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Deep Vein Thrombosis and Pulmonary Embolism following Hemorrhagic Stroke

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Venous thromboembolism (VTE) after stroke is an infrequent but potentially fatal medical complication. The incidence of VTE was shown to be higher in hemorrhagic stroke than in ischemic stroke by several studies; however, no strategy for VTE screening and prophylaxis has been established. Lower extremity ultrasonography (US) is the diagnostic method of choice, but routine application for stroke patients is still debated. For prevention, graduated compression stockings (GCS) have little effect on VTE, and thigh-high GCS should be selected. Early use of intermittent pneumatic compression (IPC) has strong evidence for preventing VTE and is recommended in several clinical guidelines for managing intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Prophylactic heparin products are still debated for preventing VTE despite the risk of rebleeding or hematoma enlargement. To date, administering low-dose, low-molecular-weight heparin (LMWH) seems the best method to prevent VTE with less risk of hemorrhagic complications. However, the optimal product, dose, and timing are unclear.

Keywords: Venous thromboembolism; Deep Vein Thrombosis; Pulmonary Embolism; Stroke; Intracerebral hemorrhage

BACKGROUND

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) are potenetially fatal medical complications following intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). The incidence of PE after stroke (including both ischemic and hemorrhagic) is less than 1%; however, PE causes more than 50% of early deaths after stroke[1)]. As in ischemic stroke, patients with hemorrhagic stroke are prone to DVT due to immobility, possible hemiplegia, and older age.

Methods to prevent and properly manage VTE after ischemic stroke are relatively well established[3,4)]; however, strategies for hemorrhage stroke are not.

REVIEW

Incidence and risk factors

The incidence of VTE after stroke varies from 10-75% depending on the diagnostic criteria, tools, and study design[3,13,21,24)]. Many studies have reported a higher incidence of DVT or PE after ICH and SAH than after cerebral infarction or transient ischemic attack[39)]. In 2003, Gregory et al. retrospectively reported the incidence of DVT after hemorrhagic (n=1,926) and thromboembolic (n=15,599) stroke as 1.9% and 0.5%, respectively[18)]. Hemorrhagic stroke and length of hospital stay were independent risk factors for DVT. Skaf et al. reported a VTE incidence of 1.93% (1.37% of DVT and 0.68% of PE) in 1,605,000 ICH patients in 2005[38)]. In 2014, Stecker et al.

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reported that the VTE incidence was 1.3% (33 of 2613 stroke patients, DVT=25, PE=3, both=5) and was higher in SAH and ICH than in ischemic patients. Higher National Institutes of Health Stroke Scale (NIHSS) score and heart failure were statistically significant risk factors in their study.

Meanwhile, the incidence of DVT is much higher in studies that used lower extremity ultrasonography (US). Lacut et al. reported a DVT incidence of 15.9% up to 10 days after ICH development[27]. Yablon et al. reported 16% DVT up to 120 days[43]. In a Japanese series, Ogata et al. reported that 21 of 52 ICH patients developed DVT[32]. Kawase et al. performed venous duplex US to detect DVT in 81 ICH patients, and 4, 9, and 17 (21%) patients were diagnosed at 1, 7, and 14 days, respectively. Female sex was the only independent predictor of DVT.

Although risk factors for stroke-related DVT are still debated, advanced age, high NIHSS score, hemiparesis, immobility, female sex, atrial fibrillation, intravenous or intra-arterial tissue plasminogen activator (tPA), and length of hospital stay have been identified[16,28,29]. Male sex is considered to be highly associated with DVT in the general population[2,12,26,30,31,37].

Diagnosis

The location and extent of DVT should be identified, because DVT in infra-popliteal calf veins (below-knee or distal DVT) can spontaneously resolve and seldom results in PE[22]. However, continuous monitoring is crucial because 1 in 6 distal DVTs progresses to proximal DVT, which carries a greater risk of PE[20]. Clinical symptoms of DVT appear as local pain or tenderness and local leg edema in approximately 2/3 of DVT patients; however, these symptoms can be hidden in unalert hemorrhagic stroke patients. A clinical DVT prediction score (Wells score) can be useful but is still limited. Thus, it should be combined with D-dimer, (i.e., increased serum C-reactive protein [CRP] with normal fibrinogen with a fever of unknown origin[3]) for evaluation[4,42].

The most important diagnostic tool is venous duplex US, which is accurate, safe, simple, and portable. Directly watching flow physiology with real-time Doppler imaging (duplex, continuous-wave and color-flow Doppler imaging) provides another advantage[20]. To detect DVT, US has high sensitivity (93.2-95.0%) and specificity (93.1-94.4%)[17]. The limitation of US is that it is only suitable to detect proximal DVT, not distal DVT or DVT above the inguinal canal. In those cases, MR and CT venography of the lower extremity and pelvis with contrast provide high sensitivity and specificity[35,41].

Prophylaxis & treatment

Graduated compression stockings (GCS) / intermittent pneumatic compression (IPC)

The CLOTS (Clots in Legs or Stockings After Stroke) trials included three randomized trials assessing the preventive effect of graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) in DVT in stroke patients. In CLOTS 1, 2518 stroke patients (including 232 ICH patients) were enrolled to investigate the preventive effect of thigh-high GCS and did not show reduced DVT, PE, or death[8]. In CLOTS 2, the effectiveness of below-knee GCS and thigh-high GCS were compared in 1406 stroke patients. The incidence of DVT was higher in the below-knee GCS group (8.8% versus 6.3%; absolute difference, 2.5% points; 95% confidence interval, [CI] 0.7 to 4.4)[9]. Finally, CLOTS 3 enrolled 2876 stroke patients (including 376 ICH patients) and found that applying IPC as soon as possible reduced the incidence of DVT. The preventive effect was more prominent in ICH patients (6.7% versus 17.0%; odds ratio [OR], 0.36; 95% CI 0.17–0.75)[10,14]. In the 2015 American Heart Association (AHA)/ American Stroke Association (ASA) Guidelines for the Management of Spontaneous ICH[19], GCS is considered not beneficial (Class III, level of evidence [LOE] A), but IPC should be used just after admission (Class I, LOE A). AHA/ASA Guidelines for the Management of Aneurysmal SAH do not describe the use IPC or GCS[11], but European Stroke Organization (ESO) Guidelines for the Management of Intracranial Aneurysms and SAH[40] in 2012 and Korean Clinical Practice Guidelines for Aneurysmal SAH[7] in 2018 recommended applying IPC, GCS, or both to prevent DVT.

Unfractionated heparin (UFH) / low-molecular-weight heparin (LMWH)

In ischemic stroke, prophylactic use of heparin or heparinoids has been broadly recommended[36]. Kamphuisen et al. performed a meta-analysis of 16 randomized controlled trials dealing with heparin use to prevent VTE after acute ischemic stroke. They defined low-dose, unfractionated heparin (UFH) as ≤ 15,000 IU/day and low-dose, low-molecular-weight heparin (LMWH) as ≤ 6000 IU/day or weight-adjusted dose ≤ 86 IU/kg/day. High-dose UFH reduced PE but increased ICH or extracranial hemorrhage (ECH), and low-dose UFH reduced thrombosis but not PE and increased the risk of ICH or ECH. Meanwhile, high-dose LMWH decreased both DVT and PE but increased the risk of ICH or ECH, and low-dose LMWH decreased the risk of both DVT (OR=0.34, 95%; CI=0.19—0.59) and PE (OR=0.36, 95%; CI=0.15—0.87) without increased risk of ICH (OR=1.39, 95% CI=0.53—3.67) or ECH (OR=1.44, 95% CI=0.13—16). ESO guidelines for VTE in immobile patients with acute ischemic stoke recommend prophylactic anticoagulation with UFH

(5000IU q 12 or 8 hours), LMWH, or a heparinoid[15].

Prophylactic use of heparin or heparinoids to prevent DVT after hemorrhagic stroke has not received consensus agreement due to the increased risk of hemorrhage or rebleeding[6]. In 1991, Boeer et al. administered low-dose UFH (5000 IU per 8 hours) 2 and 10 days after ICH in 68 patients and reported significantly reduced PE without increasing ICH[5]. They suggested that heparin can re-open occluded vessels in cerebral infarctions but seldom expands hematomas surrounding cerebral tissue due to elevated pressure. They ultimately recommend its use. Despite several limitations of the study design, several small prospective studies were performed thereafter. Kiphuth et al. reported no fatal PE and a moderate increase in hematoma (20-30%) after using LMWH (Enoxafarin 4000IU, dalteparin 2500 IU) within 36 hours for 97 ICH patients[25]. Orken et al. showed that administering LMWH did not increase ICH but failed to decrease VTE compared to GCS only. In 2011, Paciaroni et al. reported a meta-analysis of four controlled (randomized or non-randomized) studies of heparin use to prevent DVT in ICH patients and found that heparin (UFH or LMWH) significantly reduced PE (1.7% vs. 2.9%; RR, 0.37; 95% CI, 0.17–0.80; p = 0.01) but not DVT (4.2% vs 3.3% [RR, 0.77]; 95%CI, 0.44–1.34; p = 0.36). However, hemorrhage did not increase significantly (8.0%vs. 4.0%; RR, 1.42; 95% CI, 0.57–3.53; p = 0.45) and mortality decreased non-significantly (16.1% vs. 20.9%; RR, 0.76; 95% CI, 0.57–1.03; p = 0.07). They concluded that heparin use should be considered with caution for high-risk patients[33]. Khan et al. performed a systematic review of DVT in acute stroke and concluded that UFH administration should be considered for high-risk patients even in ICH and SAH. However, their conclusion does not seem to be clear. AHA/ASA Guidelines for the Management of Aneurysmal SAH and Korean Clinical Practice Guidelines for Aneurysmal SAH also indicate a lack of sufficient evidence for heparin use in SAH patients[7,11]. However, the AHA/ASA Guidelines for the Management of Spontaneous ICH recommend low-dose LMWH or UFH for immobile ICH patients 1-4 days from onset until after bleeding stops (Class IIb, LOE B)[19]. To date, real-world recommendations for low-dose LMWH use are unclear, including optimal timing, dose, and products.

Inferior vena cava (IVC) filter

Inferior vena cava (IVC) filter insertion is a common method to prevent PE when therapeutic anticoagulation is impossible. However, information comparing IVC filter and anticoagulation is extremely limited[23]. Moreover, the IVC filter itself can induce thrombosis at the insertion site, perforation of the IVC and adjacent tissue, fracture, or migration. Additionally, IVC filter insertion does not eliminate the need for anticoagulation. Nevertheless, AHA/ASA Guidelines for the Management of Spontaneous ICH recommend IVC filter placement in ICH patients with symptomatic DVT or PE (Class IIa, LOE C)[19].

CONCLUSION

Because DVT following hemorrhagic stroke is an uncommon but fatal complication, early detection is crucial. Lower extremity US is the most recommended diagnostic tool, but clinical signs are preferred for immobile patients. IPC should be applied just after admission to the intensive care unit to prevent DVT. Although, the evidence is still limited, heparin could be used for high-risk patients; low-dose LMWH seems to be the most preferred form.

Abbreviation

ICH	Intracerebral hemorrhage
SAH	Subarachnoid hemorrhage
PE	Pulmonary embolism
DVT	Deep vein thrombosis
VTE	Venous thromboembolism
CT	Computed tomography
MRI	Magnetic resonance imaging
US	Ultrasonography
UFH	Unfractionated heparin
LMWH	Low-molecular-weight heparin
GCS	Graduated compression stockings
IPC	Intermittent pneumatic compression

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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