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REVIEW

Prophylaxis for Venous Thrombo-Embolism in Neurocritical Care: A Critical Appraisal

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Abstract Venous thrombo-embolism (VTE) is frequently encountered in critically ill neurological and neurosurgical patients admitted to intensive care units. This patient population includes those with brain neoplasm, intracranial hemorrhage, ischemic stroke, subarachnoid hemorrhage, pre- and post-operative patients undergoing neurosurgical procedures and those with traumatic brain injury, and acute spinal cord injury (SCI). There is a wide variability in clinical practice for thromboprophylaxis in these patients, in part due to paucity of data based on randomized clinical trials. Here, we review the current literature on the incidence of VTE in the critically ill neurological and neurosurgical patients as well as appraise available data to support particular practice paradigms for specific subsets of these patients. Data synthesis was conducted via search of Medline, Cochrane databases, and manual review of article bibliographies. Critically ill neurological and neurosurgical patients have higher susceptibility to VTE. Intermittent compression devices with or without anti-thrombotics is generally the method of choice for thromboprophylaxis. Low molecular weight heparin is the method of choice in certain patient subgroups such as those with SCI and ischemic stroke. Inferior vena cava filters may play a role in thromboprophylaxis in selected cases. Without clear guidelines that can be universally applied to this diverse group of patients, prophylaxis for VTE should be tailored to the individual patient with cautious assessment of benefits versus risks. There is a need for higher level evidence to guide VTE prophylaxis in certain subgroups of this patient population.

Keywords Deep vein thrombosis · Venous thromboembolism · Heparin · Intermittent compression devices · Compression stockings

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Introduction

Deep Venous Thrombosis (DVT) and consequent pulmonary embolism (PE) are frequently encountered in critically ill neurological and neurosurgical patients admitted to intensive care units (ICUs). The purpose of this review is to evaluate the current literature on the methods of thromboprophylaxis and incidence of DVT in this subset of patients as well as critically appraise available data to support particular practice paradigms for specific subsets of these patients including those with brain neoplasm, intracranial (intraparenchymal, subdural, epidural) hemorrhage (ICH), ischemic stroke, subarachnoid hemorrhage (SAH), operative neurosurgical patients undergoing craniotomy and spinal surgery, and those with traumatic brain injury (TBI) and spinal cord injury (SCI).

In this review, the term venous thrombo-embolism (VTE) encompasses both DVT and PE. While the prevention of VTE in critically ill patients with neurological

disease is the major focus of this review, a discussion of pathophysiology of VTE and methods of detection are beyond its scope.

Surveillance for VTE

Venous thrombo-embolism is often asymptomatic and screening for its early detection is frequently utilized in critically ill patients. Duplex ultrasonography has been shown to be an adequate method for VTE screening [1] in most patients [2]. The concept of routine and frequent surveillance bias explains the high incidence of VTE diagnosis in centers that adhere to this practice. The value of surveillance for VTE is early diagnosis of DVT and timely interventions to prevent PE [3].

Two main controversies are highlighted pertaining to surveillance for VTE. First, the role of routine DVT surveillance has been studied in patients with trauma; some data suggest benefits in these patients [4, 5] while other data suggest low cost-benefit [6]. Second, with what frequency should surveillance screening be conducted in critically ill patients with neurologic disease? To date there have been no randomized controlled trials (RCTs) comparing no surveillance versus screening protocols for the prevention of PE. In one study, Misra et al. [7] compared rates of DVT and PE between the neurosurgical ICU and other ICUs in a single institution. The neurosurgical ICU utilized a biweekly protocol to screen for DVT in combination with treatment with twice daily 5,000 IU of heparin and intermittent compression devices (ICDs). The rate of PE was significantly lower in the neurosurgical ICU (0.09%; $n = 1{,}094$) versus all other ICUs (1.06%; $n = 4{,}233$). The rate of DVT was also significantly lower in the neurosurgical ICU (2.55%) versus other ICUs (5.62%).

Presently, there are no standardized DVT surveillance protocols or guidelines in the US. Based on available data, we believe surveillance for DVT should be undertaken in high risk patients on a biweekly regimen, otherwise, individualized surveillance is warranted.

Methods of Thromboprophylaxis

Pharmacologic Prophylaxis remains the mainstay of prevention of VTE [8]. Several classes of drugs are presently being used, under development or being tested for this purpose. In this manuscript, pharmacologic prophylaxis is discussed with each clinical setting. A summary of the major classes of pharmacologic agents used in VTE prophylaxis along with their mechanism of action and dosing [9–13] are presented in Table 1.

Prophylaxis with Mechanical Devices

Mechanical methods are frequently and widely utilized in critically ill neurologic and neurosurgical patients. However, there is little evidence from RCTs supporting their safety or efficacy either in this subset of patients or in medical-surgical ICU patients in general [14–17]. Two types of mechanical prophylaxis are employed commonly: compression stockings (CS) and intermittent compression devices (ICD). In general, ICD are used when there is a contraindication to pharmacologic prophylaxis and it is recommended that the use of CS be reserved for patients with an absolute contraindication to pharmacological prophylaxis [18]. Inferior vena cava (IVC) filters have never been examined rigorously in a prospective clinical trial for thromboprophylaxis. Despite this lack of evidence for efficacy, IVC filters are widely used partly because the licensing requirements are very lenient for this procedure [19]. The theoretical benefits for the use of IVC filters are misleading and, in fact, they may increase the risk of DVT even in anticoagulated patients [20]. Importantly, although removable filters are now widely available, they are actually removed in less than 20% of patients [21]. The American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy recommends against the use of IVC filters as prophylaxis for DVT [17], and should be considered in specific circumstances.

Brain Neoplasm

Incidence and Epidemiology

In general, brain neoplasms increase the risk of VTE [22]. In addition to the inherent prothrombotic nature of brain tumors themselves, the constellation of functional impairment to mobility as a consequence of the neoplasm, high-dose corticosteroid therapy, pharmacologically induced dehydration and major neurosurgical procedures present enhanced risk for developing VTE [23].

The overall risk of DVT varies markedly with mode of detection. In an evidence-based review investigating the risk of VTE in patients with malignant glioma [22], the incidence of DVT ranged from 3 to 60% and varied with the implemented prophylaxis regimen, the diagnostic method employed, and study design. Beyond 6 weeks post-operatively, the rates of DVT ranged from 0.013 to 0.023 per patient-month of follow-up. This review [22] identified a single study with no significant methodological flaws which found a 24% rate of incidence of symptomatic DVT over the 17 months of follow-up beyond the first 6 post-operative weeks [24]. Based on the 6 studies included in the review, the presence of lower extremity paresis, histological diagnosis of glioblastoma multiforme (GBM),

Table 1 Pharmacologic agents for prophylaxis and treatment of VTE

Drugs	Mechanism [9–11]	Dose [12, 13]
Coumadins [9]	Interfere with the cyclic interconversion of vitamin K and its 2, 3 epoxide; Vit K-dependant coagulation factors are inactivated	Adjust dose based on INR
Warfarin		2–15 mg oral or IV QD, adjust dose based on INR
Acenocoumarol and phenprocoumon		1–10 mg QD; adjust dose based on INR
Brodifacoum		Not used in clinical practice; a poison
Phenindione		50–150 mg/day; 50 mg of phenindione = 3 mg of warfarin; not recommended for clinical use
Heparin [10]	Formation of heparin/Antithrombin complex which inactivates thrombin and factor Xa	Prophylactic dose: 5,000 U SC, Q 12 h or Q 8 h
		Therapeutic dose: usual starting dose = 15–18 U/kg/h IV; adjust dose based on PTT
Low molecular weight heparins [10]	Similar to heparin, but with higher activity toward Xa inactivation than AT activity	No need for monitoring PTT, Xa activity can be measured but very seldom used in clinical practice
Nadroparin (Fraxiparin)		Prophylactic: 2,850 U/day SC
		Therapeutic: 85 U/kg SC Q 12 h
Enoxaparin (Lovenox/clexane)		Prophylactic: 30 mg SC Q 8–12 h
		Therapeutic: 1 mg/kg SC Q 12 h or 2 mg/kg SC/day
Dalteparin (Fragmin)		Prophylactic: 5,000 U/day SC
		Therapeutic: 200 U/kg/day SC
Adreparin (Normiflo)		50 antifactor Xa U SC/kg of the patient's actual body weight
Tinzaparin (Innohep)		Prophylactic: 75 U/kg/day SC
		Therapeutic: 175 U/kg/day SC
Reviparin (Clivarine)		Prophylaxis: 1,750 U/day SC
		Therapeutic: 4,200 U/day SC
Danaparoid (Orgaran)		Prophylactic: 750 anti-Xa U SC Q 8–12 h
		Therapeutic: Initial 1,500–3,750 U based on weight, then 600 U IV/h × 4 h, then 400 U IV/h × 12 h, then 300 U IV for maintenance
Synthetic pentasaccharide inhibitors of factor Xa [11]	Similar to heparin and low molecular weight heparin	No need for monitoring PTT, Xa activity can be measured but very seldom used in clinical practice
Fondaparinux		Prophylactic: 2.5 mg SC daily
		Therapeutic: 5 mg/kg/day for body weight <50 kg; 7.5 mg/kg/day for body weight 50–100 kg; 10 mg/kg/day for body weight >100 kg
Idraparinux		2.5 mg once weekly; still experimental
Direct anti-thrombin inhibitors [11]	Direct inactivation of anti-thrombin III	Most of the drugs not used in the settings of VTE but rather in coronary or cerebral thrombosis or heparin-induced thrombocytopenia; dose monitored by PTT
Argatroban		Argatroban: 0.5–10 μg/kg/min, adjust based on PTT
Lepirudin		Initial 0.075 mg/kg/h, adjust based on PTT

age > 60 years, large tumor size, use of chemotherapeutic agents, and length of surgery > 4 h were identified as possible risk factors. In the largest retrospective analysis [25] reporting the incidence of symptomatic VTE in patients with malignant glioma ($n = 9,489$), the 2-year cumulative incidence of VTE was 7.5% (715 cases), with a rate of 16.1 events per 100 person-years during the first 6 months; 391 of these cases (55%) were diagnosed within 61 days of major neurosurgery. Risk factors for VTE included older age, histopathology demonstrating GBM, 3 or more chronic co-morbidities, and a neurosurgical procedure within 61 days. Patients in whom a VTE was present were at higher risk for death within 2 years. In a nested case–control analysis of all VTE cases, there was no

association between placement of an IVC filter and the risk of a recurrent VTE.

Prophylaxis with Mechanical Devices

A few small RCTs have evaluated the efficacy of CS and/or ICD to prevent DVT in a mixed neurosurgical population with a substantial number of patients undergoing surgery for intracranial neoplasm. Turpie et al. [26] randomized patients ($n = 239$; 117 with brain tumors) to CS alone, CS in combination with ICD, or no prophylaxis and found a reduction in frequency of DVT from 20% in patients without prophylaxis to 9% in both treatment arms. Another randomized study [27] compared ICD with ICD + CS and found similar rates of DVT in 70 patients of whom 39 underwent surgery for brain neoplasm. In contradistinction to the two aforementioned studies, Wautrecht et al. [28] randomized 23 patients undergoing surgery exclusively for brain tumors and reported that ICD + CS was superior to CS alone in decreasing the incidence of post-operative DVT (40% in the CS group vs. 0% with combined CS + ICD). Taken together, these results suggest that mechanical prophylaxis is probably superior to no prophylaxis and that ICD with or without CS may be superior to CS alone.

Pharmacologic Prophylaxis

In 1998, a frequently cited study was published suggesting that enoxaparin increases the incidence of post-operative ICH when initiated pre-operatively for DVT prophylaxis in patients with brain tumors [29]. The authors conducted a randomized trial comparing ICD to enoxaparin and combined therapy that was started at the induction of anesthesia and continued throughout hospital stay. The ICD group ($n = 22$ patients) had no incidence of ICH but 5 of 44 patients receiving enoxaparin suffered from clinically significant ICH. This trial has resulted in reluctance of many neurosurgeons to use pharmacologic VTE prophylaxis in this subset of patients. A recent survey revealed that 76% of neurosurgeons resort to mechanical thromboprophylaxis exclusively, or nearly exclusively, following surgery for brain tumors [30]. Despite concerns raised by the aforementioned trial, subsequent evidence suggests that the increased risk of ICH may have been anomalous and that the benefits of prophylaxis outweigh risks. A meta-analysis performed in 2000 [24, 31] included 4 RCTs ($n = 827$ patients, 80% with brain tumors). Prophylaxis was begun prior to surgery in 110 patients and within 24 h after surgery in the remainder. Active treatment consisted of various regimens (enoxaparin 40 mg/day + ICD, nadroparin 7,500 anti-Xa U/day, enoxaparin 20 mg/day, and unfractionated heparin (UFH) 5,000 U Q 8 h) versus control regimens consisting either of ICD or placebo. VTE was observed in 29% of controls versus 16% in the low molecular weight heparin (LMWH) or UFH-treated groups (RR 0.48, 95% CI 0.35–0.66). The risk of major bleeding was 2.3% in the heparin group and 1.4% in the control group (RR 1.71, CI 0.69–4.7). The number needed to treat (NNT) to prevent one VTE was 7.7 and the number needed to harm (major bleeding) was 102. Since the publication of this review, two additional relevant RCTs have been reported. A study by Constantini et al. [32] randomized patients ($n = 103$) undergoing surgery for brain tumor to UFH 5,000 U Q 12 h begun 2 h prior to surgery versus placebo. The study was designed to evaluate safety and did not address efficacy of pharmacologic prophylaxis. There was no increase in intra-operative blood loss or surgeon's perception of difficulty with hemostasis in any of the treatment groups. Significant ICH occurred in one patient in the heparin group and two in the placebo group. A study by Goldhaber et al. [33] also demonstrated low rate of VTE after craniotomy for brain tumor using multi-modality prophylaxis which consisted of either enoxaparin 40 mg/day or UFH 5,000 U Q 12 h, in combination with graduated CS, ICD, and predischarge surveillance venous ultrasonography of the lower extremities. This regimen resulted in 150 consecutive patients (9.3%) without symptomatic VTE comprising mostly of isolated calf DVT [33]. Enoxaparin and heparin had comparable efficacy.

Finally, given the high prevalence of DVT in patients with brain neoplasm, there has been interest in outpatient prophylaxis with LMWH. A randomized trial—PRODIGE—was designed to address this question; patients were randomized to LMWH (dalteparin) versus placebo for primary prophylaxis. Unfortunately, the trial was not completed due to lack of supply of the study drug (results were presented in abstract form only) [http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/2011]. Of a planned goal of 512 patients, 186 patients with glioma were actually enrolled and randomized to dalteparin (5,000 anti-Xa U) versus placebo. DVT was diagnosed in 11% in the active treatment arm versus 17% of the placebo-treated group (NS); however, there was a 5%/year risk of major bleeding in the LMWH group versus 1% in the placebo group (NS). The high risk of major bleeding, although not statistically increased, argues against standard use of LMWH for primary prophylaxis in the outpatient setting.

Guidelines, Recommendations, and Special Considerations

To our knowledge, there are no published guidelines to specifically address thromboprophylaxis in patients with brain tumors in either the hospital or the outpatient setting. One of the major concerns regarding anticoagulation of

patients with brain tumors is the risk of hemorrhage within the brain tumor itself. Similarly, patients with a history of significant spontaneous ICH due to a brain tumor also should not receive pharmacologic thromboprophylaxis unless the underlying tumor has been surgically resected. In other situations it is probably safe to use pharmacologic prophylaxis and benefits likely outweigh risks. Mechanical prophylaxis alone should be considered for patients with metastatic tumors carrying a high risk of hemorrhage (thyroid, renal cell, choriocarcinoma, and melanoma; Table 2).

Acute Ischemic Stroke (AIS)

Incidence and Epidemiology

Venous thrombo-embolism is a common but preventable complication of AIS with risk reported to be up to 75% in patients with hemiplegia. Of these, 20% are at a risk for PE [28, 29, 34, 35], which results in fatality in 1–2% of patients and causes 25% of early death following AIS. Fatal PE is unusual in the first week and occurs most commonly 2–4 weeks following the ictus. The prevalence of VTE is 2–3% in patients with AIS on aspirin with or without CS within 10–14 days of onset [36].

Prophylaxis with Mechanical Devices

A 2004 Cochrane review identified only two small trials comparing methods for thromboprophylaxis (ICD and CS) with placebo in patients with AIS. The first, reported by Prasad et al. [37], randomized 26 patients within 24 h of AIS to ICD versus no ICD with follow-up at 1 and 10 days with radio-isotope scans. The 10-day scan demonstrated PE in 6/13 patients in the ICD arm versus 6/13 in controls [37]. The second study [33, 38] enrolled 97 patients and compared no treatment with two different types of CS; this study reported a non-significant trend toward a decrease in DVT in the CS groups, but the small size and high dropout rate (about 1/4) renders the study difficult to interpret. An ongoing trial—CLOTS—will examine the relative efficacy of ICD's versus no prophylaxis and compare the efficacy of full-length and below-the-knee ICD's [39]. CLOTS-1 was recently published and compared thigh-length ICDs to no

Table 2 Summary of Recommendations

Pathology	Recommendations
Brain neoplasm	No clear guidelines
	Patients with hemorrhagic tumors as well as multiple metastasis from known hemorrhagic primary tumors (thyroid, renal cell, choricarcinoma and melanoma) should not receive pharmacologic prophylaxis
	Probably safe to use pharmacologic prophylaxis after surgery as early as 12 h
	Enoxaparin and heparin are probably equally effective
AIS	2007 AHA/ASA guidelines recommend the use of SC UFH or LMWH for DVT prophylaxis
	2008 ACCP guidelines also endorse the use of UFH or LMWH for DVT prophylaxis in patients with AIS with impaired mobility starting 24 h after the ictus, for as long as there is impaired mobility, and recommend ICD with or without CS in patients in whom heparins are contra-indicated
	Special consideration should be given in patients who received r-TPA, diabetics and large volume strokes
ICH and SAH	AHA/ASA guidelines recommend mechanical prophylaxis with consideration of prophylaxis with heparin after documentation of cessation of growth of ICH
	ACCP guidelines suggest that early pharmacologic prophylaxis be considered as early as 2 days after onset of ICH and recommend ICD as initial therapy
	In SAH, aneurysms should be secured prior to initiation of pharmacologic prophylaxis
	Patients with ICH due to anticoagulation can receive pharmacologic prophylaxis
Neurosurgical patients	The ACCP guidelines recommend SCD for neurosurgical patients undergoing major elective neurosurgical procedures
	In addition, LMWH or UFH are acceptable alternatives; for patients at particularly high risk, it is suggested that LMWH or UFH be used
TBI	The Brain Trauma Foundation guidelines recommend the use of mechanical thromboprophylaxis with ICD or CS in all patients with TBI until ambulatory, unless lower extremity injury precludes their use
	Pharmacologic prophylaxis with LMWH or UFH should be considered in addition to mechanical prophylaxis, but they may carry an increased risk of ICH expansion
SCI	LMWH is the standard prophylaxis of VTE in patients with acute SCI
	Prophylactic IVC filters are not indicated in patients with acute SCI

prophylaxis after stroke. There was no significant absolute risk reduction of VTE in between the two groups. The authors concluded that data did not lend support to the use of thigh-high ICDs in acute stroke; furthermore, they recommended revision of the national guidelines for stroke [http://www.strokecenter.org/trials/TrialDetail.aspx?q8hours=287].

Pharmacologic Prophylaxis

Efficacy of pharmacologic prophylaxis against VTE following AIS is well established. The 2004 Cochrane review [40] reported a decreased risk of DVT and PE in stroke patients treated acutely with UFH, LMWH or heparinoids. Combining these studies incorporating 916 patients, treatment was associated with a 79% decrease in risk of DVT (RR 0.21, 95% CI 0.15–0.29), and among more than 22,000 patients, the risk of symptomatic PE decreased 40% (RR 0.60, CI 0.44–0.81). The corresponding NNT to prevent one DVT was 3.6; however, because of the small incidence of symptomatic PE, the NNT for symptomatic PE was approximately 250.

Given the clear benefit of various types of heparins in DVT prevention, three important trials during the past decade have examined whether LMWH is superior to UFH. Hillbom et al. [41] provided evidence that enoxaparin is at least as effective as UFH via a RCT with 212 patients that demonstrated that enoxaparin 40 mg/day was superior to UFH 5,000 U Q 8 h when initiated within 48 h of AIS for preventing VTE (OR 0.46, 95% CI 0.22 to 0.97). The PROTECT trial ($n = 545$), a RCT published in 2006 [42], demonstrated similar efficacy to another LMWH, certoparin (3,000 U anti-Xa activity), to UFH (5,000 U Q 8 h) for the prevention of thromboembolic complications in patients with AIS. The PREVAIL study [43] enrolled 1,762 patients and demonstrated a statistically significant reduction in VTE (10 vs. 18%, RR 0.57, 95% CI 0.44–0.76) those patients randomized to enoxaparin 40 mg QD compared to those receiving UFH 5,000 U Q 12 h. While the rates of ICH (1% in each) and bleeding of any type were similar in the enoxaparin and UFH groups, there was a statistically significant increase in major extracranial bleeding (1 vs. 0%) and in symptomatic ICH in the UFH group. A subsequent meta-analysis pooling the results of the three trials comparing LMWH to UFH demonstrated an overall significant risk reduction in VTE (OR 0.54, 95% CI 0.41–0.70), proximal DVT (OR 0.53, 95% CI 0.37–0.75), and PE (OR 0.26, CI 0.07–0.95) without a significant increase in ICH or extracranial bleeding [44]. It should be pointed out that the PREVAIL trial was underpowered to detect differences in risk for ICH between LMWH and UFH; the subsequent meta-analysis was also underpowered for this particular outcome.

Guidelines, Recommendations, and Special Considerations

The 2007 American Heart Association (AHA)/American Stroke Association (ASA) guidelines recommend the use of subcutaneous UFH or LMWH for DVT prophylaxis in patients with AIS [45, 46] (Table 2). The 2008 ACCP guidelines also endorse the use of UFH or LMWH for DVT prophylaxis in patients with AIS with impaired mobility starting 24 h after the ictus, for as long as there is impaired mobility, and recommend ICD with or without CS in patients in whom heparins are contra-indicated [40, 47].

Pharmacologic prophylaxis should be withheld in certain scenarios following AIS. In the first 24 h following administration of thrombolytics (r-tPA), all anticoagulation should be withheld. In patients with significant hemorrhagic transformation, anticoagulation should be deferred until bleeding has stabilized. Finally, where there is very high risk of hemorrhagic transformation—e.g., with large strokes, especially in patients with diabetes or —consideration of mechanical prophylaxis alone for the first few days following the ictus is reasonable.

Intraparenchymal Hemorrhage (IPH) and Subarachnoid Hemorrhage (SAH)

Incidence and Epidemiology

Patients with IPH have up to a four-old greater risk of DVT compared to patients with AIS [48, 49]. This is likely the result of lower rates of pharmacologic prophylaxis [49], cessation of anticoagulation in patients with anticoagulant-associated IPH, and a higher degree of neurologic impairment. Review of a database from the National Hospital Discharge Survey encompassing more than 14 million patients with ischemic stroke and 1.6 million patients with IPH revealed PE in 0.51% of patients, DVT in 0.74% of patients with ischemic stroke compared with PE in 0.68% and DVT in 1.37% of patients with IPH. A single center study reported a rate of 1.8% for PE and 1.1% for DVT in 988 patients with IPH [50].

Prophylaxis with Mechanical Devices

Lacut et al. [51] randomly allocated patients with documented IPH to treatment with CS alone or in combination with ICD. The combined devices significantly decreased the occurrence of asymptomatic DVT for patients with IPH (RR 0.29; 95% CI 0.08–1.00).

Pharmacologic Prophylaxis

Evidence from retrospective studies suggests that DVT prophylaxis can be administered safely soon after ictus. A Finnish study retrospectively assessed safety and efficacy of DVT prophylaxis with enoxaparin 20 mg/day ($n = 232$ patients) as compared with ICD ($n = 175$ patients). The risk of hematoma expansion ($>33\%$) was equivalent in both groups (9% in the enoxaparin group vs. 7% in the ICD group) [52].

Two small RCTs have been performed. In the first study, 68 patients with spontaneous IPH were treated with subcutaneous (SC) heparin prophylaxis (5,000 U Q 8 h) initiated at day 2, 4 or 10 after the ictus. The study found a significantly decreased risk of PE in the day-2 group without an increase in the risk of recurrent IPH [53]. Dickmann et al. [47, 54] conducted a RCT of low-dose heparin SC started at day 4 after ictus for prevention of DVT and PE in patients with IPH ($n = 64$ patients). There was no significant reduction of the incidence of VTE by low-dose heparin therapy.

Guidelines, Recommendations, and Special Considerations

The AHA/ASA guidelines (Table 2) recommend mechanical prophylaxis with consideration of prophylaxis with heparin after documentation of cessation of growth of IPH [55]. The ACCP guidelines suggest that early pharmacologic prophylaxis be considered as early as 2 days after onset of IPH and recommend ICD as initial therapy [48].

There is a subset of patients who develop IPH while receiving anti-coagulants for various indications. Those patients constitute a therapeutic dilemma for the treating physician. Bertram et al. [56] suggested that heparin used both in full dose or low dose are safe in these patients, based on a case series demonstrating no rebleeding events in this subset of patients. IVC filters are only used if the diagnosis of DVT is established and the risk of PE is substantial (i.e., above knee DVT). IVC filters do not prevent DVT, but decrease the occurrence of developing PE. Their use is associated with short- and long-term risks [57] as well as the subsequent need of anti-coagulation in a substantial number of patients.

Finally, there is paucity of data on the prophylaxis of VTE in patients with SAH. The general rules for VTE prophylaxis can be extended to patients with SAH, but, it is recommended that anti-coagulation be withheld until aneurysm is secured. One study [58] examined enoxaparin (40 mg) use in patients with SAH to test the hypothesis that anti-coagulation can improve outcome after SAH due to its possible effect of reducing delayed ischemic neurologic deficits (DIND). The study demonstrated no effect on neurological outcome or DIND, but an increased incidence of ICH in the early post-operative period was noted. Therefore, the authors concluded that heparin should not be initiated in the early post-operative period.

Neurosurgical Patients

Incidence and Epidemiology

Neurosurgical patients are at high risk of VTE post-operatively particularly those with malignancy, the elderly, those undergoing prolonged surgery, and patients with pre-existing or post-operative paresis [59, 60]. Rates of DVT and PE have varied widely, ranging from 0 to 34% for DVT [59] and 0 to 3.8% with symptomatic PE [60]. A meta-analysis by Danish et al. [61] of studies involving more than 5,500 patients reported that patients without any DVT prophylaxis who underwent craniotomy had a 4.3% risk of DVT and a 1.4% risk of PE. With mechanical thromboprophylaxis, the corresponding risks of DVT and PE were 1.4 and 0.68%, respectively [60]. A meta-analysis by Collen et al. [59] encompassing 7,770 patients undergoing craniotomy as well as spinal procedures found even higher rates of DVT—12–15% in patients without prophylaxis or those with CS only, compared to a risk ranging from 0.9 to 4.1% in patients treated with mechanical or pharmacologic thromboprophylaxis. The risk of PE ranged from 0.2 to 0.4% depending on modality of prophylaxis.

Prophylaxis with Mechanical Devices

ICD with or without CS are accepted as standard of care for DVT prophylaxis in the neurosurgical population at most institutions [60]. The optimal antithrombotic efficacy of ICD is achieved when they are worn continuously [61, 62]. Ting et al. [63] demonstrated that mechanical prophylaxis using ICD resulted in low incidence of proximal DVT during the peri-operative period in patients undergoing craniotomy.

The meta-analysis by Collen et al. [59] identified three randomized control trials comparing ICD with CS and two trials comparing ICD with placebo. The three RCTs did not identify a clear benefit of ICD over CS, although there was a non-significant trend favoring ICD over CS. When compared to placebo, use of ICD demonstrated a substantial benefit in terms of DVT prevention and a trend toward benefit in preventing PE; the RR for DVT in the ICD group was 0.41 (95% CI 0.21–0.78) and 0.37 for PE (95% CI 0.03–4.06).

Pharmacologic Prophylaxis

Although evaluated in numerous cohort studies and randomized trials, pharmacologic prophylaxis is used on a routine basis in very few neurosurgical units because of the perceived risk of potentially devastating ICH. For example, a survey of 44 neurosurgical units in U.K. found that only 32% used pharmacological prophylaxis in the peri-operative period [64].

Two randomized trials have compared LMWH with CS and three have compared UFH with placebo. Both RCT's comparing LMWH with CS showed a significant advantage for LMWH. A study by Agnelli et al. [16] randomized patients ($n = 307$) to enoxaparin 40 mg/day + CS versus CS alone. The vast majority of patients (299/307) underwent surgery for tumors (predominantly intracranial). LMWH was begun within 24 h of surgery. DVT was reduced from 32% in the CS only group to 17% in the CS + LMWH group (RR 0.52, 95% CI 0.33–0.82). A RCT by Nurmohamed et al. [65] enrolled 345 patients and compared nadroparin (a LMWH) with CS; the rate of DVT was decreased from 26 to 19% (RR 0.66, 95% CI 0.44–0.98) and rate of proximal DVT + PE was decreased from 12 to 7%. In this trial, 400/485 patients underwent surgery for CNS tumors.

Two trials have compared LMWH with ICD. The first by Dickinson et al. [29] involving 66 patients with brain tumors showed no benefit but an increased risk of bleeding with a regimen of enoxaparin 30 mg Q 12 h begun preoperatively. The second reported by Kurtoglu et al. [66] reported in 2004 enrolled 120 patients with TBI who required surgery (primarily for epidural hematoma, subdural hematoma, or contusion). Patients were treated with enoxaparin 40 mg/day after a CT scan of brain within 24 h of surgery showed that bleeding was stabilized and repeat surgery would not be required. This study also demonstrated no benefit from enoxaparin, but neither was there an increase in the risk of bleeding.

Three trials have compared the use of UFH with placebo. Only one of these demonstrated a benefit [67]. This small randomized trial enrolled 100 patients with CNS neoplasms. Patients were randomized to UFH 5,000 Q 12 h or placebo; incidence of DVT was reduced from 34 to 6% (OR 0.18, 95% CI 0.06–0.56). Two other small trials—one with 103 patients with brain tumor and one involving 50 patients with spine disorders—compared UFH with placebo (regimens were 5,000 U Q 12 h and 2,500 U Q 12 h) and found no benefit. Pooling these trials demonstrated a trend for benefit from UFH which was not statistically significant (OR 0.50, 95% CI 0.10–2.38) [59].

Most of the aforementioned studies [16, 65–67] included patients predominantly undergoing surgery for brain neoplasm. Therefore, conclusions drawn from these studies can be cautiously extrapolated to patients with brain neoplasm especially those undergoing surgery.

In summary, randomized data suggest that LMWH is superior to CS for DVT prevention. In addition, there was a trend toward benefit when comparing the efficacy of UFH to placebo, though this benefit did not reach statistical significance. Notably, the vast majority of patients enrolled in all of these trials were treated for brain tumor. Because LMWH appears to be significantly better than CS, while UFH was not shown to be statistically superior to placebo, indirect evidence suggests that LMWH might be more effective than UFH in preventing DVT. In fact, four trials compared LMWH with UFH; all found these two pharmacologic methods to be equivalent. Regimens compared included enoxaparin 40 mg/day vs. heparin 5,000 U Q 12 h [68], dalteparin 2,500 U anti-factor Xa vs. UFH 5,000 U Q 12 h [69], 1,500 U APTT certoparin QD vs. UFH 5,000 U Q 8 h begun on the evening prior to surgery [70], and 1,500 U APTT LMWH QD started 2 h prior to surgery [71].

Despite concerns of increased risk of bleeding complications due to peri-operative administration of pharmacological prophylaxis for DVT, a total of four studies comparing LMWH with mechanical strategies found no statistically significant increase in ICH, minor bleeding events or major bleeding events. The RR for LMWH was 1.97 (95% CI 0.64–6.09). For the three studies comparing UFH to non-pharmacological management, findings were similar; there was no statistically significant increase in ICH or other bleeding events, with a RR for ICH of 2.11 (95% CI 0.39–11.31). Furthermore, despite the report by Dickinson et al. [29] suggesting an increased risk of ICH with heparin prophylaxis begun preoperatively, the study by Collen et al. [59] did not find any suggestion of a trend of increased ICH in relation to early institution of pharmacologic prophylaxis.

Guidelines, Recommendations, and Special Considerations

For neurosurgical patients considered as a group, overall evidence suggests that pharmacologic prophylaxis is neither substantially better than mechanical prophylaxis for DVT and PE prevention nor substantially more dangerous in terms of the risk of ICH or other major bleeding. The ACCP guidelines [47] recommend SCD for neurosurgical patients undergoing major elective neurosurgical procedures. LMWH or UFH are an acceptable alternative. For patients at particularly high risk, it is suggested that LMWH or UFH be used. Appropriate high risk features are not defined in the in the guidelines (Table 2).

Traumatic Brain Injury (TBI)

Incidence and Epidemiology

In most, but not all studies, TBI is a significant independent risk factor for development of VTE. For example, in the National Trauma Data Bank, a registry enrolling 450,375 patients, the incidence of VTE was 0.36%. TBI was an independent risk factor for VTE with OR 2.59 (95% CI 2.31–2.90). In another study, by far the most powerful predictor of VTE was >3 ventilator days, with OR 10.6 (95% CI 9.3–12.1) [72].

Prophylaxis with Mechanical Devices

To our knowledge, the efficacy of mechanical prophylaxis with ICD or CS has not been compared with placebo in a RCT. Some observational data suggests that ICD is more effective than CS or other alternatives in patients with TBI in whom heparin was not used for prophylaxis [73].

Pharmacologic Prophylaxis

For patients with TBI and without evidence of ICH, pharmacologic prophylaxis is likely effective and safe. For example, a study by Geerts et al. [74] randomized 344 patients with severe trauma (13 patients had TBI and 40 patients had spine injuries) to UFH 5,000 U Q 12 h versus enoxaparin 30 mg/day within 36 h of injury. The risk of proximal DVT was reduced from 15% in the UFH group to 6% in the LMWH group (RR 0.42, 95% CI 0.13–0.88) [74]. Patients with TBI as the major site of bleeding made up only 5% of the total group. There was a single patient with a subdural hematoma treated with LMWH. A systematic review of VTE prophylaxis in trauma patients found an overall reduction of incidence of DVT of about 20% with UFH compared with a reduction of about 50% with LMWH [75].

Trauma complicated by TBI, especially in the context of ICH, has not been well studied. As mentioned previously RCT reported by Kurtoglu et al. [66], demonstrated no benefit with enoxaparin 40 mg/day when treated within 24 h of surgery, although there was no increased incidence of bleeding. This study was underpowered with regard to both safety and efficacy. Some observational cohort studies have raised concerns about the possibility increased risk of ICH or rebleeding. For example, prospective observational studies [76–78] all suggest a possible increase in ICH with pharmacologic prophylaxis. Gerlach et al. [76] showed higher risk of postoperative hematomas in neurosurgical patients that included several traumatic hematomas and decompressive craniectomies without a specific elaboration in the rate of post-operative hematoma in the trauma subgroup. Kleindienst et al. [78] had a higher incidence of postoperative hematomas in the head injury group compared to elective craniotomy group, both received posteropative LMWH for DVT prophylaxis. Norwood et al. [78] reported that 23% of patients with TBI had worsening of their hemorrhage when receiving enoxaparin. However, on critical review of this study, 19% of patients worsened prior to initiating therapy with enoxaparin and only 4% worsened following its institution. Kim et al. [79] retrospectively evaluated the early use (before 72 h), late use (after 72 h) of UFH or no use in patients with severe closed TBI. The main focus was the safety of use, and found no increase in ICH or deterioration on neurological examination as a result of UFH administration.

Imaging studies documenting that contusions, subdural or epidural hematoma are stable prior to initiation of pharmacologic prophylaxis may ultimately represent the best means of control for the use of pharmacologic prophylaxis. A recent large prospective observational study including 6,247 trauma patients (174 patients with TBI), examined prophylaxis with LMWH 5,000 U initiated after patients were hemodynamically stable and CT 12–24 h after initial injury demonstrated no evidence of progression from initial scans. In patients with TBI there were no patients with extension of ICH [80].

Because of the potential increased risk of VTE in patients treated with pharmacologic prophylaxis and persistently high rates of VTE despite mechanical prophylaxis, placement of prophylactic DVT filters has been advocated at some centers. Unfortunately, placement of filters does not appear to provide substantial benefit. For example, a recent observational study compared the VTE rates before and after the widespread use of retrievable filters in trauma patients at a single trauma center. The groups were comprised of 5,042 patients before the common use of filters and 5,038 afterward. Filters were employed three times more frequently in the second group, yet there was no change in the incidence of PE and filters could be successfully removed in only 21% of patients. Skepticism about a role for prophylactic IVC filter placement has been echoed by several experts [15, 81].

Guidelines, Recommendations, and Special Considerations

The Brain Trauma Foundation guidelines [82] recommend the use of mechanical thromboprophylaxis with ICD or CS in all patients with TBI until ambulatory, unless lower extremity injury precludes their use. The authors also suggest the use of pharmacologic prophylaxis with LMWH or UFH but acknowledge that there may be an increased risk of expansion of ICH with these therapies (Table 2).

Spinal Cord Injury (SCI)

VTE is a common complication in patients with acute SCI [83] with its overall incidence ranging from 18 to 100% [84, 85] within the first 12 weeks, and with the highest risk of occurrence in the first 2 weeks [86, 87]. Rarely do these events occur within the first 3 days after injury. In one report the incidence of VTE in acute SCI over a decade remained essentially unchanged [88]. Clinical PE in patients with acute SCI and in those with major orthopedic trauma ranges from 4 to 10%; with risk of fatal PE from 0.2 to 5% [15]. Because SCI patients have higher risk of VTE, the use of anti-coagulants in VTE prophylaxis is the most prevalent practice.

The spinal cord medicine consortium issued practice guidelines in 1998 regarding VTE prophylaxis in SCI [89], which included either adjusted UFH or LMWH use. Wade et al. [90] conducted a cost analysis study comparing UFH and enoxaparin and concluded that UFH produced a cost savings over enoxaparin 30 mg every 12 h. This was based on data from RCT (level 1 evidence) supporting the use of enoxaparin in major orthopedic trauma, which included acute SCI [70]. Deep et al. [91] conducted a retrospective review ($n = 276$ patients) and demonstrated that LMWH plus mechanical devices are effective in VTE prophylaxis. Thumbikat et al. [92] suggested following a retrospective review of two cohorts of patients with SCI that traditional protocol of warfarin/heparin for VTE prophylaxis in SCI remains a safer option than enoxaparin. The "DETECT" trial [93] compared dalteparin to enoxaparin for VTE prophylaxis in acute SCI and major orthopedic trauma patients and demonstrated that dalteparin 5,000 U SC daily may not be clinically inferior to enoxaparin 30 mg SC twice daily.

Guidelines, Recommendations, and Special Considerations

LMWH, e.g., enoxaparin is currently the standard prophylaxis for VTE in patients with acute SCI. The routine use of prophylactic IVC filters was shown not to be indicated after acute SCI by Maxwell et al. [94] in a landmark publication. The incidence of VTE and PE were lower in their subjects than previously reported, suggesting that implementation of guidelines advocated by the consortium for spinal cord medicine [89] is effective in reducing VTE (Table 2).

Conclusions

Critically ill neurological and neurosurgical patients are a diverse group of patients, but, they do share the higher susceptibility to VTE. Venous stasis, paresis, and the underlying condition, all enhance the increased risk of VTE. Few guidelines exist for the VTE prophylaxis in each specific subgroup. ICD with or without anti-thrombotics is generally the method of choice. LMWH is the method of choice in certain subgroups such as acute brain neoplasm and AIS. Warfarin and/or heparin remain a safer option for patients with SCI. Evidence for the risk of use of pharmacologic prophylaxis in the patients in the neurocritical care setting in general is weak. IVC filters are not an indicated for routine use; however, in certain selected cases, they may be considered. Without clear guidelines that can be universally applied to this diverse subset of patients, VTE prophylaxis needs to be tailored to the individual patient with cautious assessment of benefits versus risks. There is a need for higher level evidence to guide VTE prophylaxis in patients with SAH, spontaneous ICH as well as anticoagulant-associated ICH and those following neurosurgical procedures such as craniotomy. A summary of recommendations concluded by this manuscript is in Table 2.

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