Review article

Deep vein thrombosis and pulmonary embolism in neurosurgical patients

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Deep vein thrombosis (DVT) is a common complication reported in the neurosurgical population. Some cases of DVT are followed by pulmonary embolism (PE), which can be a serious cause of morbidity and mortality in the postoperative period. Significant risk factors of DVT development in patients undergoing intracranial surgery have been reported. Therefore, screening methods for early detection, measures of prophylaxis and DVT treatment have been proposed and utilized widely. However, the controversy remains over whether a single method or combination of pharmacological and mechanical methods is more effective in preventing DVT, while minimizing surgical bleeding, which is a serious problem for neurosurgeons. **Chiang Mai Medical Journal 2016;55(1):41-8.**

keywords: Keywords: deep vein thrombosis, pulmonary embolism, venous thromboembolism, neurosurgical patients

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are included in venous thromboembolism (VTE)[1] and should be of concern because they can result in postoperative morbidity and mortality[2]. Significant risk factors of VTE development in patients undergoing intracranial surgery have been documented. Nevertheless, there is neither a standard guideline in the prevention of DVT or PE in neurosurgery nor a general protocol in the management of early postoperative DVT or PE after craniotomy[2]. Perhaps, the risk of intracranial hemorrhage (ICH) following heparin prophylaxis for preventing VTE is not fully verified[3].

Incidence

Generally, isolated DVT is not a life-threatening event. Nevertheless, its incidence in the neurosurgical population is high at 19-50%[4,5]. While only 1.5-5% of patients with DVT develop PE, the fatality rate of PE is high at 9 to 50%[4,5]. In adult patients undergoing craniotomy for brain tumors, the incidence of DVT and PE in the perioperative period is 2-17%[3,6,7] and 1.4-1.8%, respectively[7,8]. The VTE rates are similar in patients undergoing both clipping and coiling cerebral aneurysm, in which the overall rates of VTE (DVT or PE), DVT, and PE are 4.4%, 3.5%, and 1.2%, respectively[8]. It is difficult to interpret reported articles because there is no standard definition for DVT (e.g., clinically silent or manifested) or

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differences in screening methods[9]. A major challenge is comparing rates across studies, due to the number of various factors[10], of which the technique of DVT screening, such as light-emitting diode (LED), increased the rate of DVT to 6.3% over time from 2009 to 2010; whereas PE rates were relatively stable[9]. The incidence of DVT was reported to be as high as 72% when using more sensitive screening methods, such as 125I-fibrinogen-uptake tests[11]. Nevertheless, the clinical incidence of DVT ranges up to 32%[12].

Diagnosis

Diagnosis of DVT and PE is generally unreliable when using clinical examination alone[12-14]. Radiologic examination plays a potential role in confirming and localizing the site of DVT and occurrence of PE. Doppler venous ultrasound may be sufficiently accurate in detecting asymptomatic VTE prior to clinical manifestation. Doppler ultrasound is a noninvasive diagnostic tool, but less sensitive when compared to contrast venography[15-17]. In general, venography and MRI are not ordered routinely.

Of the varied screening and diagnostic methods ordered in each neurosurgical center, some institutions use only LED to screen patients with leg swelling and pain, whereas other hospitals perform routine screening studies in all patients or only those at high risk[8,18,19]. However, studies using contrast venography and 125I fibrinogen reported higher rates of DVT than those using LED[4,20,21]. Duplex scan; a combination of traditional and Doppler ultrasound, offers sensitivity and specificity of over 90% in the diagnosis of DVT, especially for proximal DVT[22,23]. In 1995, Well *et al* developed a clinical model for predicting deep vein thrombosis[24]. The clinical parameter checklist was divided into major and minor points. The probability of DVT was classified into 3 groups of high, moderate, and low (Table 1). Several years later, the original Well clinical model for predicting the probability of DVT[25] was simplified, as shown in Table 2.

Computed tomography (CT) PE protocols were recommended for patients with clinical

Table 1. Clinical model for predicting pretest probability of deep vein thrombosis

Clinical parameter checklists	Clinical probability
Major points - Active cancer (treatment ongoing or within previous 6 months or palliative care) - Paralysis, paresis, or recent immobilization of the lower extremities - Recently bed-ridden >3 days and/or major surgery within 4 weeks - Localized tenderness distributed along the deep venous system - Thigh and calf swelling (should be measured) - Calf swelling 3 cm > symptomless side (measured 10 cm below tibial tuberosity) - Strong family history of DVT (≥2 first degree relatives with history of DVT)	High ≥3 major points and no alternative diagnosis ≥2 major points and 2 minor points no alternative diagnosis Low 1 major point+ ≥2 minor points+ has an alternative diagnosis 1 major point+ ≥1 minor point+ no alternative diagnosis 0 major points+ ≥3 minor points+ has an alternative diagnosis 0 major points+ ≥2 minor points+ no alternative diagnosis
Minor points - History of recent trauma (≥60 days) to the symptomatic leg - Pitting edema; symptomatic leg only - Dilated superficial veins (non-varicose) in symptomatic leg only - Hospitalization within previous 6 months - Erythema	Moderate All other combinations

Table 2. Simplified clinical model for assessment of deep vein thrombosis

Clinical variables	Score
Active cancer (treatment ongoing or within previous 6 months or palliative care)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness distributed along the deep venous system	1
Entire leg swelling	1
Calf swelling at least 3 cm larger than that on the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis less likely than DVT diagnosis	-2

Original score	Dichotomized score
< 0 points = low	≤ 1 = DVT unlikely
0-2 points = intermediate	≥ 2 = DVT likely
> 2 points = high	

symptoms and signs such as shortness of breath, chest pain, tachypnea, tachycardia, and/or oxygen desaturation[6]. Ventilation–perfusion scans had been investigated before 2002 to confirm PE diagnosis[12]. Clinical criteria were developed from either the Wells or revised Geneva rule for identifying "likely" or "unlikely" PE patients[26] (Table 3).

Associated factors

Multiple risk factors for DVT were reported in neurosurgical operations. Surgery on the brain could release thromboplastin tissue and activate coagulation cascade, due to the highest concentration of thromboplastin in the brain[27,28]. Patients undergoing craniotomy for malignancy, traumatic brain injury, old age, obesity, history of thromboembolic events, lengthy surgical procedure and massive surgical blood loss are reported to be at increased risk of postoperative DVT[11,29-33].

Kimmel *et al* concluded that patients who had undergone craniotomies for tumor removal were at higher risk of VTE than those with non-neoplastic indications[10]. High-grade gliomas and meningiomas were reported to be associated with increased risk of postoperative DVT and/or PE[6,12]. Some studies speculated that malignant gliomas induces hypercoagulability secondary to secretion of prothrombotic factors from tumor cells[32,34,35]. Patients with ICH had 4-times higher rates of DVT and PE than those with acute ischemic stroke[36,37]. Among the various risk factors analyzed, immobilization of more than 3 hours in a postoperative period is found to be highly significant for development of VTE[3].

Kshettry *et al* reported that VTE was associated with an increased risk of pulmonary/cardiac, infectious, ventriculostomy and vasospasm complications with an odds risk (OR) of 2.8, 2.8,1.8 and 1.3, respectively, in aneurysmal subarachnoid hemorrhage patients[8]. VTE patients with an OR of 3.3 also stayed longer in hospital. Nevertheless, VTE could be a consequence of poor neurological status, medical complications, and prolonged hospital course.

Prophylaxis and treatment

Both mechanical and pharmacological measures such as application of sequential compression stockings, postoperative early mobilization, and prophylactic administration of low-molecular weight heparins have been recommended in order to prevent DVT[5,18,19]

Table 3. Clinical variables considered for predicting the probability of PE

The Wells rule		Modified Geneva rule	
Clinical variables	Points	Clinical variables	Points
Signs or symptoms of DVT	3	Age ≥ 65 years old	1
Alternative diagnosis less likely than PE diagnosis	3	Previous DVT or PE	3
		Surgery or fracture within 1 month	2
Heart rate > 100 bpm	1.5	Active malignancy	2
Immobilization/ surgery within previous 4 weeks.	1.5	Unilateral lower limb pain	3
		Pain or deep palpitation of the lower limb and unilateral edema	4
Prior history of DVT or PE	1.5		
Hemoptysis	1	Hemoptysis	0
Active cancer	1	Heart rate 75-94 bpm	3
		Heart rate ≥ 95 bpm	5
Traditional		Modified	
> 6.0 = high		< 3 points = low	
2.0-6.0 = moderate		4-10 points = intermediate	
< 2.0 = low		> 10 points = high	
Simplified		Simplified	
> 4 = PE likely		≤ 2 = PE unlikely	
≤ 4 = PE unlikely			

and reduce general postoperative thromboembolic events and neurological surgeries[38]. In a reported craniotomy series, the incidence of DVT and PE was higher in patients who had not received prophylactic methods[28,39,40]. Prophylaxis starts in the preoperative period and significantly decreases the incidence of VTE, especially in the high risk group. A meta-analysis in 2011 revealed that heparin prophylaxis had significantly reduced the risk of symptomatic and asymptomatic VTE in relative terms by 42% in patients undergoing neurosurgery. However, it increased the risk of ICH relatively by 48% and doubled the risk of minor hemorrhage with statistical significance[41]. Previous multiple randomized control trials[5,17,42] and meta-analyses[41,43] provided no definitive evidence of the overall safety of heparin products in craniotomy patients. Currently, there are no standard recommendations for an anticoagulant drug, its dosage or timing of administration[2]. Hence, the value of a routine chemical VTE prophylaxis remains in doubt. The guidelines of the American College of Chest Physicians recently recommended heparin for use in clinical practice in patients at very high risk (risk > 10%) of intracranial malignancy, and so on[44]. However, the level of evidence is low in supporting this recommendation (Grade 2 c)[7].

Up to 13% of patients with intracranial hemorrhage reported clinically evident VTE, which usually occurs within 2 and 7 days of hospitalization, and carries a high risk of fatality because of PE[45-47]. Regarding the high incidence of VTE, the patients concerned might benefit from a pharmacological prophylaxis. In a large nationwide registry, Prabhakaren *et al*[46] observed that prophylactic anticoagulation was given in less than 20% of ICH patients, in which less than half had a pharmacological VTE prophylaxis within 2 days after ICH onset. Currently, there are no large randomized clinical trials of a pharmacological DVT prophylaxis in ICH patients[46]. For prevention of VTE in ICH patients, the American Heart Association/American Stroke Association guidelines (2007) recommend a low-dose of unfractionated heparin (UFH) or low-molecular weight heparin, initiated within the first to fourth day after the onset of ICH, or immediately after the cessation of active bleeding. (Class IIb, level of evidence B)[48,49].

A comprehensive, multimodality approach to VTE prophylaxis was shown to maximize efficacy and safety. The study of Goldhaber *et al*[17] showed that in 150 patients enoxaparin at

40 mg/day or UFH 5,000 U bid, combined with progressive compression stockings, intermittent pneumatic compression, and predischarge surveillance of venous ultrasonography of the legs, led to a significantly low overall symptomatic VTE rate of zero, and asymptomatic DVT rate of 9.3%. Some previous trials supported a multimodality approach of VTE prophylaxis. Agnelli *et al*[5] used contrast venography for DVT detection in craniotomy patients, and reported a rate of 32% and 17% with mechanical prophylaxis and the addition of enoxaparin, respectively. However, the symptomatic DVT rate was only 6% in the former group and 1% in the latter.

Though heparin lowered the VTE rate remarkably, hemorrhagic complications following either heparin or enoxaparin prophylaxis were reported clinically[3,6]. Danish *et al* concluded that benefit of the VTE pharmacological prophylaxis outweighed the hemorrhagic risk only when the incidence of PE approached 1.4%, owing to the reported incidence of associated ICH[9].

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ภาวะลิ่มเลือดในหลอดเลือดดำส่วนลึกและลิ่มเลือดอุดตันในหลอดเลือดแดงปอดในผู้ป่วยศัลยกรรมประสาท

อานันท์ชนก ศฤงคารินกุล, ปฐมพร ปิ่นอ่อน และ ยอดยิ่ง ปัญจสวัสดิ์วงศ์
ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

ภาวะลิ่มเลือดในหลอดเลือดดำส่วนลึกเป็นหนึ่งในภาวะแทรกซ้อนที่พบได้บ่อย ซึ่งถูกรายงานในผู้ป่วยศัลยกรรมประสาท โดยผู้ป่วยที่มีลิ่มเลือดในหลอดเลือดดำส่วนลึกบางราย เกิดภาวะลิ่มเลือดอุดตันในหลอดเลือดแดงปอด ซึ่งเป็นสาเหตุของผลเสียที่ตามมา และการตายในช่วงหลังการผ่าตัดได้ ปัจจัยเสี่ยงที่สำคัญในการเกิดภาวะลิ่มเลือด ในหลอดเลือดดำส่วนลึกในผู้ป่วยที่ได้รับการผ่าตัดสมอง ได้ถูกตรวจสอบ ดังนั้นวิธีการตรวจหาเบื้องต้นในระยะแรก มาตราการป้องกันและการรักษาได้ ถูกนำเสนอกันอย่างแพร่หลาย อย่างไรก็ตามยังมีข้อขัดแย้งถึงการใช้เพียงวิธีการเดียว หรือการใช้ร่วมกันระหว่างการใช้ยาป้องกันลิ่มเลือดและการใช้การบีบรัดหลอดเลือด ว่าวิธีใดมีประสิทธิภาพที่ดีกว่าในการป้องกันลิ่มเลือดในหลอดเลือดดำส่วนลึก ในขณะเดียวกันช่วยลดโอกาสการเกิดเลือดออกหลังการผ่าตัด **เชียงใหม่เวชสาร 2559;55(1):41-8.**

คำสำคัญ: ภาวะลิ่มเลือดในหลอดเลือดดำส่วนลึก ลิ่มเลือดในหลอดเลือดดำ ลิ่มเลือดอุดตันในหลอดเลือดแดงปอด ผู้ป่วยศัลยกรรมประสาท