Peri-operative renal protective strategies in cardiac surgery

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Abstract

Introduction

Acute kidney injury develops in up to 30% of patients, who undergo cardiac surgery, with up to 3% of patients requiring dialysis. The requirement for dialysis after cardiac surgery is associated with an increased risk of infection, prolonged stay in critical care units and long-term need for dialysis. The development of acute kidney injury is independently associated with substantial short- and long-term morbidity and mortality. Its pathogenesis involves multiple pathways. Haemodynamic, inflammatory, metabolic and nephrotoxic factors are involved and overlap each other, which lead to kidney injury. High-risk patients can be targeted for renal protective strategies. Nonetheless, there is little compelling evidence from randomised trials supporting specific interventions to protect or prevent acute kidney injury in cardiac surgery patients. The aim of this critical review was to discuss the peri-operative renal protective strategies in cardiac surgery.

Conclusion

Several strategies have shown some promise, including less invasive procedures in those with greatest risk, natriuretic peptide, fenoldopam, pre-operative hydration, pre-operative optimisation of anaemia and post-operative early use of renal replacement therapy. Large-scale trials are required to confirm their efficacy.

Introduction

Pharmacological interventions have been inconsistent with their efficacy, and currently there are no known drugs that have conclusively conferred renal protection. This failure might be related to a number of factors, which are as follows:

- The pathophysiology of acute kidney injury (AKI) following cardiac surgery is complex, and simple approaches to target single pathways are unlikely to succeed.
- Late pharmacological intervention (measured by a rise in serum creatinine [sCr]) is likely to meet with failure. By the time sCr is elevated, the person may already have lost 50% of kidney function.
- Patient populations that have been studied are often at low risk for renal dysfunction post-cardiopulmonary bypass (CPB); thus, potentially masking small beneficial effects of therapies.
- Most clinical trials enrolled a small number of subjects and are therefore, inadequately powered to detect small benefits.

Renal protective strategies are summarised in Table 1.

This critical review describes the various renal protective strategies being used in cardiac surgery.

Discussion

In this critical review, the author has referenced some of his own studies. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees associated to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in the studies.

Pre-operative strategies

In the pre-operative period, the major goals include optimising cardiac output, avoiding intra-vascular volume depletion and continuing congestive heart failure treatment before surgery. Optimising renal function in elective surgery for patients, with reversible AKI should be considered.

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AKI, acute kidney injury; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; RRT, renal replacement therapy.

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Aspirin use has been shown to reduce the risk of cardiovascular events in patients with coronary artery disease. Thus, patients commonly are taking aspirin when they present for cardiac surgery. Mangano and the Multicentre Study of Peri-operative Ischemia Research Group, study the impact of aspirin use, within 48 hours of CABG surgery on renal outcomes, including AKI, AKI requiring dialysis (AKI-D) and death caused by renal failure in a multinational prospective cohort study of 5,065 patients. Aspirin therapy was associated with a 74% reduction in the incidence of renal failure and death from renal failure. These findings were confirmed by a recent observational study evaluating the impact of pre-operative aspirin on major outcomes in patients, who had cardiac surgery. Among 2,868 patients, who met the inclusion criteria, 1,923 patients took aspirin (81–325 mg daily) at least once, within five days preceding their surgery versus 945 patients, who did not take aspirin (non-aspirin therapy). Pre-operative aspirin therapy was associated with a significant decrease in the risk for 30-day mortality and post-operative renal failure.

Pre-operative use of diuretic has been associated with increased risk of renal replacement therapy (RRT) in a retrospective study. Patients may benefit from avoiding pre-operative anaemia, defined as haemoglobin <12.5 mg/dL. A recent pilot study found that the administration of erythropoietin, before surgery, reduced the risk of AKI and improved renal function. Yoo et al. reported the results of a single-centred randomised controlled trial of single-dose erythropoietin plus an iron supplement or placebo given a day before surgery. They found a significant reduction in AKI (24% versus 54%), in the intervention group. As transfusion is an independent risk factor for AKI after cardiac surgery and the transfusion rate was lower in the erythropoietin group, it is unclear whether the preserved post-operative renal function was because of a renoprotective effect of erythropoietin or reduced transfusion. Recent data suggest that transfusing packed red blood cells (PRBC) pre-operatively, could be associated with a lower peri-operative free iron and transferrin saturation, with a trend towards lower AKI rates after surgery. Further studies are required to affirm the benefit of transfusing PRBC or optimising haemoglobin pre-operatively in anaemic patients. Nephrotoxic agents such as non-steroidal anti-inflammatory drugs (NSAIDs) should be discontinued. Exposure to radiocontrast agents should be avoided or minimised, along with time to allow for renal recovery whenever possible. Whether angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blocker (ARB) should be discontinued before surgery to reduce cardiac surgery-associated (CSA) AKI is still controversial.

The pre-operative prophylactic use of RRT on patients with sCr >2–2.5 mg/dL has been shown to decrease morbidity and mortality in two randomised controlled trials. However, the cost-effectiveness of pre-operative prophylactic use of RRT is required to be further studied. Therefore, these results need to be replicated in further trials before prophylactic haemodialysis can be recommended for all patients with pre-existing impairment of renal function.

So far studies optimising peri-operative haemodynamic using fluids and/or inotropes, have not been designed to examine renal outcomes. Some data suggested a significant reduction in length of hospital stay and in post-operative complications. Pre-operative intravenous hydration may reduce the incidence of AKI in patients with chronic kidney disease (CKD), undergoing cardiac surgery. A small randomised trial using an intravenous infusion of 0.45% normal saline at 1 mL/kg/h for 12 hours, before surgery versus no hydration, showed that AKI developed in 9 of the 30 (30%) patients in the hydration group versus 8 of the 15 (53%) patients in the control group. Four patients in the control group (27%), but none in the hydration group required dialysis after surgery (p < 0.01). Even though results are required to be validated by larger trials, the data suggest that patients should be euvoletic and off diuretics before surgery to avoid AKI.

Intra-operative management strategies
An association between intra-operative anaemia, blood transfusion and AKI has long been observed. However, there is evidence to suggest that low pre-operative and intra-operative haemoglobin levels are associated independently with CSA-AKI, but ironically, there is also evidence to suggest that intra-operative transfusion is independently associated with CSA-AKI. Karkouti et al. found that it is not the absolute level of haemoglobin that is important, but its change from baseline. They found that the risk of AKI was significantly increased when haemoglobin decreased more than 50% below baseline. The impact of glucose control on renal outcomes remains controversial. The benefits of a tight glucose control strategy have not been replicated in multicentre studies, and the lack of benefit and increased potential harm was confirmed again in a recent meta-analysis. The large multicentre Nice Sugar study demonstrated no outcome benefit in tight glucose control compared with a regimen that targeted a blood sugar level of less than 180 mg/dL and had an unacceptable incidence of hypoglycaemia.

With regard to the mean arterial pressure (MAP) required during CPB, a recent prospective observational study on 410 patients showed that a higher magnitude and duration of MAP below the lower limit of cerebral autoregulation was independently associated with AKI. Whether maintaining MAP above the lower limit of cerebral autoregulation

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is renal protective should be further studied. A recent meta-analysis on 1,185 patients, suggests that pulsatile perfusion during CPB is beneficial in renal preservation and should be considered. It was found that the pulsatile perfusion group had significantly higher creatinine clearance (p = 0.004) and lower serum lactate levels (p = 0.012) in the intensive care unit (ICU).

Recent data suggest an increased risk of AKI-D associated with the use of hydroxyethyl starch (HES) for fluid resuscitation in ICU. Therefore, we should use caution when using these colloids for resuscitation in cardiac surgery.

**Surgical strategies**

Off-pump CABG (OPCABG) allows systemic pulsatile flow and no exposure to an extracorporeal circuit, thus reducing the inflammatory cytokine response. Most available data does not support a decreased risk of AKI requiring RRT associated with OPCABG procedures. However, data does support a decreased risk of mild AKI, associated with OPCABG. In 2009, Shroyer et al. reported data from a multicentre randomised controlled trial, the ROOBY trial, on 2,203 patients undergoing CABG surgery, either ‘off pump’ or ‘on pump’. Data showed no significant differences in RRT requirements (0.8% vs 0.9%, RR = 0.90 (0.37–2.20), p = 0.82). However, the trial has some important limitations. The trial enrolled low-risk male patients, in whom avoidance of CPB was unlikely to greatly improve the expected excellent outcomes, though conversely surgeons were remarkably inexperienced in the off-pump procedure. The CORONARY trial was recently published by Lamy et al. It is a multicentre randomised controlled trial with 4,752 patients. This data suggest that OPCABG was associated with no significant differences in RRT requirement (HR = 1.04 (0.61–1.76), p = 0.59). However, a definition for initiation of RRT was lacking. Hence, patients with the same clinical situation might have been managed differently. Furthermore, OPCABG was associated with a significant decrease in mild AKI, defined by RIFLE-Risk (HR = 0.87 (0.76–0.98), p = 0.02) or AKIN stage 1 (HR = 0.87 (0.80–0.96), p = 0.01). The CORONARY trial at 1 year follow-up, showed no difference in RRT requirements and mild AKI were not analysed.

Miniature CPB systems may be directly and indirectly renoprotective. Minimally invasive parasternotomy might be also renoprotective.

**Pharmacological renal protection**

Several pharmacologic and therapeutic strategies have been used in an attempt to decrease the incidence of CSA-AKI. Although some appeared promising in early studies, conclusive evidence to support their widespread use is lacking. The use of prophylactic fenoldopam, a selective dopamine receptor-1 agonist, during cardiac surgery, has been suggested to have renoprotective effects. Landoni et al. in a meta-analysis of 13 randomised and case-matched studies on 1,059 patients, undergoing cardiac surgery, concluded that the use of fenoldopam significantly decreased the requirement for RRT, and decreased ICU length of stay and in-hospital mortality. Zangrillo et al. in a recent meta-analysis of 440 patients, focusing only on randomised placebo-controlled trials, showed that fenoldopam consistently and significantly reduced the risk of CSA-AKI (OR = 0.41; 95% confidence interval [CI], 0.23–0.74; p = 0.003), with no difference with regard to RRT requirement and mortality. The authors suggest that because the size of this benefit is so large for a single intervention, it is likely implausible. Because the number of the enrolled patients was small and there was no effect on RRT or survival, a large, multicentre and appropriately powered trial is required to confirm these promising results. A large randomised controlled trial on 1,000 patients is underway to assess the effectiveness of fenoldopam on CSA-AKI prevention (NCT00621790).

Haase et al. in a pilot double-blind, randomised controlled trial with 100 patients, found a significant reduction (p < 0.043) in post-operative AKI, liberally defined as an increase of 25% from baseline creatinine within the first five post-operative days, as well as a significant decrease in urinary neutrophil gelatinase-associated lipocalin (NGAL), associated with the use of sodium bicarbonate infusion. However, no differences were found when consensus definition of AKI (RIFLE or AKIN) was used. Furthermore, a recent multicentre double-blind randomized controlled trial on 350 high-risk patients for developing CSA-AKI showed that more patients receiving bicarbonate developed CSA-AKI (defined as an increase in sCr concentration greater than 25% or 0.5 mg/dL [44 μmol/L] from baseline to peak value at any time within the first five days after CPB) compared to control patients (47.7% vs 36.4%, OR = 1.60 [95% CI; 1.04–2.45]; unadjusted p = 0.032). After multivariable adjustment, a non-significant unfavourable group difference affecting patients receiving sodium bicarbonate was found for the primary endpoint (OR = 1.45 [0.90–2.33], p = 0.120). A greater post-operative increase in urinary NGAL in patients receiving bicarbonate infusion was observed compared to control group patients (p = 0.011). The incidence of the post-operative RRT was similar, but hospital mortality was increased in patients receiving sodium bicarbonate compared to control group (6.3% vs 1.7%, OR = 3.89 [1.07–14.2], p = 0.031)31. In this study, a slightly larger dose of bicarbonate was used compared to the Haase et al. study (5.1 mmol/kg vs 4 mmol/kg during 24 h). Both studies used the same definition of CSA-AKI. Whether the difference in sodium bicarbonate dose used in both studies might have any impact on renal outcome might be further studied. The debate is still ongoing.

**FOR CITATION PURPOSES:**

Lamy et al.24. It is a multicentre randomised controlled trial. The CORONARY trial ably inexperienced in the off-pump procedure. The CORONARY trial at 1 year follow-up, showed no difference in RRT requirements and mild AKI were not analysed25.

Miniature CPB systems may be directly and indirectly renoprotective26. Minimally invasive parasternotomy might be also renoprotective27.

Pharmacological renal protection Several pharmacologic and therapeutic strategies have been used in an attempt to decrease the incidence of CSA-AKI. Although some appeared promising in early studies, conclusive evidence to support their widespread use is lacking. The use of prophylactic fenoldopam, a selective dopamine receptor-1 agonist, during cardiac surgery, has been suggested to have renoprotective effects. Landoni et al.23, reported data from a multicentre randomised controlled trial, the ROOBY trial, on 2,203 patients undergoing CABG surgery, either ‘off pump’ or ‘on pump’. Data showed no significant differences in RRT requirements (0.8% vs 0.9%, RR = 0.90 (0.37–2.20), p = 0.82). However, the trial has some important limitations. The trial enrolled low-risk male patients, in whom avoidance of CPB was unlikely to greatly improve the expected excellent outcomes, though conversely surgeons were remarkably inexperienced in the off-pump procedure. The CORONARY trial was recently published by Lamy et al.24. It is a multicentre randomised controlled trial with 4,752 patients. This data suggest that OPCABG was associated with no significant differences in RRT requirement (HR = 1.04 (0.61–1.76), p = 0.59). However, a definition for initiation of RRT was lacking. Hence, patients with the same clinical situation might have been managed differently. Furthermore, OPCABG was associated with a significant decrease in mild AKI, defined by RIFLE-Risk (HR = 0.87 (0.76–0.98), p = 0.02) or AKIN stage 1 (HR = 0.87 (0.80–0.96), p = 0.01). The CORONARY trial at 1 year follow-up, showed no difference in RRT requirements and mild AKI were not analysed25.

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Critical review

AKI after cardiac surgery is a major peri-operative complication that is associated with significant morbidity, mortality and associated costs. Preventive strategies are limited and the evidence for most interventional therapies is as yet not substantive. As our understanding of the pathogenesis of AKI after cardiac surgery grows, we will be able to direct preventive and therapeutic strategies better. Current approaches include deferring elective surgery, until there is adequate recovery following pre-existing renal injury, careful perioperative risk stratification of patients and consideration of less invasive procedures in those at greatest risk. Intra-operatively, the aim should be ‘haemodynamic optimisation’ with goal-directed therapy that includes volume enhancement and judicious use of blood transfusion and inotropic support. We should attempt to avoid renal injury associated with prolonged aortic cross-clamping, prolonged CPB, intravenous haemolysis or contrast dye exposure. The most promising prospects for pharmacologic renal protection appear to lie with atrial natriuretic peptide and fenoldopam, but much more data are required. Finally, early treatment by RRT of

Statins attenuate inflammation and oxidative stress. However, Liakopoulos et al.32, in a meta-analysis of 30,000 cardiac surgery patients, found that pre-operative statin use was associated with an absolute risk reduction in mortality, atrial fibrillation and stroke, but not myocardial infarction or AKI. A retrospective analysis of 324 patients, found that the incidence of AKI was lower when statins were restarted early post-operatively, and higher in patients, in whom statin therapy was withdrawn33. A randomised control trial is underway to assess the effectiveness of statins on CSA-AKI prevention (NCT00791648).

A multicentre, randomised, placebo-controlled trial of nesiritide versus placebo in 303 patients, with left ventricular dysfunction (LVEF <40%) undergoing cardiac surgery with CPB found that peri-operative renal function was better in the nesiritide group (lower peak rise in sCr, smaller decrease in estimated Glomerular Filtration Rate (eGFR) and greater 24-hour urine output)34. These findings were even more pronounced in the subgroup with baseline renal insufficiency (sCr >1.2 mg/dL). Furthermore, length of hospital stay was shorter in the nesiritide group. In a recent Cochrane meta-analysis35 including 493 patients undergoing cardiovascular surgery from 8 randomised controlled trials there was no difference in mortality between the ANP and control groups (RR 0.73, 95% CI 0.37 to 1.43). ANP was associated with a significant reduction in the need for RRT (RR 0.35, 95% CI 0.18 to 0.70). Another recent meta-analysis36, including 934 adult patients from 13 randomised controlled trials, showed that natriuretic peptide administration was associated with a reduction in acute renal failure requiring dialysis (OR 0.32 [0.15-0.66]) and a statistically non-significant trend toward a reduction in 30-day or in-hospital mortality (OR 0.59 [0.31-1.12]). Recently, there has been three trials showing benefit from using human ANP in on-pump CABG surgery in three different types of patient populations: patients with pre-operative normal renal function37, patients with pre-operative ventricular dysfunction38 and patients with pre-operative CKD39. The benefits of using hANP on the first two studies were only seen in laboratory-based markers (i.e., creatinine and eGFR). Conversely, the randomized controlled trial involving patients, with pre-operative CKD showed a benefit regarding not only AKI, but also AKI requiring RRT. However, these same authors concluded that their observations required confirmation in a larger, adequately powered, prospective multicentre study.

Post-operative strategies
The early use of RRT after cardiac surgery, compared to late RRT, has repeatedly been associated with improved in-hospital survival in patients with CSA-AKI30,41. A retrospective study of 1,264 patients showed an association between increased survival and early RRT (0.78 + 0.2 days) compared to late RRT (2.5 + 2.2 days) after cardiac surgery40. RRT duration was similar (p > 0.05). However, in-hospital mortality was 22% versus 43% for early and late RRTs, respectively. Data from a multicentre retrospective study41 suggested that early RRT (<3 days after cardiac surgery) was associated with significantly decreased ICU length of stay (12.5 + 17.5 days vs 7.9 + 10.7 days) and mortality (80.4% vs 53.2%). Interestingly, the group with better outcome and early RRT had worse baseline (sCr = 1.58 + 1.14 mg/dL vs 1.26 + 0.52 mg/dL, p = 0.014) and 48 h post-operative renal function (increase from baseline sCr = 124.2% + 160.4% vs 68.3% + 87.1%). The early use of RRT may be an important factor used to increase survival in patients with CSA-AKI.
patients early diagnosed by panels of biomarkers may improve outcomes.

Abbreviations list
AKI, acute kidney injury; AKI-D, AKI requiring dialysis; CABG, coronary artery bypass graft; CI, confidence interval; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; eGFR, epidermal growth factor receptor; ICU, intensive care unit; MAP, mean arterial pressure; NGAL, neutrophil gelatinase-associated lipocalin; OPCA/BCG, off-pump CABG; PRBC, packed red blood cells; RRT, renal replacement therapy; sCr, serum creatinine.

References
Critical review


