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Deep Venous Thrombosis after Intracerebral Hemorrhage, Gender and Ethnicity: A Challenge for Therapeutic Approaches

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Primary intracerebral haemorrhage (ICH) is estimated to affect over 1 million people worldwide each year [1] and is associated with the highest mortality rate, with a 1-month case fatality of 42% [2]. The incidence of ICH is higher in certain populations, including blacks/African Americans and Asians. Up to 40% of strokes in China are hemorrhagic [3], and ICH represented 30% of strokes in one Japanese study [4]. Although the higher prevalence in blacks is attributed to hypertension, the reason for the excess of ICH in Asians is disputable (e.g. hypertension, low serum cholesterol, higher prevalence of alcohol use).

Venous thromboembolism is an important cause of morbidity and mortality for patients in critically ill conditions. Without venous thromboembolism prophylaxis, up to 75% of patients with hemiplegia after stroke develop deep-vein thrombosis (DVT). Pulmonary embolism diagnosed at autopsy is present in a substantial proportion of patients with fatal stroke and accounts for about 10% of deaths after stroke, but is clinically evident in less than 2% of patients [5]. Patients with ICH may in fact be at higher risk for DVT than ischemic stroke patients [6]. A retrospective cohort study revealed a relative risk for clinical DVT after ICH of 4.0 (1.8 vs. 0.4%) [7]. The relative risk for pulmonary embolism was 3.5 (0.4 vs. 0.1%). Data comparing patients with ICH included in the International Stroke Trial with ischemic stroke patients also suggest an increased risk of clinical pulmonary embolism – 1.3 versus 0.7% ($p = 0.06$) – even after controlling for severity of the disease [8].

In this issue of the journal, Kawase et al. [9] report on the prevalence and variables associated with DVT in 81 Japanese patients with acute ICH. Using duplex ultrasonography, they found that, at 2 weeks, 21% of patients had DVT and that female sex was the only independent predictor for DVT, contrary to the findings from western countries. It is worth mentioning that neither intermittent pneumatic compression nor heparin were used. Patients with paralysis involving the legs were required to wear below-knee elastic stockings.

The authors speculate that the excess of DVT in women may be caused by the use of oral contraceptives or hormone replacement therapy, decreased muscle pumping, variations in hormone concentration, obesity and genetic features. The incidence of DVT in this study was much higher than the 3% of DVT in the placebo group of the Factor Seven for Acute Hemorrhagic Stroke trial [10], but in line with another recent Japanese study, in which DVT was detected in 40.4% of patients with ICH after 2 weeks [11]. Differences in the ratio of complications between randomized clinical trials and the real world scenario could explain this discrepancy; however, in one report from a tertiary care center in the USA, the incidence of DVT was only 1.1% [12]. Although an alternative explanation for this excessive frequency of DVT may be less intense prophylactic measures in Asian patients, a recent study showed that Asians had a strong trend toward a higher risk of DVT (odds ratio = 3.22, $p = 0.09$) than Caucasians [13].

Analysis of the Antithrombotic Trialists' Collaboration database disclosed that mechanical compression methods reduced the risk of DVT by about two thirds when used as monotherapy and by about half when added to a pharmacological method [14]. These benefits were similar irrespective of the particular method used (graduated compression stockings, intermittent pneumatic compression or foot pumps). Despite the existence of several clinical trials of DVT prevention in ischemic stroke, only two trials addressed the prophylaxis of DVT after ICH [15, 16]. A double-blind randomized phase IV trial has started, assessing the safety and efficacy of enoxaparin (starting 24–48 h after the onset of ICH) in the prevention of venous thromboembolism [17]. Unfortunately, none of the trials above involved Asians.

Based on the few randomized clinical trials mentioned above, international guidelines suggest that patients with acute primary ICH and hemiparesis/hemiplegia should have intermittent pneumatic compression for the prevention of DVT (class I or grade 1B recommendation) [18–20]. Optionally, after documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered in patients with hemiplegia after 2–4 days from onset (class IIb, grade 2C recommendation). Whether the safety of heparin in the acute phase of ICH can be extrapolated to Asians is unknown.

Finally, the study of Kawase et al. [9] teaches us three important lessons: (1) DVT is common after ICH, and some patient characteristics (e.g. female sex, Asians) may put them in a higher risk category; (2) randomized clinical trials are needed and must include Asians, and (3) in the meanwhile, all ICH patients with hemiparesis/hemiplegia should receive intermittent pneumatic compression from the first day of admission, until the highest-level evidence for standardization of the prophylaxis and acute management of DVT is obtained.

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