Deep vein thrombosis and pulmonary embolus in patients with traumatic brain injury: a prospective observational study

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Critically ill patients in general, and trauma patients in particular, are at significant risk of deep vein thrombosis (DVT).[1] Most thrombi are asymptomatic and are confined to the deep veins of the calf. About 20%–30% of untreated calf vein thrombi extend proximally into the thigh, where, if untreated, they pose a 40%–50% risk of pulmonary embolism (PE) and a mortality rate of about 25%.[2] Autopsy studies indicate that many PEs are clinically undetected and likely contribute to additional morbidity and mortality.[3] Further, a significant number of patients who develop DVT will suffer residual venous morbidity — persistent occlusion, valvular incompetence, leg swelling, leg pain or discomfort or venous ulceration.

The published incidence of DVT among critically ill patients varies, depending on the patient subgroup, the mode of thromboprophylaxis (mechanical, pharmacological or both) and the mode of screening. Clinical examination is insensitive, and up to 88% of DVTs found by compression ultrasonography were undetected on clinical examination.[4] Compression ultrasonography is a simple, non-invasive bedside test associated with minimal, if any, complications. It is now frequently used for critically ill patients. Although venography is the gold standard for DVT detection, it is invasive and may be associated with significant morbidity among critically ill patients.

In the Prophylaxis of Thromboembolism in Critical Care Trial (PROTECT), of 3764 critically ill patients (surgical and medical, but excluding trauma) who were receiving thromboprophylactic medications, compression ultrasound screening revealed a proximal DVT rate of 5.1%–5.8%.[5] Trauma patients are usually considered to be at particularly high risk of DVT — in a 1994 study of 716 major trauma patients without thromboprophylaxis at a single centre, using impedance plethysmography and lower-extremity contrast venography, proximal DVT was reported in 18% of participants.[6] The traumatic brain injury (TBI) subgroup in this study (without thromboprophylaxis) had a rate of proximal leg DVT of 19%.[6] In another study of major trauma patients receiving prophylaxis, the reported proximal DVT rate was 15% for heparin and 6% for enoxaparin.[7]

Since the mid 1990s, guidelines have been published for thromboprophylaxis for trauma[1] and TBI patients.[8] Graduated thromboembolic compression stockings (TEDS) or intermittent pneumatic compression devices (PCDs) are recommended, as is pharmacological prophylaxis with low-molecular-weight

ABSTRACT

Background: Intensive care patients with traumatic brain injury (TBI) are at high risk of developing deep vein thrombosis (DVT). A high rate of DVT was reported before routine thromboprophylaxis, but the current DVT rate in TBI patients receiving best-practice mechanical and pharmacological prophylaxis is unknown.

Objectives: To determine the prevalence of DVT among TBI patients.

Design, participants and setting: A prospective observational pilot study of adult patients admitted to the intensive care unit of a level 1 trauma centre within 72 hours of sustaining a TBI (Glasgow Coma Scale score ⩽ 14).

Main outcome measures: Rate of DVT determined using twice-weekly compression ultrasound; rate of pulmonary embolism (PE) and length of stay.

Results: 36 patients (28 men; mean age, 40.3 years) were included. Six had moderate and 21 had severe TBI. Two patients (6%) developed a DVT and two patients (6%) developed a PE. The proximal leg DVT rate was 3%, but the overall venous thromboembolism rate was 11% (4 patients).

Conclusions: Mechanical and pharmacological prophylaxis appeared to be effective. The incidence of clinically identified PE is of concern and suggests that thromboembolic sources other than large leg veins may not be being adequately controlled by modern thromboprophylaxis regimens.

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Abbreviations

DVT	Deep vein thrombosis
GCS	Glasgow Coma Scale
IQR	Interquartile range
LMWH	Low-molecular-weight heparin
PCD	Pneumatic compression device
PE	Pulmonary embolism
TBI	Traumatic brain injury
TEDS	Thromboembolic compression stockings

Table 1. Baseline characteristics of 36 patients with traumatic brain injury, Alfred Hospital, Melbourne, 2008

Characteristic	
Mean age in years (SD; range)	40.3 (15.5; 20–82)
Mean admission GCS score (SD)	8 (3.8)
Median ICU LOS in days (IQR)	9 (4–12)
Median hospital LOS in days (IQR)	19 (10.0–31.5)

GCS = Glasgow Coma Scale. ICU = intensive care unit. LOS = length of stay. IQR = interquartile range.

heparin (LMWH). In TBI patients, however, timing and optimal dosing of pharmacological prophylaxis is frequently delayed by bleeding or perceived bleeding risks. Among these patients, the incidence of proximal DVT is of concern and unknown. Early use of LMWH may increase cerebral bleeding and extend intracranial haematoma; accordingly, mechanical devices are usually advised from admission, and thromboprophylaxis is only initiated when considered safe by clinicians.[8] These factors likely place TBI patients at higher risk of venous thromboembolism than other critically ill patients.

In this prospective observational pilot study, we sought to establish the incidence of DVT among high-risk TBI patients receiving conventional mechanical and pharmacological thromboprophylaxis, in the intensive care unit of a level 1 trauma centre, using twice-weekly compression ultrasonography screening.

Methods

The study was reviewed and approved by the Alfred Human Research Ethics Committee (project no. 89/08).

Patients were enrolled from 30 June 2008 until 7 December 2008. All patients admitted to the ICU of the Alfred Hospital, a level 1 trauma centre, were screened daily by experienced research coordinators for eligibility criteria. Investigators were contacted when a patient was eligible and assessed for inclusions and exclusions. Patients were included if they were 18 years or older, had a TBI (Glasgow Coma Scale [GCS] score $\leqslant 14$, and history and computed tomography scan consistent with TBI), and had been admitted less than 72 hours previously. Exclusion criteria were lack of informed consent from a surrogate decisionmaker, bilateral lower limb injuries precluding ultrasound examination, or expectation of death within 24 hours.

Baseline demographic data included age, sex, severity of TBI and other injuries, risk factors for DVT, presence of intracranial pressure monitoring devices, coagulation profile and platelet count. DVT prophylaxis on admission was also recorded.

While in the ICU, patients had twice-weekly compression ultrasounds performed by experienced sonographers (using an ATL HDI5000 ultrasound machine [Philips, Amsterdam, Netherlands] with a linear 7.4 MHz transducer). The first scan was always performed within 72 hours of admission to the ICU. The protocol for the compression ultrasounds was predefined. A proximal leg ultrasound was performed at 1 cm intervals and examined the trifurcation of the deep calf veins, the distal and proximal popliteal vein, and the distal superficial, mid superficial and common femoral vein. The results of these were interpreted by the sonographers and checked by a consultant radiologist. The diagnosis of DVT on ultrasound required non-compressibility of one or more deep venous segments. Each time a patient had an ultrasound, the DVT prophylaxis being used was recorded.

Table 2. Type and severity of traumatic brain injury among 36 patients, Alfred Hospital, Melbourne, 2008

	No. (%)
Glasgow Coma Scale score	
13–14	9 (25%)
9–12	6 (17%)
3–8	21 (58%)
Type of injury	
Subdural haemorrhage	20 (56%)
Extradural haemorrhage	11 (31%)
Subarachnoid haemorrhage	20 (56%)
Intracranial haematoma	16 (44%)
Contusion	15 (42%)
Intraventricular haemorrhage	7 (19%)

We originally intended to follow patients to ICU discharge. However, as one patient developed a PE shortly after discharge from the ICU to a ward, despite a negative ultrasound screen, the censoring date was increased to hospital discharge, and the hospital trauma and radiology databases were reviewed to determine all inhospital venous thromboembolism events.

Statistical analysis was performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA). Proportions are reported as number (%) or as per cent (95% CI). Normally distributed variables are reported as mean (SD) and non-normally distributed data as median (interquartile range [IQR]).

Results

A total of 36 patients were enrolled. The patients' mean age was 40.3 years and the mean admission GCS score was 8. Twenty-eight patients (78%) were men (Table 1).

Most patients had severe TBI (GCS score, 3–8; 21/36; 58%), six had moderate TBI (GCS score, 9–12; 17%) and nine had mild TBI (GCS score, 13–14; 25%). The median head Abbreviated Injury Scale score was 4 (IQR, 4–5). Most patients (30; 83%) had a cerebral mass lesion (subdural haemorrhage,

Table 3. Non-cerebral injuries among 36 patients, Alfred Hospital, Melbourne, 2008

Site	No. (%)
Pulmonary	11 (31%)
Upper limb	2 (6%)
Lower limb	6 (17%)
Pelvic	5 (14%)
Splenic	4 (11%)
Other abdominal	5 (14%)
Face	14 (39%)
Cervical spine	4 (11%)

extradural haemorrhage or subarachnoid haemorrhage) (Table 2). Twenty-seven patients (75%) received an external ventricular drain (12) and/or a parenchymal intracranial pressure monitor (Codman ICP Monitoring System, Codman, Raynham, Mass, USA) (17). Most patients had multiple traumatic injuries in addition to TBI (Table 3). Facial (14; 39%) and pulmonary (11; 31%) injuries were common. The median Injury Severity Score was 28 (IQR, 23–39.5).

Thromboprophylaxis included TEDS and PCDs in all patients, and/or LMWH usually after 4–8 days (Table 4). At enrolment, 32 patients (89%) had both TEDS and PCDs on both lower limbs. Two patients had both on only one leg owing to a lower limb injury and two patients had neither TEDS or PCDs initially. Two patients were already receiving enoxaparin thromboprophylaxis at enrolment. The other 34 patients (94%) had a contraindication to early pharmacological prophylaxis. Before discharge from ICU, 14 patients (39%) were receiving LMWH, and the mean time to commencement of LMWH was 5.6 days (SD, 2.2 days).

The mean number of compression leg ultrasounds per patient was 2.3 (SD, 1.2). Two DVTs were identified during the study (6%), both in patients with severe TBI. One patient developed a proximal DVT (right femoral vein), and the other had a distal DVT (left popliteal vein). Two patients with severe TBI developed PEs shortly after discharge from ICU, even though their ICU leg ultrasound screening had been negative. The first developed a PE 36 hours after discharge from ICU; the source was a left upper extremity thrombosis associated with a subclavian catheter. This patient had negative bilateral lower limb ultrasounds 24 hours before and after diagnosis of the PE. The second patient developed a symptomatic PE 24 hours after discharge from ICU, and no source thrombosis was identified. This patient's right calf could not be screened because of a plaster cast, and was the likely source.

The overall rate of proximal DVT was 3% (95% CI, 0–8%), of all DVT was 6% (95% CI, 0–13%), of clinically detected PE was 6% (95% CI, 0–13%) and of total venous thromboembolism was 11% (95% CI, 1%–22%). In patients with severe TBI, the rates were 5% (95% CI, 0–14%), 10% (95% CI, 0–22%), 10% (95% CI, 0–22%) and 19% (95% CI, 2%–36%), respectively.

Table 4. Thromboprohylaxis among 36 patients, Alfred Hospital, Melbourne, 2008

Baseline prophylaxis	No. (%)
TEDS	
No lower limb	2 (6%)
One lower limb	2 (6%)
Two lower limbs	32 (89%)
PCDs	
No lower limb	2 (6%)
One lower limb	2 (6%)
Two lower limbs	32 (89%)
Enoxaparin at ICU admission	2 (6%)
Enoxaparin at ICU discharge	14 (39%)
Mean time to commencement of enoxaparin, days (SD)	5.6 (2.2)

TEDS = graduated thromboembolic compression stockings. PCD = intermittent pneumatic compression device. ICU = intensive care unit.

Discussion

The patients in this study were typical of TBI patients in Australian ICUs at many trauma hospitals. Their age, sex, type of injury, incidence of other injuries, admission GCS score and length of stay were similar to previously published studies in trauma patients.[6,9-11] Most had severe TBI and a long stay in ICU and hospital. Despite prospective screening and numerous patient risk factors, the rate of proximal DVT was surprisingly low, while the rate of clinically detected PE was of concern, particularly among patients with severe TBI.

To our knowledge, no previous study has prospectively measured the DVT rate in unselected critically ill TBI patients in the era of mechanical and pharmacological prophylaxis. Previously reported rates of 1%–6% have included mixed patient types, and the very high rates of over 50% were reported before thromboprophylaxis therapies were routine. A recent retrospective study in TBI patients selected patients at high risk, and reported a high rate of 25%.[12] That study reported a high rate of femoral vein catheterisation, which was likely causally associated.[12]

Although confidence intervals were quite large due to our small sample size, the rate of proximal lower limb DVT identified in our study was low. This was unexpected, but is also likely to be correct. The low rate could be due to insensitivity of the screening methodology with compression ultrasound, but this seems unlikely. More likely, currently practised thromboprophylactic regimens, with very early implementation of lower limb mechanical devices and routine use of LMWH when bleeding risks had subsided, effectively prevented lower limb DVT.

Nevertheless, the clinical PE rate in our cohort, despite all these considerations, is disturbing, especially considering that the rate of clinically recognised PE is a substantial underestimate. It seems likely that lower limb compression devices may be effective for lower limb DVT, but were not effective for upper limb, pelvis and/or catheter-related venous thromboses, which all continue to be potential sources of PE in high-risk critically ill TBI patients, whose delayed onset of pharmacological prophylaxis was frequently necessitated by bleeding risks. In this study, all venous thromboembolism was in patients with severe TBI, and in keeping with our hypotheses.

The strengths of this pilot study were the prospective design, including screening of all TBI patients, the study population reflecting the TBI patients found in many level 1 trauma centre ICUs, and the routine use of current best-practice venous thromboembolism prophylaxis regimens.

The major limitation was the small size of the patient population. The second was that compression ultrasonography may have missed some real thromboses, which may have been detectable using contrast venography. Sensitivity of ultrasonography is between 89% and 96%, and specificity is in the range of 96%–100%.[13] However, missed thromboses are usually subocclusive and usually not clinically relevant.

Our observed prevalence of DVT in TBI patients should be confirmed in large multicentre prospective observational trials, and one such a study is in progress. The Erythropoietin in Traumatic Brain Injury (EPO-TBI) Study (ClinicalTrials.gov no. NCT00987454) will primarily determine the efficacy of erythropoietin in moderate and severe TBI for improving neurological function in TBI patients, and has a second goal of determining the true rate of DVT by routine compression ultrasound in 606 critically ill TBI patients receiving either erythropoietin or placebo.[14]

Despite the low rate of proximal DVT in our study group, the rate of clinically identified PE was concerning and suggested, within the limitations of the study, that current regimens for thromboprophylaxis in this population may not be effective to prevent thromboembolism from other sources. The current multicentre EPO-TBI Study will add clarity to these observations and potential concerns.

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Competing interests

None declared.

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