2. Evaniew N, Files C, Smith C, et al. The fragility of statistically significant findings from randomized trials in spine surgery: a systematic survey. *Spine J*. 2015;15:2188–2197.

DOI: 10.1213/ANE.0000000000001747

In Response

Postoperative Cognitive Dysfunction and the Change of Regional Cerebral Oxygen Saturation in Elderly Patients Undergoing Spinal Surgery

We thank Grocott for his interest in our recent article.[1] We agree with his concern regarding the marginal statistical meaning of our study. However, we already noted that the distribution of regional cerebral oxygen saturation (rSO_2) data was wide and skewed (mean and standard deviation of T60 are 122.9 and 119.4, respectively), and the time unit of the odds ratio (OR) is "minute." If the duration of rSO_2 <60% in a population would be more than 120 minutes, the OR would be almost doubled.

In addition, although our study was not a large-scale design, we did observe a statistically significant association between the duration of decline in rSO_2 and the development of postoperative cognitive dysfunction (POCD) with a fairly narrow confidence interval (Table).

In regard to the multiplicity, we stated that "As an earlier assumption was based on a previous study, we used an arbitrary cutoff value of 60%." In the initial design of this study, our sample size calculation was based on a previous study[2] addressing the relationship between POCD and rSO_2 in patients undergoing thoracic surgery (extensive surgery). At that time, we could not find any other appropriate references that would encompass elderly patients undergoing extensive surgeries. In that study,[2] a cutoff of 60% was identified as exhibiting the highest OR for developing POCD, so we calculated the sample size based on that threshold. Therefore, our use of a 60% cutoff was a priori and not post hoc. To be more discrete, we had further analyzed 55% and 50%. Considering statistical multiplicity, the duration of decline in rSO_2 <60% is 0.042 with Bonferroni adjustment. The statistical significance does not change after conservative statistic correction.

Grocott also mentioned about "statistically fragility." Fragility index is a measure of the robustness (or fragility) of the results of a randomized controlled trial.[3] This index helps to identify the number of events required to change statistically significant results to nonsignificant results. Basically, it cannot be applied to a continuous variable such as the duration of rSO_2. Our study was designed as an observational study and not as a randomized controlled trial.

Notwithstanding the mentioned concerns, we clearly stated in our manuscript "Considering the relatively low OR of the duration of rSO_2 <60%, it is also possible that our results may merely indicate a weak correlation between rSO_2 and POCD." However, we found evidence that more extensive surgeries lead to POCD more often, but evidence regarding the relationship between POCD and rSO_2 in elderly patients undergoing extensive surgeries is scarce at best. Thus, we believe that the novelty of the current study lies in our addressing the missing evidence, especially that regarding elderly patients.

Table. Multiple Logistic Regression Model (Diabetes + the Duration of rSO_2 <60%)

Unit (min)	Odds Ratio (95% Confidence Interval)
60	1.396 (1.070–1.821)
90	1.649 (1.106–2.456)
120	1.948 (1.144–3.314)

Abbreviation: rSO_2, regional cerebral oxygen saturation.

Jeongmin Kim, MD, PhD
Jae-Kwang Shim, MD, PhD
Jong Wook Song, MD, PhD
Young Lan Kwak, MD, PhD
Department of Anesthesiology and Pain Medicine
Severance Hospital, Anesthesia and Pain Research Institute
Yonsei University College of Medicine
Seoul, Republic of Korea
ylkwak@yuhs.ac

REFERENCES

1. Kim J, Shim JK, Song JW, Kim EK, Kwak YL. Postoperative cognitive dysfunction and the change of regional cerebral oxygen saturation in elderly patients undergoing spinal surgery. *Anesth Analg*. 2016;123:436–444.
2. Tang L, Kazan R, Taddei R, Zaouter C, Cyr S, Hemmerling TM. Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction. *Br J Anaesth*. 2012;108:623–629.
3. Walsh M, Srinathan SK, McAuley DF, et al. The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index. *J Clin Epidemiol*. 2014;67:622–628.

DOI: 10.1213/ANE.0000000000001741

If the Goal Is Balance, Why Not Fresh Frozen Plasma?

To the Editor

I recently read Mitrophanov et al's[1] article comparing in vitro thrombin generation in diluted plasma treated with various anticoagulant and procoagulant factors. The authors' work is timely and helps to demonstrate in an in vitro model what has been observed clinically with increasing frequency, the potential for serious thrombotic complications when procoagulant factors are administered off-label without careful consideration for the existing anticoagulant-procoagulant balance.

One of the major findings of the study was that treatment of diluted plasma with simulated 3-factor prothrombin complex concentrate (PCC) and antithrombin-3 (AT3) restores in vitro thrombin generation to a baseline pattern, whereas the administration of simulated 4-factor PCC without AT3 increases peak thrombin generation and endogenous thrombin potential above baseline predilution values.

PCCs have been used off-label with increasing frequency in a variety of settings including cardiac surgery and major trauma. A recent study from members of the Food and Drug Administration suggested that PCC administration is associated with a 7-fold increase in the risk of same or next day thromboembolism.[2] There are

potential advantages of PCC compared with fresh frozen plasma (FFP) including reduced infectious disease transmission, more rapid correction of procoagulant factor levels, and reduced risk of transfusion-associated lung injury that occurs in up to 1.3% of transfused perioperative patients.[3] However, high-level evidence supporting off-label PCC use is lacking and indiscriminate use can cause harm.

On the basis of the study's findings, the authors suggest that the administration of PCC with AT3 might be a "promising" approach. However, if restoration of the anticoagulant-procoagulant balance is a major goal of hemostatic resuscitation, it is unclear what significant advantage PCC-AT3 therapy would have over FFP transfusion. FFP contains all anticoagulant and procoagulant factors, restores plasma volume in patients with ongoing hemorrhage, and is cheaper than PCC-AT3. FFP may also have other beneficial properties in hemorrhage including restoration of the normal glycocalyx and reduction in inflammation.[4,5]

Michael Mazzeffi, MD, MPH
Department of Anesthesiology
University of Maryland School of Medicine
Baltimore, Maryland
mmazzeffi@anes.umm.edu

REFERENCES

1. Mitrophanov AY, Szlam F, Sniecinski RM, Levy JH, Reifman J. A step toward balance: thrombin generation improvement via procoagulant factor and antithrombin supplementation. *Anesth Analg*. 2016;123:535–546.
2. Ekezue BF, Sridhar G, Ovanesov MV, et al. Clotting factor product administration and same-day occurrence of thrombotic events, as recorded in a large healthcare database during 2008-2013. *J Thromb Haemost*. 2015;13:2168–2179.
3. Clifford L, Jia Q, Subramanian A, et al. Characterizing the epidemiology of postoperative transfusion-related acute lung injury. *Anesthesiology*. 2015;122:12–20.
4. Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesth Analg*. 2011;112:1289–1295.
5. Potter DR, Baimukanova G, Keating SM, et al. Fresh frozen plasma and spray-dried plasma mitigate pulmonary vascular permeability and inflammation in hemorrhagic shock. *J Trauma Acute Care Surg*. 2015;78:S7–S17.

DOI: 10.1213/ANE.0000000000001759

In Response

We are grateful to the correspondent for his interest and comments on our work.[1] Fresh frozen plasma (FFP) transfusions are a mainstay of trauma care and a standard procedure in cases of hemorrhage that may be complicated by coagulopathy. They constitute a part of the widely accepted resuscitation paradigm, according to which plasma, platelets, and red blood cells are administered to trauma patients at a 1:1:1 ratio. Yet, as pointed out by the correspondent, FFP has its limitations and undesirable side effects. The side effects include significant hemodilution and risk of transfusion reactions. Given that FFP contains approximately 1 IU/mL of clotting factors, it requires transfusion of approximately 20 to 50 times more volume than either prothrombin or antithrombin concentrates.

The use of prothrombin complex concentrates (PCCs) to improve the clotting ability of blood in surgical and trauma patients is a rapidly evolving approach that may provide an alternative to FFP. The value of this alternative rests in the potential advantages offered by PCC use, some of which have been mentioned by the correspondent. PCCs do not have the detrimental side effects of FFP such as multiple organ failure[2] and transfusion-associated circulatory overload.[3] During FFP preparation and handling, coagulation factors become diluted and partially deactivated (eg, factor VIII can lose up to 40% of its activity[4]), which may increase the required transfusion volume. If major bleeding is controlled surgically, with a tourniquet, or via hemostatic dressings, then transfusion of partially deactivated/diluted clotting factors beyond a certain level contributes more to circulatory overload than to coagulopathy reversal. Together with the inconvenience of blood-type matching and thawing/warming needed for FFP, this complication justifies a search for alternative solutions. Comparison of the costs of PCCs with those of FFP was not a focus of our work. Nevertheless, some studies suggest that the total costs of allogenic blood products are often underestimated and that the overall cost of hemostatic therapy can be reduced by using PCCs.[5]

The efficacy and safety of a PCC are expected to depend on its clotting factor composition.[5] Although numerous PCC products with different compositions exist, no single composition has been recognized as preferred or optimal. This uncertainty, combined with the currently heightened interest in PCCs, motivated us to conduct our study.[1] Because we did not use any actual PCC products, we did not compare any PCCs currently on the market or the effects of PCCs with those of FFP. Our study investigated the effects of combined procoagulant and anticoagulant protein administration on thrombin generation reduced by plasma dilution. The overall implication of our results is that blood coagulation in coagulopathy can be improved in a more balanced way when the therapeutic intervention is itself balanced. In the context of our study, by "balanced intervention," we mean an intervention that combines procoagulant factors with equally (or at least comparably) strong anticoagulant factors.[1] Although this is not yet achieved in existing PCC formulations,[5] their compositions can be adjusted to accommodate this concept. This flexibility is another general advantage of PCCs. Further studies are certainly warranted to determine the best approach to coagulopathy correction.

Disclaimer

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Army or the US Department of Defense. This correspondence has been approved for public release with unlimited distribution.

Funding: This work was supported by the US Army Network Science Initiative, US Army Medical Research and Materiel Command, Ft. Detrick, MD.

Alexander Y. Mitrophanov, PhD
DoD Biotechnology High Performance Computing Software Applications Institute
Telemedicine and Advanced Technology Research Center
US Army Medical Research and Materiel Command
Ft. Detrick, Maryland
Fania Szlam, MMSc
Roman M. Sniecinski, MD
Department of Anesthesiology
Emory University School of Medicine
Atlanta, Georgia
Jerrold H. Levy, MD
Departments of Anesthesiology and Surgery
Duke University School of Medicine
Durham, North Carolina
Jaques Reifman, PhD
DoD Biotechnology High Performance Computing Software Applications Institute
Telemedicine and Advanced Technology Research Center
US Army Medical Research and Materiel Command
Ft. Detrick, Maryland

REFERENCES

1. Mitrophanov AY, Szlam F, Sniecinski RM, Levy JH, Reifman J. A step toward balance: thrombin generation improvement via procoagulant factor and antithrombin supplementation. *Anesth Analg*. 2016;123:535–546.
2. Watson GA, Sperry JL, Rosengart MR, et al; Inflammation and Host Response to Injury Investigators. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma*. 2009;67:221–227.
3. Li G, Rachmale S, Kojicic M, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. *Transfusion*. 2011;51:338–343.
4. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, et al; British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol*. 2004;126:11–28.
5. Grottke O, Levy JH. Prothrombin complex concentrates in trauma and perioperative bleeding. *Anesthesiology*. 2015;122:923–931.

DOI: 10.1213/ANE.0000000000001763

Global Health for the Global North?

To the Editor

It was with great interest that I read last year about the development of a new Global Health section in the Journal including Global Health Reports in *A&A Case Reports*.[1] The recent editorial further confirmed this commitment and the Journal's support for authors from low- and middle-income countries (LMICs).[2] Accessing good-quality anesthetic research relevant to those practicing in LMICs is challenging, and the Journal should be commended on recognizing that global anesthesia is a subject area of increasing importance.

It was therefore with much frustration that I realized that the articles relevant to global health are unable to be read by those most affected by the research because they are behind a paywall. Practitioners working in LMICs are almost certainly unable to afford the subscription fee to the Journal nor the individual article access cost. It is therefore disappointing that the Journal has chosen to restrict access to these useful and important articles. Although the Hinari program set up by the World Health Organization does enable some of those in low-income settings to access the major journals for free, the vast majority of anesthetists working at health centers and hospitals throughout low-income countries do not work in institutions eligible for Hinari subscriptions.[3] Other journals, for example, *The Lancet*, have overcome this problem by making many of their global health articles open access, thus ensuring their commitment to disseminating relevant research as widely as possible.

Too often global health issues are discussed amongst academic institutions and at conferences in high income countries, and fail to engage with those actually working in resource poor settings. There can be no hope of influencing the practice of those working in LMICs if they are unable to access the research and articles published in the Journal. If *A&A* wishes to show its real commitment to global health, it might consider making the global health content of its journals open access, or is this just global health for the global north?

Victoria C. Howell, MPH
Department of Anaesthesia
CCBRT Disability Hospital
Dar es Salaam, Tanzania
vhowell@doctors.org.uk

REFERENCES

1. Walker IA, Shafer SL. The World Federation of Societies of Anaesthesiologists, International Anesthesia Research Society, and Anesthesia & Analgesia: a shared global vision. *Anesth Analg*. 2015;120:721–724.
2. Pittet JF, Vetter TR. Continuing the terra firma and establishing a new EQUATOR for Anesthesia & Analgesia. *Anesth Analg*. 2016;123:8–9.
3. World Health Organization. Hinari access to research for health programme. Available at: http://www.who.int/hinari/en/. Accessed July 15, 2016.

DOI: 10.1213/ANE.0000000000001767

In Response

I am most grateful to Dr. Howell for raising a very important topic, that is, access to *Anesthesia & Analgesia* (*A&A*) for colleagues who work in low- and middle-income countries (LMICs).[1] With the development of the new Global Health Section, this becomes even more relevant. We take this issue seriously at *A&A* and will be taking several steps to ensure improved access for our readers in LMICs.

An important item to note is that *A&A* is "Open Archive." This means that 1 year from the date of publication, all articles in *A&A* become freely available to readers. This information is often not well known. Keeping this in mind, we then need to deal with the availability of articles in the first year after publication. As Howell points out,[1] articles can be published "Open Access." This is a choice made by the authors in which they retain the copyright and are willing to pay the costs of publication. Relatively few authors choose to do this because of the cost.

Journals can choose to publish articles with "Free Access." This means that the article is freely available to all