



Not all anemia is solely due to iron deficiency

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Heinrich and Loop (1) recently commented our study on the ultra-short term combination treatment of anemia and iron deficiency in patients undergoing cardiac surgery (2). They discussed whether such treatment might be an option in lung cancer surgery and came to the conclusion that the optimal approach in lung cancer surgery would be to treat preoperative anemia (without specifying by which means) and to administer intravenous iron in patients with a higher risk of severe postoperative anemia such as following neo-adjuvant chemotherapy or pneumonectomy. In their imagination, this makes sense, since they initially state “iron deficiency seems to be the commonest cause of anemia in the surgical population”. Two things are important to note in regard to their argument: First, their reference of Klein *et al.*, is not at all about iron deficiency but on the impact of anemia prior to cardiac surgery (3). Secondly, the assumption that because iron deficiency is the most common cause of anemia in the surgical population and cancer patients are often anemic, iron deficiency must also be the most common cause in cancer patients, is a syllogistic fallacy.

On a world-wide basis, iron deficiency anemia is indeed the most prevalent type of anemia (4). In surgical populations iron deficiency anemia as well as isolated iron deficiency are associated with increased morbidity and mortality (5,6). However, not all anemia is solely due to iron deficiency. In patients with cancer, the most common type of anemia is anemia of inflammation as recently described by Weiss *et al.* (7). The main mechanisms that finally result in anemia in this type of anemia are: (I) iron deficiency

or reduced iron availability resulting in iron-restricted erythropoiesis, (II) reduced erythropoietin response to anemia, (III) reduced erythroid cell differentiation upon erythropoietin stimulation and (IV) a shortened red blood cell life span. Since iron availability is reduced and at the same time the erythropoietin response and erythropoietin efficacy are blunted, Weiss *et al.* propose a “combination of iron therapy and erythropoiesis-stimulating agents” in such patients (7). Combining intravenous iron and subcutaneous erythropoietin thus may not only be an option but maybe the key to success in patients with anemia of inflammation.

Treating preoperative anemia in patients undergoing lung cancer surgery is important since anemia has repeatedly been shown to be a major risk factor for mortality (8) and red cell transfusions (8) which additionally increase mortality (9). Obviously, the only way out is the treatment of preoperative anemia and erythropoietin will often be part of such treatment (7). Unfortunately, there are concerns regarding the administration of erythropoietin with a number of physicians. However, preoperatively we are administering a single dose of erythropoietin and in numerous meta-analyses preoperative use of erythropoietin has been shown to be highly efficacious and not associated with side effects (10-12): in the perioperative setting, erythropoiesis-stimulating agents successfully reduce blood transfusions without increasing the risk of 45-day mortality, acute myocardial infarction, bowel ischemia, acute kidney injury or thromboembolic events (11). In the critical care setting, a meta-analysis of close to 1 million patients found the off-label use of erythropoiesis-stimulating agents to

be associated with a reduction mortality by a risk ratio of 0.76 (95% CI: 0.61 to 0.92). The same meta-analysis found no evidence of increased myocardial infarction, stroke, venous thromboembolism or any adverse events (12). While randomized trials are commonly not powered to adequately investigate safety profiles, these meta-analyses provide evidence on the safety and benefits of erythropoiesis-stimulating agents in the perioperative setting and in the critically ill patient.

Heinrich and Loop further question the transferability of a combination anemia treatment into lung cancer surgery. They doubt the necessity of such a treatment in light of an often 28-day long surgery preparation interval (1). While our study was a pragmatic approach to often time sensitive cardiac procedures, a longer preparation interval may actually improve patient outcomes by allowing more time for preoperative hemopoietic recovery. In this setting, anemia treatment may be tailored to the cause of anemia. Here however, erythropoiesis-stimulating agents are often also necessary, if e.g. anemia of inflammation is present (7).

In our original study, we analyzed the acquisition costs of red blood cells and combination drug treatment: Total costs were higher in the treatment (mean of 1,052±674 Swiss Francs) than in the placebo group (mean of 480±704 Swiss Francs) (2). In light of the total acquisition costs, Heinrich and Loop relinquish an U.S. Food and Drug Administration container label extension for red blood cell units that states the following contraindication: “Red-cell-containing components should not be used to treat anemias that can be corrected with specific hematinic medications such as iron, vitamin B12, folic acid, or erythropoietin.” (13). While resources may be sparse in current healthcare systems, we would advise to not neglect evidence-based recommendations for a mean saving of 572 Swiss Francs. Further, our study only estimated pure acquisition cost of a combination treatment or red blood cells. The systemic financial burden of blood transfusions is difficult to calculate, but has been estimated that transfused patients have a propensity matched mean higher total costs of \$1,777±36 per admission (14).

In a pragmatic way, patients undergoing major surgery resulting a red blood cell transfusion rate of ≥10% or with an expected blood loss of ≥500 mL need to be tested for hemoglobin concentration, ferritin, transferrin saturation, creatinine and C-reactive protein. With these simple laboratory data anemia and iron deficiency can be detected, the anemia broadly categorized and treated according to an algorithm. How this algorithm looks like in detail may be left to individual hospitals and incorporate the local drug

availability which varies significantly world-wide.

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Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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