Accepted April 2015

EDITORIAL

New insights for transfusion triggers in cardiac surgery

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Keywords - **transfusion triggers, red blood cells, cardiac surgery, oxygen transport, RCT, SIRS**

Abstract

Last month, Gavin J. Murphy published outcomes of a multicentre randomised trial comparing restrictive red blood cell transfusion (< 7.5 g/dl = 4.7 mmol/l) vs a liberal transfusion regimen (< 9g/dl = 5.6 mmol/l) in 2003 patients undergoing elective cardiac surgical procedures [(1)]. This study was carried out in 17 cardiac surgery centres in the UK. The primary outcome was a serious infection (sepsis or wound infection) or an ischaemic event (permanent stroke, myocardial infarction, infarction of the gut, or acute kidney injury) within three months after randomisation. Transfusion rates after randomisation were 53.4% and 92.2% in the two groups, respectively. The primary outcome occurred in 35.1% of the patients in the restrictive-threshold group and 33.0% of the patients in the liberal-threshold group (p = 0.30); there was no indication of heterogeneity according to subgroup. As a secondary outcome, there were more deaths in the restrictive-threshold group than in the liberal-threshold group after 90 days (4.2% vs 2.6%, p = 0.045), but not after 30 days. Serious postoperative complications, excluding primary outcome events, occurred in 35.7% of the participants in the restrictive-threshold group and 34.2% of the participants in the liberal-threshold group. The investigators concluded that a restrictive transfusion threshold after cardiac surgery was not superior to a liberal threshold with respect to morbidity or healthcare costs [(1)].

Non-superiority of a restrictive transfusion regimen for cardiac surgery patients is in contrast to earlier findings from several observational studies which have uniformly shown that red cell transfusion is associated with an increased risk of death and other serious adverse outcomes [(2)]. This difference is possibly due to the fact that observational analyses are confounded by prognostic factors that influence the decision to transfuse red cells.

In a recent meta-analysis of controlled trials in which adult patients undergoing cardiac or vascular surgery were randomised to different transfusion thresholds, no differences in mortality and morbidity were reported between the liberal and restrictive transfusion strategies of these RCTs. However, the authors emphasise that, given the extremely limited data, adequately powered trials are needed to assess the appropriate transfusion thresholds in these patients [(3)].

The strengths of Murphy's study are its nature as RCT, the elegant study design and its large study population. In order to be able to judge the impact of these findings for the cardiac surgical patients in the Netherlands, the following items need to be taken into account. The UK patient profile distribution in this cohort can be expected to resemble the Dutch cardiac surgical patients. On the other hand, the surgical techniques as well as the perioperative management might differ. These items are less well defined in Murphy's paper.

Compared with other surgical and critically ill patients, cardiac surgical patients are more vulnerable to global ischaemia. Contributing factors are inflammation induced by heart-lung machines (HLM) (prime volumes and blood air contact), fluid regimens, myocardial protection and operation times. Inflammation-induced fluid transport to the extravascular space impedes oxygen transport to organs. Since inflammation decreases the transport capacity of haemoglobin, global ischaemia might occur despite haemoglobin levels within accepted limits. Liberal fluid management together with high HLM prime volumes and high volume crystalloid cardioplegia administration are expected to amplify this effect. These circumstances all induce non-physiological conditions. With respect to this it may occur that the actual intravascular haemoglobin level that is measured does not reflect the believed

oxygen transport capacity accurately. These items also make the cardiac surgical patient less comparable with general surgical patients and critically ill patients. With respect to the Murphy's paper, very little information is provided about perioperative management and techniques that are used in the participating centres in the UK.

In the subgroup analysis it was found that the coronary artery bypass graft (CABG) population is in favour of the restrictive transfusion management arm of this study. It might be that an important percentage of the UK-CABG patients are operated off-pump or according to a fluid restrictive management (e.g. Mini Extra Corporeal Circuit MECC) [4]. Under these more physiological circumstances the haemoglobin levels reflect oxygen transport capacity more adequately because less inflammation is induced when these techniques are applied. Under these circumstances less organ injury/ischaemia is expected compared with a group of CABG patients that are operated on-pump.

Overlooking the outcomes of this otherwise well-designed study, local ICUs and care chain managers might need to revise their local transfusion regimens as far as cardiac surgical patients are concerned. In centres where fluid-restrictive management is administered at all care chain levels involved, inflammation and organ injury might be mild among their patients. Since more physiological perioperative conditions are maintained, haemoglobin levels do represent potential realistic oxygen transport capacity in these facilities. In centres where abundant fluid regimens are applied, a more liberal transfusion management is to be advised, as oxygen supply to the organs might be impaired despite more or less adequate haemoglobin levels.

Furthermore, the significant mortality difference between the two study arms is a relevant observation, although it was not a primary outcome in the present study and thus not predicted by any of the perioperative complications. It suggests that some patients might have suffered from global organ ischaemia without being diagnosed.

Conclusion

Murphy et al. could not prove the null hypothesis (restrictive transfusion management reduces morbidity and cost) in their paper. This editorial emphasises the risk of misinterpretation of perioperative haemoglobin levels which reflect oxygen transport capacity dependent on transfusion management regimens and the related extent of perioperative inflammation.

Until further large RCTs, such as the TRICS-III (Transfusion Requirements in Cardiac Surgery III) trial which is currently recruiting (https://clinicaltrials.gov/show/NCT02042898), serve to improve evidence on transfusion strategies, perioperative caregivers for cardiac surgery patients will have to ponder, on an individual basis, whether a certain haemoglobin level ensures adequate organ perfusion and whether blood transfusion may serve to avoid malperfusion by improving oxygen delivery.

References

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