Can J Anesth/J Can Anesth (2020) 67:388–389
https://doi.org/10.1007/s12630-019-01510-9

CORRESPONDENCE

In reply: Erythropoietin and iron: separating the builder from his blocks

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Received: 1 October 2019 / Revised: 1 October 2019 / Accepted: 3 October 2019 / Published online: 21 October 2019
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To the Editor,

We appreciate the opportunity to respond to the insightful comments by Abeysiri *et al.*[1] We agree that the hormone erythropoietin (EPO) can be considered the "builder of red blood cells (RBCs)" and that "iron is a substrate for hemoglobin" which provides the foundation for the oxygen-carrying capacity of the RBC. Thus, the active hormone or "builder" acts together with the iron "building blocks" to produce optimal erythropoiesis and minimize RBC transfusion in the setting of acute surgical blood loss.

Although we did not comment on iron status in our initial analysis, this information is important to the reported findings. Upon re-review of the manuscripts included in our review, 19 of the 25 (76%) reported iron status, with six of the 19 (32%) showing evidence of iron deficiency (i.e., low ferritin and/or transferrin saturation) (eTable, available as Electronic Supplementary Material). Interestingly, iron deficiency was an exclusion criterion in seven of the 25 (28%) studies, indicating that the purpose of therapy was not to treat iron deficiency, but rather to optimize blood management. Abeysiri *et al.* correctly point out that inclusion of studies that assess the impact of iron therapy in patients without iron deficiency may provide a source of confounding.[1] Many of the studies included patients that were not iron deficient; in these patients, iron therapy would not likely impact erythropoiesis or RBC transfusion. By contrast the addition of exogenous EPO would be expected to boost erythropoiesis, above physiologic levels, and have higher likelihood of impacting RBC transfusion avoidance.

Indeed, this was one of the important findings of our systematic review—i.e., exogenous EPO plus iron *vs* iron alone augmented erythropoiesis (elevated reticulocyte count 170% *vs* 1% increase), increased postoperative hemoglobin (increased by 9.0 $g \cdot L^{-1}$; 95% confidence interval [CI], 6.6 to 11.4), and reduced the incidence of RBC transfusion (relative risk 0.57; 95% CI, 0.46 to 0.71).[2] This may inform the optimal treatment of the surprisingly large proportion of patients (approximately 30%) who are anemic prior to undergoing elective surgery.[3] Many of these patients are iron deficient, and therefore may benefit from iron alone. In this setting, the endogenous EPO "builder" will be given adequate "building blocks" for erythropoiesis. By contrast, patients with iron-restrictive anemia, and possibly those with pure iron deficiency, may further benefit from the addition of a team of builders (i.e., pharmacological doses of exogenous EPO), that can more efficiently assemble the building blocks for optimal erythropoiesis. In addition, concerns of thrombosis with the use of exogenous EPO are accentuated by inadequate iron stores, highlighting the need for optimally bioavailable iron (i.e., intravenous iron) when utilizing exogenous EPO.[4]

From the perspective of current guidelines, based on expert opinion, patients with diagnosed iron deficiency (i.e., low ferritin and transferrin saturation) should be treated with iron alone (oral or intravenously) while patients with anemia of inflammation or chronic disease (e.g., sequestration of iron stores) would benefit from EPO

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12630-019-01510-9) contains supplementary material, which is available to authorized users.

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plus iron as the optimal therapy.[5] While these guidelines are reasonable, they are not based on outcome data from large randomized-controlled trials. Furthermore, existing data do not systematically assess the potential added value (or risk) of EPO in patients with a clear diagnosis of iron deficiency, nor the actual benefit of EPO in cases of iron-restricted anemia. We have therefore proposed the HOPE-Hb (clinicaltrials.gov; NCT03528564) study to address this issue. With the results of the completed PREVENTT trial (NCT01692418) and ongoing ITACS trial (NCT02632760), we will soon have valuable information about the efficacy of optimal intravenous iron infusion on perioperative outcomes in surgical patients. These data will further inform the need for ongoing studies that will assess the added benefit of EPO in addition to optimal intravenous iron infusion in anemic patients undergoing elective surgery.

Conflicts of interest None declared.

Editorial responsiblity This submission was handled by Dr. Hilary P. Grocott, Editor-in-Chief, *Canadian Journal of Anesthesia.*

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