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In Reply:

We do not believe that randomized controlled trials (RCTs) have shown similar outcomes with a restrictive transfusion strategy compared to a liberal one—this is true only at first sight.[1–3] Indeed, a deeper analysis of these trials indicates that the reality might not be so straightforward. Just to take the latest study on blood transfusions after cardiac surgery,[3] in which the conclusion based on the primary outcome was that a restrictive transfusion threshold was not superior to a liberal threshold, there were actually more deaths in the restrictive than in the liberal threshold group (4.2 *vs.* 2.6%; hazard ratio, 1.64; 95% CI, 1.00 to 2.67; $P = 0.045$).

Importantly, in these large RCTs, it is more than likely that there were patients in each arm who experienced benefit and others who were harmed. In other words, there will have been some patients who received a transfusion simply because they were randomized to the high threshold group, although in normal practice a transfusion would not have been considered; similarly, some patients at higher risk who would normally have been transfused will have received no transfusion because they were randomized to the low threshold group. This concept was highlighted by an analysis of the data from the landmark Canadian Transfusion Requirements in Critical Care study by Deans *et al.*,[4] showing that 30-day mortality rates were different and opposite in the liberal compared with the restrictive arm depending on the presence (21 *vs.* 26%) or absence (25 *vs.* 16%) of ischemic heart disease ($P = 0.03$).

The need for erythrocyte transfusion and the benefit/risk ratio vary according to individual patient characteristics, including age and comorbidities, so large-scale RCTs in heterogeneous groups of patients may not be the most appropriate tool to investigate these issues; smaller RCTs in carefully defined patient groups may provide more useful information.[5] Observational studies including a sufficient number of covariates have also indicated that blood transfusions can be associated with better outcomes in critically ill patients.[6–8]

Our results[9] clearly show that a liberal strategy of erythrocyte transfusion, in comparison with a restrictive one, reduced mortality and major complications in our population of surgical cancer patients. We focused on cancer patients undergoing major abdominal surgery during their ICU stay because there is good evidence that transfusions are most beneficial in the sickest patients,[4,10] and the majority of postoperative complications happen in the ICU setting.[1–3] Our RCT included well-balanced groups in terms of baseline demographic data and preoperative characteristics. As Dr. Waters and colleagues will know, calculations of *P* values should not be used to compare baseline data[11] and are avoided in the leading journals.[3] The intervention was clearly different in the two groups. The proportion of patients who received a transfusion was about 50% lower in the restrictive group than in the liberal one, both during the ICU stay and during the hospital stay. The restrictive group received a total of 88 erythrocyte units and the liberal group 134 units. The average hemoglobin concentration was higher in the liberal strategy group than in the restrictive strategy group before transfusion (7.9 ± 0.5 *vs.* 6.8 ± 0.5 g/dl; $P < 0.001$) and during the ICU stay. As a result, the restrictive group was exposed to more postoperative severe anemia than the liberal group, which may explain their higher rates of complications.

Drs. Sharifpour, Hall, and von Heymann comment that our results were different from those of the Transfusion Requirements in Septic Shock trial.[2] However, there are some clear differences between our study and the Transfusion Requirements in Septic Shock trial, in which patients were already in septic shock with marked organ failure (median Sequential Organ Failure Assessment score of 10 in both groups). This was not the case in our study. At that stage of septic shock, few interventions have been shown to improve outcome.

We agree with Dr. Xue *et al.* that low serum albumin concentration is a common finding in patients with cancer and has been associated with poor outcome in surgical patients in previous studies. We reported the serum albumin concentration of patients, along with other laboratory and clinical data, to describe our population. We do not believe that intraoperative adverse events and different reasons for admission could have influenced our results. As mentioned above, prerandomization characteristics were well balanced between groups, including intraoperative factors, such as type of anesthesia, duration of surgery, and rates of erythrocyte transfusion. We agree with Dr. Xue *et al.* that in clinical practice we also consider clinical variables to guide our transfusion decisions, but this potential limitation was

also present in the other studies on this subject. In addition, physicians in the trial could decide to give a blood transfusion out of protocol in life-threatening situations.

We agree with Drs. Hall and Sharifpour that there is still a shortage of robust evidence from large RCTs that leukodepleted blood and shorter duration of blood storage can improve outcomes in surgical patients. As mentioned in the article, we agree with Dr. Sharifpour that despite the apparent benefits of a liberal strategy of erythrocyte transfusion in cancer patients undergoing abdominal surgery on short-term outcomes, the effects of this therapy on long-term outcomes such as cancer recurrence are not known.

As pointed out by von Heymann *et al.*, anemia may represent a heavy burden in oncologic patients with severe comorbidities and a substantial postoperative risk. Our RCT clearly showed that in a well-balanced population of cancer patients, a restrictive strategy of postoperative transfusion was associated with worse outcomes after abdominal surgery. This specific group of patients may not adapt well to anemia, presenting a higher incidence of complications, including 30-day cardiovascular events and mortality. Our results are in agreement with other data reported in the literature.

Competing Interests

The authors declare no competing interests.

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Heparin for Cardiac Surgery: Old and Forgotten?

To the Editor:

We read with interest the article by Karkouti *et al.*[1] published in the March 2015 issue regarding a transfusion algorithm based on point-of-care coagulation tests in cardiac surgery.

We wish to shed light on an issue that was not touched upon in the article but represents the first step in their algorithm and, without dispute, the first and most important single intervention in managing postcardiopulmonary bypass coagulopathy.

The dose of the heparin neutralization by protamine is shown in the algorithm as a ratio of milligrams to milligram. It has long been recommended that heparin should not be quantified in milligram, but in units.[2–4] In fact, to our knowledge, none of the currently available commercial heparins display its potency in milligram. This quantification of heparin in milligram introduces risk if the ordering physician is unfamiliar with the milligram to unit conversion.

The impression that 1 mg unfractionated heparin currently contains 100 units is widely accepted but dated and