## **EDITORIAL**

# No Safety Concerns Over Transfusion of Red Blood Cell Concentrates in Patients With Intracerebral Hemorrhage

David J. Seiffge D, MD

Ithough treatment of acute ischemic stroke makes huge progress adding and expanding the beneficial effects of mechanical thrombectomy<sup>1,2</sup> and intravenous thrombolysis<sup>3</sup> to a steadily growing number of patients, treatment and outcome of intracerebral hemorrhage (ICH) remains often frustratingly stagnating.

### See Article by Poyraz et al.

Research in acute treatment of ICH has taught us that this is a complex disease involving different treatment targets in the acute phase, including prevention of hematoma expansion, reduction of hematoma volume, and mitigating secondary brain damage.<sup>4,5</sup> Secondary brain damage summarizes a wide spectrum of potential mechanisms including a supposed "perihemoghic penumbra."

Anemia was found to be associated with poor outcomes in patients with ICH in different independent observational studies.<sup>6–8</sup> Although the exact mechanism is not clear—increased rate of hematoma expansion, oxygen deprivation in the penumbra, or overall surrogate for severe comorbidity—this represents a potential therapeutic target. However, data on this topic are sparse.

In the current issue of the *Journal of the American Heart Association (JAHA)*, Poyraz and colleagues<sup>9</sup> investigated the association between anemia, red blood cell transfusion, and outcomes in a cohort of 587 consecutive patients with nontraumatic ICH. During the study period, patients were treated according to international guidelines with conservative hemoglobin thresholds for transfusion. The first surprising finding was that 15% of all patients received any red blood cell transfusion during hospitalization. Most patients received multiple transfusions, and the median number of transfusions per patient was 3. This number is high considering that the median hematoma volume was just about 15 mL and ICH does not cause sufficient blood loss causing anemia. This high need for red blood cell transfusions points toward severe comorbidities in this patient group expressed by higher ICH scores and medical disease severity in this study. The second finding was that although patients receiving red blood cell transfusions had more complications (64.8% versus 35.9%), there was no association between transfusion and complications in multivariate regression models adjusting for relevant confounders (adjusted odds ratio [aOR], 0.71 [95% CI, 0.42-1.20]). Finally, again after adjusting for confounders, there was no significant association between transfusion and mortality (aOR, 0.87 [95% CI, 0.45-1.66]) or poor discharge functional outcome (aOR, 2.45 [95% CI, 0.80-7.61]). Poyraz and colleagues should be complimented for their study, which adds to the growing body of evidence surrounding the role of hemoglobin levels, anemia, and outcomes in patients with ICH.

Key Words: Editorials 
anemia 
hematoma expansion 
intracerebral hemorrhage 
outcome 
red blood cell transfusion

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: David J. Seiffge, MD, Department of Neurology, Inselspital University Hospital Bern and University of Bern, Freiburgstrasse, Bern 3010, Switzerland. Email: david.seiffge@insel.ch

This manuscript was sent to Luciano A. Sposato, MD, MBA, FRCPC, Associate Editor, for editorial decision and final disposition. For Disclosures, see page 2.

<sup>© 2023</sup> The Author. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

It is reassuring to see that there seem to be no safety concerns regarding red blood cell transfusions in patients with ICH. Lessons from platelet transfusions in patients with antiplatelet-associated ICH<sup>10</sup> raised potential safety concerns in the past. One fundamental difference between platelet infusions in the PATCH (Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Hemorrhage Associated With Antiplatelet Therapy) trial and red blood cell transfusion in this study is timing, as platelet transfusions were given in the hyperacute phase, while the median delay between ICH onset and red blood cell transfusion was 3 days in this study. This delay between hemorrhage onset to red blood cell transfusion points toward potential complications during the acute hospitalization requiring treatment. The major strength of this study was the granularity of data on timing of transfusion and complications, allowing a balanced and informed analysis of the association.

The remaining question is: Does red blood cell transfusion improve outcomes in patients with ICH and clinically significant anemia or with low hemoglobin levels? The study was underpowered to find a potential beneficial effect. Further, functional outcome was measured at discharge, that is, a few days after onset, which seems too early to assess outcomes in patients with ICH.<sup>11</sup> Most importantly, this study opens the door to conduct further studies in the acute setting given the lack of safety issues found in this article. There is still much to do to improve outcome in patients with ICH. Poyraz and colleagues help us to better understand the complexity of the problem and inform future research.

#### **ARTICLE INFORMATION**

#### Affiliation

Department of Neurology, Inselspital University Hospital Bern and University of Bern, Bern, Switzerland.

#### **Disclosures**

None.

#### REFERENCES

- Alemseged F, Nguyen TN, Coutts SB, Cordonnier C, Schonewille WJ, Campbell BCV. Endovascular thrombectomy for basilar artery occlusion: translating research findings into clinical practice. *Lancet Neurol.* 2023;22:330–337. doi: 10.1016/S1474-4422(22)00483-5
- Fayad P. Improved prospects for thrombectomy in large ischemic stroke. N Engl J Med. 2023;388:1326–1328. doi: 10.1056/NEJMe2300193
- Tsivgoulis G, Katsanos AH, Sandset EC, Turc G, Nguyen TN, Bivard A, Fischer U, Khatri P. Thrombolysis for acute ischaemic stroke: current status and future perspectives. *Lancet Neurol.* 2023;22:418–429. doi: 10.1016/S1474-4422(22)00519-1
- Puy L, Parry-Jones AR, Sandset EC, Dowlatshahi D, Ziai W, Cordonnier C. Intracerebral haemorrhage. *Nat Rev Dis Primers*. 2023;9:14. doi: 10.1038/s41572-023-00424-7
- Hostettler IC, Seiffge DJ, Werring DJ. Intracerebral hemorrhage: an update on diagnosis and treatment. *Expert Rev Neurother*. 2019;19:679– 694. doi: 10.1080/14737175.2019.1623671
- Acosta JN, Leasure AC, Kuohn LR, Both CP, Petersen NH, Sansing LH, Matouk CC, Testai F, Langefeld CD, Woo D, et al. Admission hemoglobin levels are associated with functional outcome in spontaneous intracerebral hemorrhage. *Crit Care Med.* 2021;49:828–837. doi: 10.1097/ CCM.0000000000004891
- Diedler J, Sykora M, Hahn P, Heerlein K, Schölzke MN, Kellert L, Bösel J, Poli S, Steiner T. Low hemoglobin is associated with poor functional outcome after non-traumatic, supratentorial intracerebral hemorrhage. *Crit Care*. 2010;14:R63. doi: 10.1186/cc8961
- Roh DJ, Albers DJ, Magid-Bernstein J, Doyle K, Hod E, Eisenberger A, Murthy S, Witsch J, Park S, Agarwal S, et al. Low hemoglobin and hematoma expansion after intracerebral hemorrhage. *Neurology*. 2019;93:e372–e380. doi: 10.1212/WNL.000000000007820
- Poyraz FC, Boehme A, Cottarelli A, Eisler L, Elkind MSV, Ghoshal S, Agarwal S, Park S, Claassen J, Connolly ES, et al. Red blood cell transfusions are not associated with incident complications or poor outcomes in intracerebral hemorrhage patients. *J Am Heart Assoc.* 2023;12:e028816. doi: 10.1161/JAHA.122.028816
- Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, Majoie CB, Beenen LF, Marquering HA, Vermeulen M, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet*. 2016;387:2605–2613. doi: 10.1016/S0140-6736(16)30392-0
- Shah VA, Thompson RE, Yenokyan G, Acosta JN, Avadhani R, Dlugash R, McBee N, Li Y, Hansen BM, Ullman N, et al. One-year outcome trajectories and factors associated with functional recovery among survivors of intracerebral and intraventricular hemorrhage with initial severe disability. *JAMA Neurol.* 2022;79:856–868. doi: 10.1001/ jamaneurol.2022.1991