The Prevalence of Venous Thromboembolism of the Lower Extremity among Thermally Injured Patients Determined by Duplex Sonography

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Background: Morbidity and mortality from venous thromboembolism (VTE) remains a significant problem for hospitalized patients. Despite the ample prospective literature defining the prevalence of VTE in hospitalized patient populations, the prevalence of VTE in the thermally injured population remains largely unknown.

Methods: We prospectively studied 148 thermally injured patients with hospital stays of greater than 3 days with lower extremity duplex ultrasonograms obtained at admission and discharge.

Results: Nine patients experienced VTE (6.08%). Eight of the nine deep venous thromboses were proximal. One of the two pulmonary embolisms was fatal. Treatment risk factors that were associated with VTE were the presence of a central venous line ($p = 0.020$) and transfusion of more than 4 units of packed red blood cells ($p = 0.023$). These treatment factors were significantly related to each other ($p < 0.0001$), to body surface area burned, and to intervention.

Conclusion: The prevalence of VTE in burn patients is similar to that of moderate- to high-risk general surgical patients for whom VTE prophylaxis is recommended. VTE prophylaxis of burn patients, especially those requiring central venous lines and more than 4 units of packed red blood cells, should be considered.

Key Words: Venous thromboembolism, Burn injuries, Surgery, Deep venous thrombosis, Pulmonary embolism, Central venous lines, Duplex sonography, Transfusion.

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Morbidity and mortality from venous thromboembolism (VTE) remains a significant problem for hospitalized patients. Its silent nature, compounded by a not infrequent initial presentation as a pulmonary embolism (PE), demands vigilance in all patients deemed to be at risk for VTE. However, as surveillance remains costly and treatment entails potential complications, a population at risk needs to be identified to maximize the risk-to-benefit ratio. General risk factors for VTE have been well delineated and include age, immobility, malignancy, hormone replacement, stroke or paralysis, previous VTE, major surgery, trauma, obesity, varicose veins, cardiac dysfunction, and indwelling central venous catheters.[1] Additional studies have focused on identifying factors that increase the risk of VTE in select populations to better risk-stratify patients needing prophylaxis or more intensive monitoring.[2–4]

Despite the ample prospective literature defining the prevalence of VTE in hospitalized trauma, general surgery, medical, and obstetric patient populations, the prevalence of VTE in the thermally injured population remains largely unknown (Table 1).[1] Conventional wisdom and practice uses no or selective VTE prophylaxis for burn-injured patients on the basis of the premise that risk of bleeding outweighs the risk of VTE. However, the burn population is characterized by several risk factors that favor the formation of VTE. Immobilization, multiple transfusions, long operations, and hemostatic disturbances place them at risk. The hemostatic disturbances in the burn population are, in fact, similar to those seen in the trauma population.[5] Despite these predisposing factors, few prospective studies have delineated the natural history of VTE in burn patients.[6–8] These prospective studies report deep venous thrombosis (DVT) rates of 19.6% to 60%. These studies, however, are either small, limited to a specific subgroup of burned individuals, or not contemporary. The more numerous and larger retrospective studies further obscure the prevalence of VTE. As VTE remains largely a silent disease, these studies reporting DVT rates of less than 3% potentially significantly underestimate the problem.[9–14] Therefore, the need for prophylactic treatment of VTE in the burn-injured population remains controversial. In this study, we prospectively address the above controversy by documenting the prevalence of VTE in hospitalized thermally injured patients using surveillance duplex ultrasonography (DUS).

PATIENTS AND METHODS

Three hundred eighty-nine patients with burn injuries were admitted to our burn treatment center from December

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Table 1 Studies Addressing VTE in Thermally Injured Patients

Reference	No. of Patients	Study Type	DVT Prevalence (%)	PE Prevalence (%)
Sevitt and Gallagher (1961)[17]	169	Autospy	60	5.5 (16.3% minor)
Foley et al. (1968)[19]	233	Autopsy		25.3
Warden et al. (1973)[18]	139	Autopsy	36.7	30.2 (16.7% micro only)
Purdue and Hunt (1988)[13]	2,106	Chart review		0.4
Harrington et al. (2001)[20]	1,300	Chart review	1.8	0.7
Rue et al. (1992)[11]	2,103	Chart review	1.2	0.9
Desai et al. (1989)[9]	6,589	Chart review	2.7	1.7
Wahl and Brandt (2001)[12]	327	Chart review	2.6	0.6
Mayou et al. (1980)[8]	15	Prospective, FUT	60	0
Wait et al. (1990)[6]	71	Prospective, DUS	19.6	0
Wahl et al. (2002)[7]	30	Prospective, DUS	23	3.3

DVT, deep venous thrombosis; PE, pulmonary embolism; FUT, fibrinogen uptake scan; DUS, duplex ultrasonography.

1999 to July 2001. Two hundred thirty-five had an expected length of stay (LOS) greater than 3 days and were eligible for study entry. One hundred forty-eight patients consented to participate in the study and constituted our study group.

Patients were evaluated at admission for study entry. Outpatients were not enrolled. Patients were excluded if they were anticoagulated before admission, had an expected LOS less than 3 days, or did not undergo DUS within 30 days of discharge. Eligible patients underwent initial DUS of their lower extremities at admission (average time postadmission to DUS, 3.74 ± 4.70 days). Discharge scans were obtained before discharge or at the first follow-up clinic visit. The average day to the final scan was 1.90 ± 8.68 days before discharge. Twenty-eight of the 143 final scans (20.0%) were obtained after discharge (average, 13.1 ± 5.3 days postdischarge).

All patients underwent resuscitation according to the Parkland formula adjusted to adequate perfusion endpoints. Walking was begun on completion of resuscitation. All patients were assessed at admission and followed when necessary by unit-dedicated occupational and physical therapists. Routine burn wound care consisted of daily cleansing and topical antimicrobial care. Enteral feeding and early operative debridement were instituted for burn wounds generally greater than 15% and for those wounds not expected to heal by 3 weeks, respectively. Tourniquets were used for extremity burn wound debridement when possible. The inflation pressure was adjusted to 1.5 times the patient's systolic pressure. Femoral catheters were inserted exclusively for volume replacement. The majority of these catheters were inserted perioperatively. Patients were allowed to walk 24 hours postoperatively, except for those undergoing lower extremity grafting, who were placed at bed rest for 48 hours.

Routine heparin or mechanical prophylaxis was not used. Three patients in the study group did, however, receive intermittent prophylaxis (subcutaneous heparin in two patients and 2 days of enoxaparin in one patient). One of these patients developed a DVT (patient 4) (Table 2).

Data collected included age, body surface area burned (BSAB) and burn distribution, body mass index (BMI), pertinent medical and medication history, LOS, days of bed rest after admission and operations, injury history including associated trauma, operative history including tourniquet use and times, infections, number of transfusions (packed red blood cells [PRBCs]), and central venous line (CVL) placement. BMI greater than 25 kg/m^2 is overweight, BMI greater

Table 2 Characteristics of Study Patients with VTE

Patient	Burn Type	Age (y)	BSAB	Smoker	Location of DVT	PE	Symptomatic	Days to Diagnosis
1	Flame	75	10.5	No	L Pop–Pt	Yes	Yes	3
2	Flame	59	20.0	Yes	L iliac–CFV–Pop–Pt, R GSV/CF V jx	No	Yes	9
3	Scald	86	20.0	No	R CFV	No	No	42
4**	Flame	25	4.0		L CFV, SFV	No	Yes	12
5	Electrical	28	20.2	No	B Iliac	Yes	Yes	24
6	Flame	53	11.5	No	B SFV	No	No	28
7	Flame	17	60.0	No	R CFV	No	No	50
8	Flame	20	65.0		R CFV	No	No	65
9	Flame	51	14.0		L Pt	No	No	13

L, Left; Pop, popliteal vein; Pt, posterior tibial vein; CFV, common femoral vein; R, right; GSU, greater saphenous vein; V jx, venou, junction; B, both.

** This patient was ventilated for 45 days secondary to an inhalation injury. He received subcutaneous heparin before his DVT.

than 30 kg/m^2 is obese, and BMI greater than 40 kg/m^2 is morbidly obese. Inhalation injury was defined as airway injury identified by laryngoscopy or bronchoscopy. DVT was defined by DUS (see below). PE was defined by high-probability ventilation perfusion scan or autopsy.

DUS examinations were performed with an Advance Technology Laboratories HDI 1000CV Ultrasound System (ATL Ultrasound, Bothell, WA) with a linear 7-MHz transducer probe. When possible, the entire lower extremity venous system consisting of the iliac vein, common femoral vein, superficial femoral vein, popliteal vein, and calf veins were evaluated for compressibility, augmentation, and intraluminal echoes. There were 31 incomplete examinations secondary to wounds and dressings, for a complete scan rate of 87.7%. These incomplete scans included nonvisualization of the calf veins in 13 examinations; a combination of calf veins and the popliteal vein in nine; a combination of the superficial femoral vein, popliteal vein, and calf veins in four; the iliac and common femoral vein in two; and an entire lower extremity in two examinations (one scan had a combination of the above). An abnormal study was defined as lack of compressibility with the presence of low-level intraluminal echoes and absent or continuous Doppler velocity signal.

Trained vascular technicians from our Intersocietal Commission for the Accreditation of Vascular Laboratories-certified laboratory conducted the studies. The vascular surgeon reviewing the static images was also a registered vascular technologist (J.J.H.). Complete studies were recorded for detailed review.

Statistical analysis was performed using SAS software (SAS version 8, SAS Institute, Inc., Cary, NC). Student's t test and Fisher's exact test were used when appropriate. Medical risk factors for DVT analyzed were age, BMI, smoking history, hormone replacement, history of congestive heart failure, and history of malignancy. Burn risk factors for DVT were BSAB, lower extremity burn, and lower extremity donor sites. Treatment risk factors were days of bed rest, operative intervention and the length of operations, presence of a femoral venous line, and the use of a tourniquet. Significance was determined at $p < 0.05$. Interquartile (25–75%) ranges (IQRs) and confidence intervals (CIs) are presented when indicated. Our university's institutional review board approved the study.

RESULTS

Demographic Data

Representative of the burn population, the majority of our study patients were young, healthy male patients injured by flame-related causes. The mean age of the population was 37.5 ± 20.4 years (IQR, 22–48 years) with a male-to-female ratio of 3.3 (112 male patients and 36 female patients). There were 17 children aged 15 years or less in the study group. Over half of the injuries were flame related (97 patients [65.5%]), with a mean burn size of 19.4 ± 16.6% (IQR, 8–26%). Eighty-nine (60.1%) patients sustained lower extremity burns. Four patients had inhalation injury and were intubated for an average of 20.5 ± 16.6 days (range, 9–45 days). Five patients had concurrent traumatic injuries. No patient had injury to the spine, pelvis, or lower extremities. No patient had a history of congestive heart failure or malignancy. Only four patients had a history of a DVT or PE. These patients did not receive prophylaxis, nor were any of these patients positive for VTE in the study. Four patients were on oral contraceptives or hormone replacements. When recorded, one third of the population were nonsmokers (46 [31.0%]) and nonobese (45 [34.1%]; mean BMI, 27.5 ± 9.2).

Hospital Course

Operative intervention was undertaken in 120 patients (81.1%). Surgery was performed in all patients within at least 6 days of admission (95% CI, 5–6 days). Forty-six patients (37.7%) required multiple operations. The average amount of skin grafted was 2,671 ± 3,895 cm^2 per patient (IQR, 500–3,303 cm^2). The majority of operations were greater than 3 hours, with the median operating time (including anesthesia time) being 4 hours (IQR, 3–9 hours). Only 39 operations were completed in less than 2 hours.

Femoral CVLs were placed exclusively when a large blood loss was expected or at the request of anesthesia. A total of 65 femoral catheters were placed in 32 patients. More than half of the entire study group required transfusions (85 [57.4%]). The mean number of units transfused was 4.2 ± 11.0 (IQR, 0–3). Tourniquets were used to limit blood loss when possible. Twenty-nine (20.0%) patients had tourniquets of the lower extremities, with a mean application time of 61.1 ± 18.9 minutes per tourniquet (IQR, 49.5–76 minutes).

The mean LOS was 22.2 ± 20.4 days (IQR, 10–24 days). The majority of patients walked within 48 hours of admission (129 [90.0%]; 4 missing) and operative intervention (71 [53.8%]; 16 missing).

VTE Patients Compared with Non-VTE Patients

Nine patients were diagnosed with DVTs, for a prevalence of 6.08% in our thermally injured population (95% CI, 2.8–11.2%) (Table 2). Of these patients, two initially presented with PEs, one of which was fatal (prevalence rate of PE, 1.4%). One PE was clinically evident and one was diagnosed on autopsy after the patient died as a result of a saddle PE. Clinical signs and symptoms of DVT were noted in only five (55.6%) of the nine venous thromboses. Of the clinically evident VTEs, three presented with lower extremity edema and two presented with dyspnea and pleuritic chest pain. The average day to the clinical diagnosis of VTE was 12.2 ± 7.7 days. The remaining four DVTs were clinically occult, diagnosed only by sonography. All but one DVT was located in the proximal lower extremity. No episodes of VTE were noted in the 28 patients who underwent scans after discharge.

There was no difference between the patients with VTE and those without VTE with respect to medical or burn risk factors (Table 3). Treatment risk factors that were associated with VTE were the presence of a CVL ($p = 0.020$) and the transfusion of more than 4 units of PRBCs ($p = 0.023$). These treatment factors were related to each other ($p < 0.0001$), BSAB, and operative intervention (Table 4). Furthermore, in the five patients who had femoral CVLs and DVTs, the catheterized leg developed the DVT.

All the patients diagnosed with VTE were initially treated with intravenous heparin followed by sodium warfarin (Coumadin) for 6 months. The patient who sustained a PE had a Greenfield filter placed secondary to the occurrence of the PE immediately before operative intervention.

Study Patient Characteristics Compared with Eligible Nonenrolled Burn Patients

Eighty-seven burn patients were eligible for the study but did not receive a discharge DUS of their lower extremities. Overall, these patients were of similar age to the patients who completed the study. The nonstudy patients, however, had smaller burns, shorter LOS, and less operative treatment of their injuries (Table 5). Two patients sustained inhalation injuries and were ventilated for an average of 15.5 ± 7.8 days (range, 10–21 days).

There were 18 deaths during the study period. Of these, 12 had care withdrawn at admission to the burn center. One died from a massive pulmonary embolism (patient 5) (Table 2). The remaining five died as a result of cardiopulmonary causes. No autopsies were performed.

DISCUSSION

Thromboprophylaxis is recommended in hospitalized patients because of the high prevalence of VTE, its clinically silent nature, and the morbidity and mortality of untreated disease.[1] High-risk populations have been defined and risk stratification systems have been developed. The highest risk patients appear to be those who have sustained major trauma or an acute spinal cord injury or who have undergone lower extremity orthopedic surgery.[1] Risk factors for VTE appear to be cumulative.[2,4,15] Prophylaxis is recommended for moderate- to high-risk general surgery patients who have an estimated proximal DVT prevalence of 2% to 20% without prophylaxis.[16] VTE prophylaxis in thermally injured patients

Table 3 Medical, Burn, and Treatment Risk Factors and their Distribution in Patients with and without VTE

Risk Factor	DVT (n = 9)	No DVT (n = 139)	*p* Value
Age	51 (IQR, 25–59)	37 (IQR, 22–47)	0.342
Smoker	2 (28.6%)*	43 (34.7%)†	0.714
BMI > 30 (obese)	3 (33.3%)	41 (29.9%)*	1.0
BMI > 40 (morbidly obese)	1 (11.1%)	7 (5.11%)*	0.407
Body surface area burned	20 (IQR, 11.5–20.2)	15.1 (IQR, 8.0–26.0)@	0.457
LE burns	4 (44.4%)	85 (61.2%)@	0.484
LE donor sites	5	91 (65.9%)@	1.0
Femoral central line	5 (55.6%)	26 (18.7%)	0.020
PRBC > 4 units	5 (55.6%)	27 (19.4%)	0.023
Bed rest > 48 h	5 (55.6%)	64 (46.0%)	0.734
Operative intervention	7 (77.8%)	113 (81.3%)	0.679
Average surgery time (h)	4.5 (IQR, 1.5–12.5)	4 (IQR, 2–6)	0.224

DVT, deep venous thrombosis; BMI, body mass index; LE, lower extremity; PRBCs, packed red blood cells.
* Missing data for two patients.
† Missing data for 15 patients.
@ Missing data for one patient.

Table 4 Factors Related to Transfusion of Greater than 4 Units of PRBCs and Femoral CVL Insertion in Our Thermally Injured Population

Related Factors	PRBCs > 4 Units (vs. PRBCs ≤ 4 Units)	Femoral CVL (vs. No Femoral CVL)
BSAB	34.0 vs. 11.75 ($p < 0.0001$)	36.0 vs. 12.2 ($p < 0.0001$)
OR	32/32 (100%) vs. 88/116 (75.9%) ($p < 0.001$)	30/31 (96.8%) vs. 90/117 (76.9%) ($p < 0.01$)

Table 5 Study Patients Compared with Eligible Nonstudy Burn Patients

	Age (IQR)	Gender (IQR)	BSAB* (IQR)	OR (y/n)†	LOS* (IQR)
Study Patients (n = 148)	37.5 ± 20.4 (22–48)	112/36 (3.1)	19.4 ± 16.6 (8–26)	120	22.2 ± 20.4 (10–24)
Nonstudy Patients (n = 87)	38.0 ± 25.0 (21–55)	64/23 (2.8)	11.0 ± 10.4 (3–16)	53	16.1 ± 36.6 (6–15)

* $p < 0.0001$.
† $p = 0.0012$.
OR, operation.

remains controversial largely because the prevalence is unknown. In this prospective study, we found a prevalence of 6.08% (95% CI, 2.8–11.2%) for VTE in the burn population. Our results support the use of prophylaxis for VTE in this population.

The body of literature defining the prevalence of VTE in the burn population is small. The prevalence varies depending on the method of detection (Table 1). Burn autopsy studies report some of the highest prevalences with DVT rates of 36.7% to 60%.[17–19] Although autopsy is highly sensitive and specific for DVT detection, the clinical significance of these thromboses remains questionable. In the study by Sevitt and Gallagher, at least 48% of the entire autopsy-diagnosed DVTs involved only the calf veins.[17] As pulmonary emboli originate more from the proximal veins, the prevalence of proximal vein thromboses is more clinically relevant.[14] The true clinically significant PE prevalence may also have been overstated. If the microscopically diagnosed PEs were eliminated, the prevalence of PE would have decreased from 25.3% to 6.4% in the study by Foley et al. and from 30.2% to 25.2% in the study by Warden et al.[18,19] As acknowledged by Warden et al., the higher rate in their study was further associated with the use of older, more thrombogenic central catheters, emphasizing the difficultly in extrapolating these studies conducted 30 years ago to today's thermally injured population.

Larger, more recent retrospective studies report a much lower prevalence of VTE when they have examined clinically diagnosed VTE.[9,11–13,20] The reported prevalence rate for VTE in these retrospective studies was several orders of magnitude less than in the autopsy studies, ranging from 1.2% to 2.6%. A few of these studies found an association of VTE with age, BSAB, and location of burn.[11,12,20] Unfortunately, as many VTE events are clinically silent, the reported prevalence rate of VTE in these retrospective studies is most likely artificially low.[1]

Only three prospective studies have addressed VTE in thermally injured patients.[6–8] One early prospective study using fibrinogen uptake scanning in 15 thermally injured patients demonstrated a DVT prevalence of 60%. However, no clinical information regarding the patients or their treatment was provided.[8] Two more recent prospective studies used serial DUS of all four extremities to determine the DVT prevalence.[6,7] Wait et al. selectively scanned 71 patients who required the insertion of a CVL, reporting a prevalence of 19.7%, with 8 of the 19 DVTs occurring in the upper extremities.[6] By scanning only patients requiring a CVL, however, the authors may have selected a high-risk group and inflated the prevalence of VTE. The other prospective study using DUS found a DVT prevalence of 23.3% in 30 patients. The upper extremity DVT prevalence was 3.3%.[7] This is an ongoing study and, as such, does not have sufficient power to risk-stratify patients. Despite their limitations, these studies report a higher than expected prevalence of DVT in thermally injured patients. Our study extends this research and verifies the higher than expected rate of VTE in thermally injured patients.

The prevalence of VTE in our population was 6.08%, with a 5.4% prevalence of proximal DVT. This lower rate of VTE compared with the other prospective studies may be secondary to patient selection and study design. Overall, this study's population was young, experienced a low incidence of inhalation injury, had limited immobility, and had a low prevalence of the comorbidities usually associated with VTE.[1] Moreover, only the lower extremities were scanned and therefore upper extremity DVTs were not captured. As none of the upper extremity DVTs were symptomatic in the study by Wait et al., this may have decreased our prevalence in comparison with the other prospective studies.[6] Finally, our VTE prevalence may be lower because scans were performed only at admission and discharge and therefore it is possible that we may have missed DVTs that occurred earlier in the patient's course.

Despite these limitations, our reported VTE rate is similar to that reported for general surgical patients judged to be at moderate to high risk for VTE and for whom prophylaxis is recommended. VTE in our population was related only to CVL and transfusion of greater than 4 units of PRBCs, both of which were related to each other, operative intervention, and higher BSAB. Both clinical risk factors have been previously associated with VTE in other patient populations.[1,3,4,21,22] In a randomized prospective study, Merrer et al. reported a significantly higher rate of thrombosis with femoral versus subclavian catheterization, with an odds ratio of 14.42 for associated thrombosis of the femoral vein.[23] As central venous catheterization is often unavoidable in burn patients, the need for a CVL, especially a femoral catheter, may identify a moderate- to high-risk burn patient in whom thromboprophylaxis should be considered. An upper extremity site is preferred, as the risk for embolization from the upper extremity is 9% to 36%, considerably lower than the 50% risk from the lower extremities.[21,22]

Given the prevalence of VTE in our thermally injured patients, prophylaxis of these patients seems justified. The efficacy, safety, and cost effectiveness of VTE have been proven in other similar risk surgical populations. Prophylaxis has been successful in reducing the risk of VTE in general surgery patients by 68% to 76%.[1] This reduction is without increased bleeding tendency and without a significant risk of thrombotic complications from heparin-induced thrombocytopenia (estimated to occur in 0.5–2.5% of patients). Countering these risks is the reported 30% occurrence of postphlebitic syndrome, the cost and morbidity of treatment for VTE, and the potential mortality associated with PE.[24] Finally, the cost effectiveness of prophylaxis has been well established in multiple populations. Although the efficacy, safety, and cost effectiveness remain to be defined for the burn population, extrapolating the risk-to-benefit ratio to our population with a 6.08% prevalence of VTE supports prophylaxis.

In conclusion, additional studies using DUS need to be conducted to better risk-stratify burn patients to define appropriate moderate- to high-risk patients for prophylaxis. As we only had nine episodes of VTE in our study population, it is likely that the statistical tests did not have sufficient power to detect a small association of VTE with clinical or treatment risk factors. However, as central venous catheterization was significantly related to VTE, it should be avoided when possible or VTE prophylaxis of burn patients with CVL (including femoral, jugular, and subclavian sites) should be considered. Furthermore, patients anticipated to need more than 4 units of PRBCs should also be considered for VTE prophylaxis.

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