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Letter to the Editor

Anticoagulant approach in COVID-19 patients with cerebral venous thrombosis

We appreciate Klein et al.[1] for reporting the case of cerebral venous thrombosis accompanied by hemorrhagic infarct in a young patient with novel coronavirus disease 2019 (COVID-19). The reporting of such a case would raise the awareness on the possibility for the occurrence of cerebral venous thrombosis during the course of COVID-19, especially among the young adults present with COVID-19 and neurological symptoms.

However, we would like to complement the discussion by Klein et al. regarding the anticoagulant approach in COVID-19 patients with cerebral venous thrombosis. Though we agree with authors that both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) can be used in patients with COVID-19 associated venous thromboembolism during the acute period, the evidence appears to be stronger with LMWHs. To illustrate, in a 2017 Cochrane systematic review and meta-analysis[2] of 29 studies that compared LMWH with intravenous or subcutaneous UFH in over 10,000 patients with acute venous thromboembolism (deep vein thrombosis and/or pulmonary embolism), it was reported that LMWH at three months was associated with significantly fewer thrombotic complications (odds ratio [OR] = 0.70, 95% confidence interval CI 0.56−0.90), significantly improved thrombus regression (OR = 0.71, 95% CI 0.61−0.82), significantly reduced rates of major hemorrhage (OR = 0.69, 95% CI 0.5-0.95), and a non-significant reduction in mortality (4.8% versus 5.7%; OR = 0.84, 95% CI 0.70−1.01).

Specifically, in patients present with acute cerebral venous thrombosis, though with limited data available, the evidence thus far shows that LMWH may be more effective than UFH. In an open-label randomized controlled trial, 66 adults with cerebral venous thrombosis were randomly assigned to treatment with either UFH or LMWH[3]. It was reported that in-hospital mortality was significantly lower in the group randomized to LMWH compared to the group randomized to UFH (0% versus 19%). In addition, the proportion of patients with complete recovery at three months was greater for the group receiving LMWH (88% versus 63%), though the difference compared to the group receiving UFH was not statistically significant. Yet, in a case-control study, it was observed that significantly higher proportion of adult patients with cerebral venous thrombosis who received LMWH (n = 119) compared with UFH (n = 302) were independent at six months (adjusted odds ratio = 2.4, 95% CI 1.0−5.7), after adjustment of confounders.[4] Besides, treatment with LMWH was also associated with slightly lower rates of mortality (6% versus 8%) and new intracranial hemorrhage (10% versus 16%), though these outcomes were not significantly different between both treatment groups.

The efficacy of LMWH relative to UFH among patients with acute cerebral venous thrombosis accompanied by hemorrhagic stroke has been addressed in a subgroup analysis of a network meta-analysis which reported that LMWH demonstrated significantly lesser odds of intracranial and extracranial bleeding as compared to UFH (odds ratio = 0.4, 95% CI 0.16−0.97). Although not statistically significant, this network meta-analysis also suggested that patients treated with LMWH were more likely to obtain good recovery and lower mortality rate as compared to UFH after development of cerebral venous thrombosis.[5] It is also worth mentioning that the 2017 European Stroke Organization guidelines for the diagnosis and treatment of cerebral venous thrombosis,[6] endorsed by the European Academy of Neurology, recommended LMWHs at therapeutic dosage instead of UFH for the treatment of adult patients with acute cerebral venous thrombosis.

In conclusion, we believe, based on currently available evidence, that LMWH may worth a consideration before UFH due to better safety and efficacy as well as more predictable pharmacokinetic profile as compared to dose-adjusted UFH (in fact, the patient described by Klein et al. received treatment with LMWH),[7] though large trials may be needed to confirm its efficacy in COVID-19 patients with cerebral venous thrombosis relative to UFH. Nevertheless, we recognized that UFH may be better suited for the critically ill patients who may need surgery or other immediate invasive operations (for example, repeated lumbar puncture or planned surgery) as the activated partial thromboplastin time could return to normal within 1 h upon stopping UFH infusion and that LMWH can only partially be reversed by protamine sulfate compared to a full reversion of UFH.[8] It should also be noted that UFH is particularly the only parenteral anticoagulant that is safe to be used in patients with renal failure which makes UFH indispensable despite the superior efficacy and safety of LMWHs. Other circumstances where intravenous UFH is preferred include when anticoagulation is required in patients with obesity since possible poor

DOI of original article: http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2020.104989.
1052-3057/$ - see front matter

subcutaneous absorption with LMWHs is a concern among this patient population.

Declaration of Competing Interest

None.

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https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105222

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