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Despite a national campaign to promote early ambulation, sequential compression devices, and chemoprophylaxis, venous thromboembolic events (VTE), including deep venous thromboses and pulmonary emboli, pose a significant burden to most hospitalized patients, especially with poor mobility. As such, many surgical specialties have published randomized clinical trials to establish best practices in prophylactic unfractionated heparin (UFH) vs low-molecular-weight heparin (LMWH).[1-3] Unfortunately, neurosurgery for a myriad of reasons has been slow to adapt, although chemoprophylactic techniques are implemented in most, if not all, of our patients. Interest in comparing the two subcutaneous injections was recently revived with a meta-analysis in neurosurgical procedures[4] followed by a survey for spine operations.[5] The authors should be congratulated for publishing their findings, "Comparison of the safety of prophylactic anticoagulants after intracranial surgery."[6] The study presents a propensity score matching of prophylactic anticoagulants after intracranial surgery.

The authors have remarkably paired 203 cranial surgery patients with LMWH to 406 patients with UFH in a 1:2 ratio. The propensity score algorithm allows for assigning patients who may not have an exact matching double. This addresses the difficulty in traditional matched cohort studies that often restricts the study population size[7] – a difficulty that we encountered in our similarly paired study in chemoprophylaxis with spinal applications (currently in production). The author's matched data unveiled a statistically significantly higher incidence of intracranial hemorrhagic complications with LMWH without a benefit in prevention of VTE. These results echo one of the first reports of LMWH in cranial surgery: in 1998, Dickinson et al[8] randomized LMWH + sequential compression device to sequential compression device alone in patients requiring surgery for treatment of intracranial neoplasms. The study was terminated prematurely because of the 10% rate of intracranial hemorrhage in the LMWH cohort vs none in the sequential compression device alone cohort. While neurosurgeons were understandably suspicious of LMWH as a result of this study, an important counterargument did beg the question: Was the increased risk of intracranial hemorrhage unique to LMWH or a phenomenon true to any comparison cohort of chemoprophylaxis vs no pharmacological anticoagulant? Over 2 decades later, the authors of the current study have attempted a more modern approach with a more statistically nuanced analysis. The former scenario seems to hold true. Hemorrhagic complications are unique to LMWH itself. The smaller molecular structure of LMWH compared to UFH confers higher anti-Xa/anti-IIa ratios.[9] These biochemical properties permit nonspecific binding to body proteins and cell surfaces of the coagulation cascade (such as endothelia and platelets), which explains LMWH's greater efficacy against VTE as well as complication profile with intracranial hemorrhages.

As with any retrospective study, there are important potential confounders and hidden bias to consider when interpreting these findings. While propensity matching can help modulate the effect of potential confounders, this is dependent on the factors that are considered in the model. One of the biggest limitations of this study is that many factors that may be associated with the primary outcomes are not considered. Specific morbidities related to frailty as well as propensity to hemorrhage are not collected within the examined data set. Additionally, both the retrospective cohort arm as well as the meta-analysis are subject to a calendar time bias. Earlier operations may have utilized postoperative prophylactic UFH, whereas more recent operations may have preferred prophylactic LMWH. This poses

several problems. On one hand, newer developments in intraoperative hemostatic agents made a profound impact on the prevention of intracranial hemorrhage.[10] This would suggest that when controlling for these hemostatic agents, hemorrhagic complications would be even higher in the LMWH group. On the other hand, however, there may be potential bias based on the aggressiveness and extent of resection, especially in the more modern cases in this series which may increase the risk of intracranial hemorrhage. These operative nuances that affect the rates of intracranial hemorrhage were unlikely to be captured in the propensity score matching on "surgical procedure." Moreover, higher resolution in postoperative imaging modalities over the years may identify subtle hemorrhages in the more recent LMWH cohort compared to the earlier UFH cohort. The authors also failed to mention preoperative antithrombotic agents, which undoubtedly alter hemorrhage rates. As the number of patients with chronic medical conditions rises, more patients are taking antithrombotic drugs than in previous years.[11] And while Coumadin (Bristol Myers Squibb) prescriptions have fallen, the number of novel oral anticoagulants whose safety profile with intracranial hemorrhages has not been completely determined has increased.[12] In summary, the higher incidence of hemorrhagic complications may reflect a change in the landscape of medical and surgical practice, rather than a change from postoperative prophylactic UFH to LMWH over the past decades.

While this retrospective analysis is helpful, chemoprophylactic efficacy truly presides in a randomized clinical trial that would compare weight-based dosing in LMWH vs UFH in a select group of neurosurgical operations. But, as noted in the author's meta-analysis, the small difference in VTE between LMWH and UFH would require an impractically sized study population to adequately power such a randomized clinical trial. A large-scale study would entail a multi-center design with funding, which poses its own difficulties. Pharmaceutical companies may be apprehensive to support such a trial that may conclude that their drug was inferior to traditional UFH, or neurosurgeons may not trust studies fraught in monetary conflicts of interest with big pharma. In the end, our choice in chemoprophylactic technique may depend on the current body of evidence in the literature mixed with anecdotal experience unique to our individualized neurosurgical practice.

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