accrues new data and deletes old data over time. Our analysis was performed using the most complete and recent data in the NBR. While clear temporal trends in VTE diagnosis rates were not observed over time (Figure 2), it is possible that systematic differences exist between patients included versus not included in the NBR. Thus, the recommendations made in this manuscript may not necessarily be generalized to all burned patients.

Notes on appropriate usage of the NBR database

The National Burn Repository is a massive database which includes hundreds of variables for over 50,000 patients. Like other large databases, the NBR is subject to "fishing expeditions". These practices have been thoughtfully described by Jeng et al in a recent "Glimmer" publication [26]:

> The hallmark of this ill-advised analytic exercise is to query…database information without a prior logical hypothesis to test; one is only interested in finding a "p value<.05" that can then have a story line fitted in a post-hoc fashion.

We agree that database "fishing expeditions" have many pitfalls and can lead to inappropriate conclusions. In their article, Jeng et al make four helpful recommendations to avoid inappropriate use of the NBR. These recommendations include 1) have a clear, a priori hypothesis, 2) include individual(s) with a statistical background on the research team, 3) use sensible statistical tests of significance and 4) generate a thoughtful scientific manuscript to share NBR-derived results with other burn surgeons. “Glimmer” publications were essential in design of our study hypotheses, methods, and analysis plan prior to receipt of the NBR database. We made every attempt to adhere to “Glimmer” recommendations while writing this manuscript. We recommend that these documents be reviewed by authors who plan to use the NBR for research purposes.

Study implications

Ultimately, the decision to provide chemoprophylaxis should be made when the patient is initially admitted. This decision should be revisited on a daily basis as the patient’s clinical circumstances change. Our predictive model shows that at admission, the combination of increased TBSA and need for ICU admission was strongly predictive (c-statistic=0.82) of those patients who developed VTE during their hospitalization. Patients with these risk factors present at admission should be strongly considered for early, aggressive VTE prophylaxis using both mechanical and pharmacologic means.

CONCLUSION

Thermally injured patients have multiple risk factors for deep venous thrombosis and pulmonary embolism. Patients with TBSA of 40-59% appear to be at highest VTE risk (2.4%). At admission, the combination of increased TBSA burned and need for ICU admission predicts patients who develop VTE with high discrimination. Patients with these risk factors may benefit from early, aggressive VTE prophylaxis.

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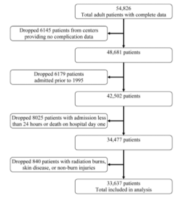

Figure 1.
National Burn Repository patient exclusion criteria

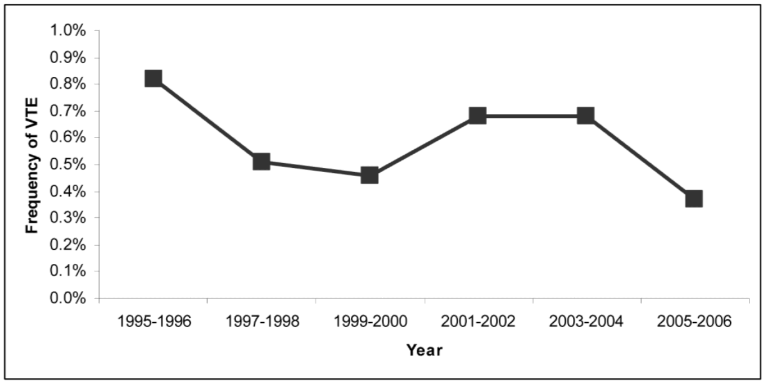

Figure 2.
Frequency of VTE diagnosis over time

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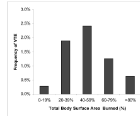

Figure 3.
Frequency of VTE by total body surface area burned

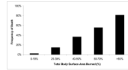

Figure 4.
Frequency of death by total body surface area burned.

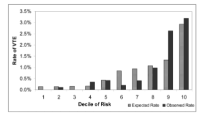

Figure 5.

Hosmer-Lemeshow goodness of fit displaying observed and expected rates of VTE by decile of risk

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Table 1

Bivariate statistics examining risk factors for VTE

Risk Factors	Odds Ratio (95% CI)	p value
Age (each year)	**1.01 (1.00-1.02)**	**0.003**
Race Caucasian African American Hispanic Asian	Comparison group 1.29 (0.85-1.96) 0.34 (0.16-0.69) 0.45 (0.11-1.84)	------ 0.239 0.003 0.226
≥ 2 medical comorbidities	1.82 (1.00-3.29)	0.05
Inhalation injury	3.57 (2.22-5.76)	<0.001
Admission to ICU	3.70 (2.53-5.41)	<0.001
Days in ICU (each additional)	1.02 (1.01-1.03)	<0.001
Central venous line placed	1.43 (0.78-2.59)	0.244
Mechanical ventilation >48 hours	6.99 (4.77-10.25)	<0.001
Ventilator days (each additional)	1.01 (1.00-1.02)	<0.001
Operative procedure (each additional)	1.08 (1.06-1.09)	<0.001

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Table 2

Bivariate statistics examining TBSA as a VTE risk factor

Risk Factor	Odds Ratio (95% CI)	p value
TBSA burned (each additional percent)	1.03 (1.02-1.04)	<0.001
TBSA burned (each additional decile)		
0-10%	Comparison group	------
10-20%	4.21 (2.35-7.59)	<0.001
20-30%	12.24 (6.92-21.65)	<0.001
30-40%	16.97 (9.13-31.55)	<0.001
40-50%	19.61 (9.95-38.65)	<0.001
50-60%	14.30 (6.18-33.08)	<0.001
60-70%	7.17 (2.10-24.46)	0.002
70-80%	11.91 (3.48-40.78)	<0.001
>80%	4.53 (1.05-19.61)	0.043