Netherlands
The Journal of Medicine

EDITORIAL

Red blood cell transfusion and furosemide in cardiac surgery: friend or foe?

C.S.C. Bouman[1*], L.G. Forni[2]

[1]Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, [2]Western Sussex Hospitals Trust, Brighton and Sussex Medical School, University of Sussex, Brighton, UK, *corresponding author: tel: +31 (0)20 5662509, e-mail: c.s.bouman@amc.uva.nl

Acute kidney injury (AKI) is one of the most common complications of cardiac surgery and even when the injury is relatively modest it is independently associated with both a high morbidity and mortality.[1,2] The pathogenesis of AKI in cardiac surgery (CS-AKI) is complex and incompletely understood with aetiological features that are both common to other types of AKI as well as some specific features.[3] The mechanisms include action of exogenous and endogenous toxins, metabolic factors, ischaemia-reperfusion injury, neurohormonal activation, inflammation and oxidative stress.[3] Each may play a role in the pathogenesis of CS-AKI throughout the process but are not necessarily temporally related. Numerous therapies for the prevention of AKI have been tested but none have been proven particularly effective.[4] This lack of effective therapies prompted Dr Vellinga and colleagues to try and identify modifiable risk factors for reducing AKI after cardiac surgery as published in this issue of *The Netherlands Journal of Medicine*.[5] The authors performed a single-centre retrospective analysis in 565 adult patients who underwent coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB). Serum creatinine (SCr) was determined at admission and at 24-hour intervals for a minimum of 48 hours and a maximum of seven days. Unfortunately urine output and fluid balance were not recorded. AKI was determined by the modified AKIN criteria employing only the serum creatinine criteria. Eighty-three patients were diagnosed with AKI, of which 74 (89%) were classified as AKIN I, 4 (5%) patients AKIN II, 3 (4%) patients AKIN III with 2 (2%) patients receiving renal replacement therapy (RRT). Despite the impressively low rate of CS-AKI both mortality rate and length of hospital stay were not reported. Based on their multivariate analysis findings the authors concluded that intraoperative and postoperative red blood cell (RBC) transfusion as well as administration of furosemide played a significant role in the development of AKI.

These findings are in keeping with some other studies and as such are not unique. Numerous studies have reported renal risk factors derived in a multivariate fashion from larger cohorts of patients undergoing cardiac surgical procedures. For example, in 2009 Karkouti *et al*. performed a large multicentre study in 3500 patients who underwent cardiac surgery with CPB using the modified RIFLE criteria (GFR criteria only) to define AKI.[6] Although the most predictive risk factors were CPB duration and intra-aortic balloon pump before surgery, three potentially modifiable and interrelated risk factors (preoperative anaemia, perioperative RBC transfusions, and the need for reexploration) were strongly associated with the development of AKI. Very recently, Parolari *et al*. performed a large single-centre study in 3669 patients who underwent on-pump cardiac surgery, using the modified AKIN (SCr only) to define AKI.[7] This demonstrated that as well as conventional preoperative risk factors for AKI such as increasing age, preoperative SCr, and diabetes, drug administration (especially inotropes, vasoconstrictors, diuretics), RBC transfusion, and perfusion or cross-clamp times were significantly associated with AKI.[7] However, an obvious limitation of all these retrospective studies is the potential for confounding effects, particularly when the trigger for intervention is not clearly defined. Thus, RBC transfusion during cardiac surgery *may* contribute to AKI but is itself often consequent to significant blood loss, the cause of which may also contribute to the development of AKI. Likewise, furosemide *may* contribute directly to AKI, but again, it may be that the administration of the diuretic was initiated by a response to oliguria heralding AKI. Therefore, despite the fact that this study implies that transfusion and diuretic administration are independent risk factors for the development of CS-AKI we are left wondering whether this is the chicken or the egg.

However, this study does raise some interesting points. Transfusion of RBCs may cause AKI through interaction

between donor RBCs and transfusion recipients as a consequence of receiving RBCs altered by processing and storage (the so-called 'storage lesion').[8] The storage lesion has effects on overlapping pathways of oxygen delivery, RBC rheology as well as effects on immune modulation.[8] It has been suggested that transfusion of 'younger' blood results in less morbidity/mortality; however, it is not currently known if clinical outcomes are affected by the age of transfused blood and uncertainty remains regarding the clinical importance of RBC storage duration as well as when 'new' blood can be viewed as 'old' blood.[9] Of note, in an experimental pig model RBC transfusion during CPB protected against AKI.[10] Another approach was recently suggested by Karkouti *et al*. in a small unblinded randomised pilot clinical trial in cardiac surgery patients showing that prophylactic transfusion one to two days before surgery limits the deleterious effects of blood transfusions compared with standard of care (transfusion as indicated).[11] The rationale for this approach was that RBC transfusion may increase the amount of circulating free iron, which could exacerbate the oxidative stress injury during surgery. Preoperative transfusion may allow time for iron metabolism to stabilise and/or chelation to occur before the effects of surgery come into play, thus keeping free iron levels at more acceptable, less damaging, levels.[11] The study, however, was not powered to detect differences in AKI. Notably, in a very recent pilot study by Haase *et al*. low preoperative levels of the iron regulatory hormone hepcidin were found to be a risk factor for mortality after cardiac surgery, adding to the evidence that altered metabolism may contribute to organ dysfunction after major surgery.[12]

Loop diuretics such as furosemide have been extensively studied because of their main pharmacokinetic actions: reduction of vascular resistance and inhibition of active transport in the thick ascending limb of the loop of Henle. This latter effect has been proposed as 'protective' with reduction in the energy requirements under ischaemic conditions. In experimental trials the administration of furosemide protected the chronically hypoxic juxtamedullary regions during ischaemic events.[13] In contrast, clinical trials were unable to reproduce this beneficial effect in humans, and it was even suggested that the use of furosemide was detrimental.[14] Nevertheless, very recently Gandhi *et al*. constructed a best evidence topic according to a structured protocol. The question addressed was 'Does perioperative furosemide usage reduce the need for renal RRT in cardiac surgery patients?'[15] Based on ten studies which represented the best evidence to answer this clinical question the authors concluded that the evidence supporting the benefit of this strategy in terms of reducing the need for RRT is weak. At the same time, current best available evidence, albeit from small RCTs, suggests that the timely introduction of continuous furosemide infusion does not increase the incidence of renal impairment after cardiac surgery.

So, where does this study leave us? Although the results are of interest, no firm conclusions can be drawn as to potential interventions to limit CS-AKI. As pointed out the need for intervention is almost certainly as relevant as the intervention itself. Clearly, when faced with a surgical patient with significant haemorrhage, for whatever reason, transfusion cannot be withheld and one may argue that not reacting to volume loss is probably a greater risk factor. Similarly, unchecked positive volume balance is also associated with increased morbidity and mortality and hence may necessitate intervention. Vaara *et al*. recently performed a prospective multicentre observational cohort study in 283 RRT-treated critically ill patients and showed that patients with fluid overload at RRT initiation had twice as high crude mortality compared with those without.[16] In another recent observational single-centre study in 502 post-cardiac surgery patients, both fluid overload and changes in SCr correlated with mortality.[17] Of note, fluid overload was the variable most related to length of stay in intensive care.[17] Perhaps the best way to limit CS-AKI is in terms of technique employed. Early observational studies comparing off-pump CABG with on-pump CABG showed a significant reduction in CS-AKI and a subsequent meta-analysis confirmed these observations.[18,19] By meta-analysis, off-pump CABG was associated with a 40% lower odds of CS-AKI although interestingly there was little effect on overall mortality. Perhaps what we should bear in mind is that all our interventions have an effect on our patients and some carry greater risks than others!

REFERENCES

1. Waikar SS, Liu KD, Chertow GM. Diagnosis, epidemiology and outcomes of acute kidney injury. Clin J Am Soc Nephrol. 2008;3:844-61.
2. Lassnig E, Auer J, Weber T, et al. [Infection sources in HNO- and jawbone regions in patients before valve replacement surgery]. Herz. 2004;29:317-21.
3. Bellomo R, Auriemma S, Fabbri A, et al. The pathophysiology of cardiac surgery-associated acute kidney injury (CSA-AKI). Int J Artif Organs. 2008;31:166-78.
4. Patel NN, Rogers CA, Angelini GD, Murphy GJ. Pharmacological therapies for the prevention of acute kidney injury following cardiac surgery: a systematic review. Heart Fail Rev. 2011;16:553-67.
5. Vellinga S, Verbrugghe W, De Paep R, Verpooten G, Janssen van Doorn K. Identification of modifiable risk factors for acute kidney injury after cardiac surgery. Neth J Med. 2012;70:450-4.
6. Karkouti K, Wijeysundera DN, Yau TM, et al. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation. 2009;119:495-502.
7. Parolari A, Pesce LL, Pacini D, et al. Risk factors for perioperative acute kidney injury after adult cardiac surgery: role of perioperative management. Ann Thorac Surg. 2012;93:584-91.
8. Doctor A, Spinella P. Effect of processing and storage on red blood cell function in vivo. Semin Perinatol. 2012;36:248-59.

9. Grazzini G, Vaglio S. Red blood cell storage lesion and adverse clinical outcomes: post hoc ergo propter hoc? Blood Transfus. 2012;10(Suppl 2):s4-s6.

10. Patel NN, Lin H, Toth T, et al. Reversal of anemia with allogenic RBC transfusion prevents post-cardiopulmonary bypass acute kidney injury in swine. Am J Physiol Renal Physiol. 2011;301:F605-F614.

11. Karkouti K, Wijeysundera DN, Yau TM, et al. Advance targeted transfusion in anemic cardiac surgical patients for kidney protection: an unblinded randomized pilot clinical trial. Anesthesiology. 2012;116:613-21.

12. Haase-Fielitz A, Plass M, Kuppe H, et al. Low preoperative hepcidin concentration as a risk factor for mortality after cardiac surgery: A pilot study. J Thorac Cardiovasc Surg. 2012 Oct 9.

13. Brezis M, Epstein FH. Cellular mechanisms of acute ischemic injury in the kidney. Annu Rev Med. 1993;44:27-37.

14. Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. BMJ. 2006;333:420.

15. Gandhi A, Husain M, Salhiyyah K, Raja SG. Does perioperative furosemide usage reduce the need for renal replacement therapy in cardiac surgery patients? Interact Cardiovasc Thorac Surg. 2012;15:750-5.

16. Vaara ST, Korhonen AM, Kaukonen KM, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care. 2012;16:R197.

17. Stein A, de Souza LV, Belettini CR, et al. Fluid overload and changes in serum creatinine after cardiac surgery: predictors of mortality and longer intensive care stay. A prospective cohort study. Crit Care. 2012;16:R99.

18. Massoudy P, Wagner S, Thielmann M, et al. Coronary artery bypass surgery and acute kidney injury--impact of the off-pump technique. Nephrol Dial Transplant. 2008;23:2853-60.

19. Seabra VF, Alobaidi S, Balk EM, Poon AH, Jaber BL. Off-pump coronary artery bypass surgery and acute kidney injury: a meta-analysis of randomized controlled trials. Clin J Am Soc Nephrol. 2010;5:1734-44.