



Preoperative treatment of anemia—could an ultra-short-term multimodal approach be beneficial for patients undergoing lung surgery?

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Lung cancer is the most common malignant neoplasm and the leading cause of cancer related death worldwide (1). Advances in treatment of patients with lung cancer have not significantly improved overall survival throughout the last decades (2,3). To increase the patients' benefit from lung surgery and to reduce intervention related morbidity and mortality, perioperative programs mainly addressing pulmonary complications have been established (4-6). As part of preoperative optimization the treatment of anemia moved more and more into the focus within in the last years. Preoperative anemia is not only the strongest risk factor for the need of perioperative red blood cell (RBC) transfusions in lung surgery patients (7). In a recently published meta-analysis of 23 studies with a total of 10,612 patients, preoperative anemia was identified as independent risk factor for a reduced overall survival after lung surgery (8). This is an important finding, as many cancer patients show reduced levels of hemoglobin (Hb) for a variety of reasons (9,10) and iron deficiency seems to be the commonest cause of anemia in the surgical population (11). Over the last decades perioperative RBC-transfusion was the standard approach to treat anemic conditions during operations. However, the knowledge about transfusion associated adverse patient outcomes has been increased throughout the last years. In non-cardiac surgical cohorts, blood transfusions were associated with an increased mortality,

prolonged hospitalization due to infections, sepsis and adverse effects in organ function (12). For specific lung cancer surgery cohorts, a meta-analysis showed a significant association between perioperative blood transfusion and worse clinical outcome (13).

In this context, the results of a recently published study investigating the efficacy of a short-term multimodal approach for the preoperative optimization of anemic patients prior to cardiac surgery are interesting (14). In a monocentric prospective randomized and double blinded setting, the authors evaluated an ultra-short-term multimodal approach for the treatment of anemic patients scheduled for cardiac surgery. The authors enclosed patients scheduled for cardiac surgery [coronary artery bypass grafting (CABG), valve surgery and combined procedures] with preoperative low hemoglobin levels according to established WHO criteria (female <120 g/L; male <130 g/L). The aim of the study was to compare a bundle consisting of single doses of subcutaneous erythropoietin (40,000 IU), intravenous iron (20 mg/kg), subcutaneous vitamin B12 and oral folate with placebo. The medication was administered as single shot at the day before surgery, or Friday if surgery was scheduled for Monday. The primary results of the study show a significantly decreased rate of RBC transfusions within the first 7 days in the treatment group (14).

Beside the pragmatic approach to address preoperative

anemia in cardiac surgery patients, this study raises some severe concerns regarding the applied methodology and transferability of the results to lung surgery patients. The first point to mention is the incidence of pre-operative anemia (around 25%), which is lower compared to other studies (up to 45%) (11). The difference may be explained by different comorbidity, which is indicated by a EuroSCORE below 5, representing patients with a medium risk. A second concern is that the study does only analyze the impact of the whole bundle of medication; the relative contribution of each component of the bundle remains unclear. Especially the preoperative use of erythropoietin (EPO) in cardiac surgery patients representing a high cardiovascular risk profile has to be discussed critically (15). In 2007 the Food and Drug Administration published a black box warning addressing the increased risk of mortality and nonfatal myocardial infarction, stroke, heart failure, and thrombosis especially when target hemoglobin levels exceeding 120 g/L. Except for single special indications, EPO for preoperative anemia treatment in various countries such in Germany is “off-label” use. A recently published meta-analysis including 32 trials with overall 4,750 mixed surgical patients showed a decreased rate of perioperative RBC-transfusion and no increased rate of thromboembolic complications (14). It will be interesting to see how the discussion about the indication areas of EPO develops against the background of the results of this meta-analysis. The study of Spahn and colleagues does not report of increased rates of adverse events related to the administered study medication. However, the study is not adequately powered to show such differences. Finally, the study also lacks of a precise anemia and iron deficiency diagnostic protocol to ensure the appropriate use of the preoperatively administered medication bundle.

Regarding the transferability of the results to lung surgery patients, some severe considerations have to be taken into account. In lung surgery, patients’ blood loss normally is below 500 mL consecutively the transfusion risk is below 10% and timing of surgery in lung cancer cases normally requires a 28-day interval (16). The benefit of applying a non-specific set of patient blood management measures to patients undergoing lung surgery is therefore questionable. Moreover, the study of Spahn and colleagues showed that combined costs of RBC-transfusions and administered preoperative drugs of the treatment group is more than twice as high compared to the RBC-transfusion costs in the placebo group. In the underlying

cardiac surgery study cohort, the mean reduction of RBC-transfusion in the treatment group within the first 7 days was 0.5 (1.9 *vs.* 2.4). Taken into account that the transfusion risk in lung surgery is much lower (below 10% *vs.* 45%), it is questionable whether a pretreatment in lung surgery patients would lead to the same reduction of RBC-transfusions. In the context of scarce financial resources of public healthcare systems, expressed in fixed case-related revenues, healthcare providers increasingly have to weigh up the costs and benefits of new treatments. With an estimated RBC-transfusion reduction of less than half a unit within 7 days and more than a doubling of the anemia treatment costs, a 1:1 transfer of the reported pre-surgery anemia treatment to lung surgery patients does not seem to make sense. Nonetheless an appropriate preoperative treatment to optimize perioperative risk factors is meaningful in lung surgery patients and includes the treatment of anemia. Whether these patients would be screened during oncological staging and anemia would be detected, abnormalities should be investigated and in case of iron deficiency treated ahead of surgical procedures with iron supplementation. However, an initial treatment with low dose oral iron may lead to a delayed timing of surgery. Therefore application of intravenous iron may be preferred for lung surgery patients with a higher risk of severe postoperative anemia (*i.e.*, neo-adjuvant, pneumonectomy *etc.*) (17-19). In conclusion, the important approach in lung surgery patients would be the detection and correction of iron deficiency, with or without anemia instead of unspecific expensive poly-pharmacological blind treatments with limited benefit for patients undergoing lung surgery.

Nevertheless, a few questions regarding the preoperative anemia treatment are still open and should be a target of clinical research:

- ❖ Which outcome data should be collected to describe evidence based multimodal approach to treat anemia preoperatively ahead of lung surgery?
- ❖ Which patient, who and where should be treated?
- ❖ Which diagnostic (iron) tests (*i.e.*, ferritin level) should be implemented and which levels of iron deficiency should be defined?
- ❖ Which drug should be recommended?
- ❖ What timing of surgery would be the best?

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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