Letter to the Editor Regarding "Viscoelastic Hemostatic Assays and Outcomes in Traumatic Brain Injury: A Systematic Literature Review"

LETTER:

The world is currently facing a critical shortage of blood products.[1] The coronavirus disease 2019 (COVID-19) pandemic has led to supply chain disruptions, staffing shortages at donation centers, and shrinking donor populations, especially as traditional settings for blood drives (including workplaces and schools) have become less and less feasible.[2] Despite social distancing and shelter-in-place mandates, health care utilization and blood product requirements remain high during the pandemic, which may be due to disproportionately elevated rates of trauma and violence, at least in the United States.[3,4] The shortage has also been compounded by hospitals seeking to restore surgical services to prepandemic levels, rescheduling procedures that were deferred during recent surges of coronavirus variants.[5] The American Red Cross, which supplies 40% of the U.S. blood supply, reports that it has drastically limited its distribution, with some hospitals receiving only 1 in 4 of the blood products required.[6] Furthermore, it is unclear at this time how the dire humanitarian crisis unfolding in Ukraine will impact the global need for blood products in the future.[7]

In the midst of this shortage, neurosurgeons are uniquely positioned to serve as stewards of blood products, by advocating for evidence-based resuscitation and transfusion strategies and by leveraging their role in the health system to support sustainable policies for blood utilization, especially in the care of trauma patients.[8] Early evidence during the pandemic highlighted the continued demand for emergent neurosurgery, despite lockdowns, with a growing proportion of resources dedicated to acute neurosurgical pathology, including neurotrauma.[9,10] It is well known that injured patients, especially patients with traumatic brain injury (TBI), often present with coagulopathy.[11-13] However, despite long-standing research efforts, the pathophysiology of TBI-induced coagulopathy is not fully understood,[14] and as a result there is significant variability across centers in the management of coagulopathy after head injury,[15,16] with many institutions still maintaining liberal transfusion strategies.[17]

The evidence is becoming increasingly clear that transfusion should not be a one-size-fits-all approach, and broader use of viscoelastic hemostatic assays (VHAs) may pave the way for more tailored treatment paradigms for coagulopathy in neurosurgery.[18] The conventional coagulation assays (CCAs) commonly used to guide blood product usage monitor only clot initiation, failing to assess complex hemostatic pathways, and often appear normal even in the presence of coagulopathy.[19] In contrast, VHAs, including thromboelastography (TEG; Haemonetics SA, Signy, Switzerland) and rotational thromboelastometry (ROTEM; Werfen, Bedford, MA), offer more detailed information about hemostatic potential, measuring the initiation, amplification, propagation, and termination of clot formation.[20] The addition of platelet mapping to these assays also isolates the contribution of platelets to clot strength.[21] As a result, some centers have used VHAs to detect functional differences in coagulation among patients with hemorrhagic stroke, which were not identifiable on CCAs but appeared responsible for hematoma expansion in their respective series.[18,22-24]

In their recent systematic review, Shammassian et al.[25] summarize the available literature on VHAs and clinical outcomes in TBI, which they argue remains inconclusive to date. As the authors explain, the heterogeneity of published studies limits comparison of VHAs and CCAs beyond the scope of each individual analysis. Moreover, because the complexity of coagulation is often reduced in binary fashion to either presence or absence of coagulopathy, there is likely residual confounding that the studies included were not powered to overcome.[25] Nevertheless, this review aligns with prior ones highlighting early associations between abnormal VHA profiles and poor outcomes after TBI.[26] TEG parameters suggesting hypocoagulability have been associated with increased risk of requiring a neurosurgical procedure, greater length of stay in the hospital and intensive care unit, and greater risk of mortality.[27-29] Multiple centers have also used point-of-care VHAs to predict clinically significant progression of intracranial hemorrhage after TBI.[30-33]

Although the existing outcomes data for VHA use in TBI are not perfect, there is ample evidence that these assays still have significant potential for curbing wasteful utilization of blood products. In non-neurosurgical populations, VHAs have shown efficacy in diagnosing early coagulopathy and predicting transfusion requirements in trauma patients[34,35]; minimizing both perioperative blood loss and blood product consumption in lung transplantation[36]; and reducing transfusion requirements in cardiac surgery, generating substantial cost savings without compromising clinical outcomes.[37-39] Recent literature has shown similar promise for goal-directed transfusion among neurosurgical populations as well.[40] In adult spinal deformity surgery, ROTEM-guided therapy has enabled early identification of hypofibrinogenemia and reduced transfusion volumes (and transfusion-related costs).[41,42] In patients with TBI, goal-directed transfusion strategies using TEG have been shown to reduce platelet transfusion requirements, without worsening intracranial bleeding, need for neurosurgical re-intervention, length of stay, or mortality.[43-46] Our institutional experience has reaffirmed these findings: in a pragmatic interventional trial, a TEG-based protocol significantly reduced platelet transfusions without risking expansion of intracranial hemorrhage among elderly patients with TBI.[47]

Although more high-quality, prospective studies required to fully demonstrate the effect of VHAs on mortality and other clinical outcomes,[48] the evidence to date is encouraging that these assays can be used to identify coagulopathic states earlier and more precisely than CCAs[49,50] for the purposes of guiding transfusion. We encourage our colleagues to explore implementation of viscoelastic testing into standardized clinical pathways, not only for its cost-saving benefits,[51] but also to fulfill our collective responsibility to support judicious transfusion practices during this difficult period.[52] With no end in sight to this shortage, such scarce resources should not be used in vain.

Stephen P. Miranda, Connor Wathen, James M. Schuster, Dmitriy Petrov
Department of Neurosurgery, Perelman Center for Advanced Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA
To whom correspondence should be addressed: Stephen P. Miranda, M.D.
[E-mail: Stephen.Miranda@pennmedicine.upenn.edu]

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

https://doi.org/10.1016/j.wneu.2022.04.040.

REFERENCES

1. Al-Riyami AZ, Burnouf T, Wood EM, et al. International Society of Blood Transfusion survey of experiences of blood banks and transfusion services during the COVID-19 pandemic [e-pub ahead of print]. *Vox Sang*. https://doi.org/10.1111/vox.13256, accessed April 1, 2022.
2. Ngo A, Masel D, Cahill C, Blumberg N, Refaai MA. Blood banking and transfusion medicine challenges during the COVID-19 pandemic. *Clin Lab Med*. 2020;40:587-601.
3. Braun AL, Gorlin JB, Peters J, Murphy S, Van Buren NL. The effect of the SARS-CoV-2 pandemic and civil unrest on massive transfusion protocol activations in Minneapolis 2020. *Transfusion*. 2021;61:2250-2254.
4. Matthay ZA, Kornblith AE, Matthay EC, et al. The DISTANCE study: Determining the impact of social distancing on trauma epidemiology during the COVID-19 epidemic—an interrupted time-series analysis. *J Trauma Acute Care Surg*. 2021;90:700-707.
5. American College of Surgeons. Clinical Updates. Addressing the Blood Shortage: the Surgeon's Role in Patient Blood Management. Available at: https://www.facs.org/publications/bulletin-brief/081021/clinical. Accessed February 6, 2022.
6. American Red Cross. Worst Blood Shortage in Over a Decade. Available at: https://www.redcrossblood.org/donate-blood/dlp/red-cross-national-blood-shortage-crisis.html. Accessed February 6, 2022.
7. American Red Cross. American Red Cross Donates $10 Million for Ukraine Crisis Relief. Available at: https://www.redcross.org/about-us/news-and-events/news/2022/ukraine-red-cross-delivers-aid-to-families.html. Accessed April 4, 2022.
8. Saillant NN, Kornblith LZ, Moore H, et al. The national blood shortage—an impetus for change. *Ann Surg*. 2022;275:641-643.
9. Shao B, Tang OY, Leary OP, et al. Demand for essential nonambulatory neurosurgical care decreased while acuity of care increased during the coronavirus disease 2019 (COVID-19) surge. *World Neurosurg*. 2021;151:e523-e532.
10. Zhang M, Zhou J, Dirlikov B, Cage T, Lee M, Singh H. Impact on neurosurgical management in Level 1 trauma centers during COVID-19 shelter-in-place restrictions: the Santa Clara County experience. *J Clin Neurosci*. 2021;88:128-134.
11. Laroche M, Kutcher ME, Huang MC, Cohen MJ, Manley GT. Coagulopathy after traumatic brain injury. *Neurosurgery*. 2012;70:1334-1345.
12. Maegele M. Coagulopathy and progression of intracranial hemorrhage in traumatic brain injury: mechanisms, impact, and therapeutic considerations. *Neurosurgery*. 2021;89:954-966.
13. Moore EE, Moore HB, Kornblith LZ, et al. Trauma-induced coagulopathy. *Nat Rev Dis Primers*. 2021;7:30.
14. Zhang J, Jiang R, Liu L, Watkins T, Zhang F, Dong JF. Traumatic brain injury-associated coagulopathy. *J Neurotrauma*. 2012;29:2597-2605.
15. Bellapart J, Boots R, Fraser J. Physiopathology of anemia and transfusion thresholds in isolated head injury. *J Trauma Acute Care Surg*. 2012;73:997-1005.
16. Naidech AM. Anaemia and its treatment in neurologically critically ill patients: being reasonable is easy without prospective trials. *Crit Care*. 2010;14:149.
17. Huijben JA, van der Jagt M, Cnossen MC, et al. Variation in blood transfusion and coagulation management in traumatic brain injury at the intensive care unit: a survey in 66 neurotrauma centers participating in the collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Study. *J Neurotrauma*. 2018;35:323-332.
18. Yoh N, Sisti J, Connolly ES, Chang TR, Roh D. Can we utilize whole blood viscoelastic coagulation assays to better identify and treat coagulopathy in patients with intracerebral hemorrhage? *World Neurosurg*. 2021;147:217-219.
19. Davenport R, Manson J, De'Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med*. 2011;39:2652-2658.
20. Bradbury JL, Thomas SG, Sorg NR, et al. Viscoelastic testing and coagulopathy of traumatic brain injury. *J Clin Med*. 2021;10:5039.
21. Riojas CM, Ekaney ML, Ross SW, et al. Platelet dysfunction after traumatic brain injury: a review. *J Neurotrauma*. 2021;38:819-829.
22. Kawano-Castillo J, Ward E, Elliott A, et al. Thrombelastography detects possible coagulation disturbance in patients with intracerebral hemorrhage with hematoma enlargement. *Stroke*. 2014;45:683-688.
23. Roh D, Chang T, Zammit C, et al. Functional coagulation differences between lobar and deep intracerebral hemorrhage detected by rotational thromboelastometry: a pilot study. *Neurocrit Care*. 2019;31:81-87.
24. Roh D, Torres GL, Cai C, et al. Coagulation differences detectable in deep and lobar primary intracerebral hemorrhage using thromboelastography. *Neurosurgery*. 2020;87:918-924.
25. Shammassian BH, Ronald A, Smith A, Sajatovic M, Mangat HS, Kelly ML. Viscoelastic hemostatic assays and outcomes in traumatic brain injury: a systematic literature review. *World Neurosurg*. 2022;159:221-236.e4.
26. Cannon JW, Dias JD, Kumar MA, et al. Use of thromboelastography in the evaluation and management of patients with traumatic brain injury: a systematic review and meta-analysis. *Crit Care Explor*. 2021;3:e0526.
27. Kunio NR, Differding JA, Watson KM, Stucke RS, Schreiber MA. Thrombelastography-identified coagulopathy is associated with increased morbidity and mortality after traumatic brain injury. *Am J Surg*. 2012;203:584-588.
28. Rao A, Lin A, Hilliard C, et al. The utility of thromboelastography for predicting the risk of progression of intracranial hemorrhage in traumatic brain injury patients. *Neurosurgery*. 2017;64(CN_suppl_1):182-187.
29. Sixta SL, Cardenas JC, Kitagawa R, Wade CE, Holcomb JB, Cotton BA. Hypocoagulability in traumatic brain injury as measured by traditional means and thrombelastography. *J Neurol Neurophysiol*. 2015;6:1-5.
30. Connelly CR, Yonge JD, McCully SP, et al. Assessment of three point-of-care platelet function assays in adult trauma patients. *J Surg Res*. 2017;212:260-269.
31. He Q, Zhou Y, Liu C, et al. Prediction of hematoma expansion in patients with intracerebral hemorrhage using thromboelastography with platelet mapping: a prospective observational study. *Front Neurol*. 2021;12:746024.
32. Nekludov M, Bellander BM, Blombäck M, Wallen HN. Platelet dysfunction in patients with severe traumatic brain injury. *J Neurotrauma*. 2007;24:1699-1706.
33. Webb AJ, Brown CS, Naylor RM, Rabinstein AA, Mara KC, Nei AM. Thromboelastography is a marker for clinically significant progressive hemorrhagic injury in severe traumatic brain injury. *Neurocrit Care*. 2021;35:738-746.
34. Da Luz LT, Nascimento B, Shankarakutty AK, Rizoli S, Adhikari NK. Effect of thromboelastography (TEG) and rotational thromboelastometry (ROTEM) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. *Crit Care*. 2014;18:518.
35. Veigas PV, Callum J, Rizoli S, Nascimento B, da Luz LT. A systematic review on the rotational thrombelastometry (ROTEM) values for the diagnosis of coagulopathy, prediction and guidance of blood transfusion and prediction of mortality in trauma patients. *Scand J Trauma Resusc Emerg Med*. 2016;24:114.
36. Durila M, Vajter J, Garaj M, et al. Rotational thromboelastometry reduces blood loss and blood product usage after lung transplantation. *J Heart Lung Transplant*. 2021;40:631-641.

37. Whiting P, Al M, Westwood M, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2015;19:1-228. v-vi.

38. Fahrendorff M, Oliveri RS, Johansson PI. The use of viscoelastic haemostatic assays in goal-directing treatment with allogeneic blood products—a systematic review and meta-analysis. *Scand J Trauma Resusc Emerg Med*. 2017;25:39.

39. Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database Syst Rev*. 2016;2016: Cd007871.

40. Kvint S, Schuster J, Kumar MA. Neurosurgical applications of viscoelastic hemostatic assays. *Neurosurg Focus*. 2017;43:E9.

41. Buell TJ, Taylor DG, Chen CJ, et al. Rotational thromboelastometry-guided transfusion during lumbar pedicle subtraction osteotomy for adult spinal deformity: preliminary findings from a matched cohort study. *Neurosurg Focus*. 2019;46:E17.

42. Naik BI, Pajewski TN, Bogdonoff DI, et al. Rotational thromboelastometry-guided blood product management in major spine surgery. *J Neurosurg Spine*. 2015;23:239-249.

43. Furay E, Daley M, Teixeira PG, et al. Goal-directed platelet transfusions correct platelet dysfunction and may improve survival in patients with severe traumatic brain injury. *J Trauma Acute Care Surg*. 2018;85:881-887.

44. Furay EJ, Daley MJ, Satarasinghe P, et al. Desmopressin is a transfusion sparing option to reverse platelet dysfunction in patients with severe traumatic brain injury. *J Trauma Acute Care Surg*. 2020;88:80-86.

45. Holzmacher JL, Reynolds C, Patel M, et al. Platelet transfusion does not improve outcomes in patients with brain injury on antiplatelet therapy. *Brain Inj*. 2018;32: 325-330.

46. Rimaitis M, Bilskienė D, Tamošuitis T, Vilcinis R, Rimaitis K, Macas A. Implementation of thromboelastometry for coagulation management in isolated traumatic brain injury patients undergoing craniotomy. *Med Sci Monit*. 2020;26: e922879.

47. Kumar MA, Kvint S, Gutierrez A, et al. A thromboelastography platelet mapping—guided reversal algorithm limits platelet transfusion in older patients with traumatic brain injury: a pilot study. *Neurocrit Care*. 2019;31:S171.

48. Maegele M, Schöchl H, Menovsky T, et al. Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management. *Lancet Neurol*. 2017;16:630-647.

49. Gratz J, Güting H, Thorn S, et al. Protocolised thromboelastometric-guided haemostatic management in patients with traumatic brain injury: a pilot study. *Anaesthesia*. 2019;74:883-890.

50. Schöchl H, Solomon C, Traintinger S, et al. Thromboelastometric (ROTEM) findings in patients suffering from isolated severe traumatic brain injury. *J Neurotrauma*. 2011;28:2033-2041.

51. Bainbridge FJ, Sinha R, Tocchetti R, et al. Introduction of point-of-care ROTEM testing in the emergency department of an Australian level 1 trauma centre and its effect on blood product use. *Emerg Med Australas*. 2021;33:893-899.

52. Ranucci M. Bank blood shortage, transfusion containment and viscoelastic point-of-care coagulation testing in cardiac surgery. *Br J Anaesth*. 2017;118: 814-815.