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Management of Post-operative Acute Kidney Injury

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Abstract

Post-operative Acute Kidney Injury (AKI) is a common complication of surgery with significant short and long term adverse consequences. The adoption of diagnostic criteria for AKI (RIFLE, AKIN, KDIGO) has facilitated comparison of data reported by different centres, confirming that even mild AKI is associated with excess mortality. It remains unclear whether this is caused by the kidney injury itself or whether AKI is simply a marker of underlying disease severity. There is no trial evidence to support the use of any specific therapeutic intervention in post-operative AKI. Best current treatment is therefore preventative by optimising hydration and avoidance of nephrotoxins, emphasising the importance of earlier detection and identification of individuals at high risk for AKI. In this review, we examine the latest literature on the management of post-operative AKI in adult patients, specifically the diagnosis and definition of AKI, epidemiology and pathogenesis and risk stratification in cardiac and non- cardiac surgery. We also review the latest evidence on pharmacological and non- pharmacological interventions.

Diagnosis and Definition of post-operative AKI

The lack of an agreed definition for acute kidney injury (AKI) has significantly limited the evidence base for AKI with increasing evidence that even mild, transient changes in serum creatinine are associated with significant adverse events. In 2004, the Acute Dialysis Quality Initiative (ADQI) group collaborated to create the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria in order to attempt to address this issue (Table 1). In 2007 the RIFLE criteria were modified to form the AKIN classification with the aim of increasing the sensitivity and specificity of AKI diagnosis. The AKIN classification includes a rise in creatinine of greater 26μmol/l and changes in creatinine over 48 hours rather than compared to a baseline value. This definition has been further modified by the Kidney Disease Improving Global Outcomes (KDIGO) group and has been uniformly adopted to define AKI (Table 1)(1). Few observational studies have defined AKI using urine output criteria probably due to the fact that urine output outwith the intensive care setting is generally poorly measured. It has been shown, however, that urine output is a more sensitive measure than serum creatinine(2). This highlights the importance of accurate urine output measurements preoperatively particularly in patients deemed high risk for developing AKI. This would facilitate earlier detection of AKI prior to a rise in serum creatinine thereby preventing more severe renal injury.

There are several limitations of a creatinine based definition for AKI and so focus has turned to developing more sensitive and specific biomarkers for AKI to allow earlier detection (Appendix).

Incidence

Post-operative AKI is a common complication of surgery. The incidence of post-operative AKI prior to 2004 was difficult to establish due to a lack of agreed definition. Incidence varies according to type of surgery with the majority of studies confined to cardiac surgery. Studies using the currently agreed definition for AKI in non -cardiac surgery are lacking with the main

ones summarised in Table 2. Using the KDIGO criteria, incidence of AKI was 11.8% ranging from 4.1% following Ear, Nose and Throat surgery to 13.2% after general surgery in a large cohort of over 16,000 United States Veterans (3). Results from a Scottish cohort of 12,482 patients are comparable ranging from 4% following gynaecological surgery to 25% after vascular surgery also using the KDIGO criteria (4). A recent systematic review of 19 studies including 82, 514 patients undergoing major abdominal surgery reported a pooled incidence of AKI of 13.4 % (95 % CI 10.9-16.4 %)(5).

Incidence of AKI following cardiac surgery is better reported. Results of a recent systematic review found an overall incidence of 25.8% in 35,021 patients undergoing cardiac surgeries(6). Incidence ranged from 12% to 43% when limited to studies using the RIFLE, AKIN or KDIGO criteria. A further larger systematic review of 91 studies encompassing 320,086 patients undergoing cardiac surgery showed similar results with a pooled AKI incidence of 22.3% (95% CI 19.8 to 25.1) with 13.6%, 3.8% and 2.7% stage 1,2 and 3(7).

Pathogenesis

The aetiology of post-operative AKI is complex and not fully understood with numerous contributing factors. Renal hypoperfusion is an important and common aetiological factor in post-operative AKI. Hypotension leads to a proinflammatory state with an increase in vasconstrictive mediators such as endothelin and angiotensin II leading to tubular ischaemia and injury. During major surgery renal hypotension has a number of aetiologies. These include hypovolaemia and reduced systemic vascular resistance caused by anaesthesia. . Other contributing factors include perioperative use of nephrotoxins such as nonsteroidal anti-inflammatory drugs (NSAIDs), inhibitors of the renin angiotensin system and intravenous contrast media which is increasingly used during vascular surgery. Inhibitors of the renin angiotensin system lead to a reduction in angiotensin II and so in the presence of reduced renal blood flow peri-operatively; they cause a drop in GFR through loss of efferent arteriolar vasoconstriction. Ischaemia alone however cannot fully explain post-operative AKI with

inflammation playing an important role. Inflammation, sepsis and a systemic inflammatory response commonly occurs in the post-operative setting through the release of pro-inflammatory cytokines and free radicals causing further renal injury. One of the causes of AKI in cardiac surgery is related to use of cardiopulmonary bypass (CPB). Contact of blood products with the CPB surface and ischaemia reperfusion injury cause renal tubular damage through inducing a systemic inflammatory response(8). Choice of prophylactic antibiotics for surgery have also been shown to be an important contributing factor to post-operative AKI with flucloxacillin and gentamicin prophylaxis associated with increased rates of AKI(4).

Risk Factors for post-operative AKI

Awareness of the risk factors for AKI in patients undergoing surgery has a number of benefits. It allows for perioperative optimisation and closer monitoring of patients deemed high risk in the post-operative period. These measures may prevent AKI or prevent more severe AKI with significant long term implications. Risk stratification also allows the physician and patient to have an informed preoperative discussion about the likelihood of developing a complication and therefore the risks and benefits of the proposed surgery. A number of risk factors for AKI in patients undergoing surgery have been identified: some of these relate to the patient and others to the surgical procedure (Table 2).

Risk scores for AKI following Cardiac Surgery

There are several risk scores in patients undergoing cardiac surgery, though not all have been externally validated. The Cleveland Clinic Foundation score was developed in a cohort of 15, 838 patients to predict AKI requiring RRT (9). It is one of the most discriminative risk scores and has been validated in several other cohorts with area under receiving operating characteristic curves (AUCs) over 0.8(10, 11).

The Society of Thoracic Surgeons (STS) bedside risk tool was developed in a cohort of 449,524 patients and validated internally in 86,009 patients undergoing coronary artery

bypass graft (CABG) and/or valve surgery (c-statistic 0.83) (12). It has been subsequently validated in 2 Canadian cohorts and a cohort from the Mayo clinic (10, 11).

The Simplified Renal Index (SRI) comprising of 8 variables was derived from a Canadian cohort of 10,571 patients undergoing cardiac surgery with CPB (11, 12). It has been validated in 2 Canadian cohorts of 2,566 and 6,814 patients both with an AUC 0.78. However, these tools all lack the ability to predict milder forms of AKI.

The Multicentre Study of Perioperative Ischemia (MCSPI) Score event was developed in a cohort of 4,801 patients from 70 centres in 17 countries of patients undergoing coronary revascularization requiring the use of CPB (13) . AKI was defined as a postoperative serum creatinine of at least 177μmol/l accompanied by an increase of at least 62μmol/l from preoperative baseline, or AKI requiring dialysis. AUC was 0.84 in the derivation cohort and 0.8 in the validation cohort. The disadvantage of this score was that it has not been externally validated. The 8 variables included comprise of both preoperative and intraoperative variables and so cannot be used as a preoperative risk score to stratify patients.

A further risk score developed in 25,992 patients undergoing cardiac surgery from 2 UK centres and validated in 4,862 patients from a third centre predicted any stage of AKI with better or equivalent discrimination than 4 previously published scores. This score did not include intra or post-operative variables allowing its application pre-operatively(14).

Risk scores for AKI following Non Cardiac Surgery

There are fewer validated risk scores in patients undergoing non cardiac surgery. Kherterpal and colleagues examined post-operative AKI in 75 952 patients undergoing general surgery in the United States (15). Older age, male sex, emergency surgery, intraperitoneal surgery, diabetes mellitus necessitating oral therapy, diabetes mellitus necessitating insulin therapy, active congestive heart failure, ascites, hypertension, mild preoperative renal insufficiency, and moderate preoperative renal insufficiency were found to be independent risk factors for

post-operative AKI. AKI was defined as a rise in serum creatinine of 177μmol/l or more from the preoperative value over the first 30 post-operative days with only 1% of their operations complicated by AKI. A recent cohort examining patients undergoing orthopaedic surgery from the United Kingdom defined AKI using the KDIGO criteria which includes a rise of greater than 26μmol/l in serum creatinine therefore including milder forms of AKI. Predictors for AKI were sex, diabetes, number of prescribed drugs, lower estimated glomerular filtration rate, use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and American Society of Anesthesiologists grade (ASA). The development cohort comprised of 6220 patients from two hospitals and externally validated in 4395 patients from a third hospital. The model's predictive performance for discrimination was good (C statistic 0.74 in development cohort, 0.70 in validation cohort) (16).

It is important to note that these epidemiological cohort studies lack urine output data which is a limits both early diagnosis and risk prediction. This however reflect clinical; practice in most hospital wards.

Adverse outcomes following post-operative AKI

Post-operative AKI is associated with adverse outcomes. These include increased hospital length of stays, mortality and future risk of developing end stage renal disease (ESRD) and increase with increasing severity of AKI. Even mild (Stage 1) AKI has been shown to be associated with adverse outcomes. In a cohort of 161,185 US veterans undergoing major surgery, rates of hospital readmission within 30 days, in-hospital mortality, mortality within 90 day and 1year as well as ESRD at 1 year were significantly higher in patients with AKI. This increased with increasing severity of AKI (3).

A further large cohort of 51, 457 patient undergoing major surgery showed that patients with AKI had significantly higher cardiovascular mortality compared to those without (HR 1.95, 95%CI 1.80 to 2.11) (17). Both these studies defined AKI using the KDIGO creatinine based criteria. In a cohort of over 10,000 patients undergoing orthopaedic from the United

Kingdom, survival was worse in patients with AKI compared with those without (adjusted hazard ratio 1.53, 95% confidence interval 1.38 to 1.70). Survival worsened with increasing severity of acute kidney injury but even mild acute kidney injury resulted in a considerably worse overall survival (adjusted hazard ratio 1.46, 1.30 to 1.63, P<0.001) (16).

A recent meta-analysis examined the effects of AKI on mortality in patients undergoing cardiac surgeries(6). Despite recovery of renal function back to baseline before discharge, there was still an associated increase in long term mortality (HR 1.31 95%CI 1.16 to1.47, p<0.001) compared to those who did not develop AKI. This increased further in patients who did not recover their renal function back to baseline (HR 2.71 95%cI 1.26 to 5.82, p=0.01).

However, caution must be applied to the interpretation of these studies due to their observational nature.

Finally, there is evidence surrounding the economic implications of post-operative AKI with significantly higher hospital cost in patients who develop AKI (18).

In view of these adverse effects of AKI, a working group of the 15thADQI conference have formulated consensus statement regarding minimal data elements and potential data sources necessary to trace the natural history of patients from onset of AKI to long-term outcome(19).

Pharmacological and non-pharmacological interventions

Diuretics

Diuretics have been widely used both to prevent and treat AKI. It is thought that loop diuretics may decrease oxygen consumption thereby potentially reducing ischaemic injury and wash out necrotic debris preventing intratubular obstruction. However, clinical studies do not support this theory with prophylactic use of furosemide found to increase rates of AKI following cardiac surgery (20). Similarly, in a recent study of non-cardiac surgery, perioperative use of diuretics was associated with increased post-operative AKI (21). No

benefit was also shown in a Cochrane systematic review examining pharmacological interventions to prevent AKI (22). Their use is now only recommended in the context of fluid overload**.**

Vasodilator Therapy

The theory behind the use of vasodilator treatments such as dopamine, fenoldopam and atrial natriuretic peptide (ANP) is that they increase glomerular filtration rate through renal vasodilation and natriuresis. Dopamine was previously widely used in AKI but its use is now not recommended(1) . A large randomised controlled study and a Cochrane review have shown no benefit in patients with AKI (22, 23). These together with the possible adverse effect of even low dose dopamine have led to the current recommendation.

Several small studies and meta-analyses have shown a beneficial effect of fenoldopam. However, a large multi-centre randomised controlled trial of patients undergoing cardiac surgery showed that in patients with AKI fenoldopam did not reduce the need for RRT or 30 day mortality but was associated with increased hypotension(24). Its use is therefore also not currently recommended.

Studies of ANP have shown a potential benefit but these have been small and underpowered causing systemic hypotension and so its use is not routinely recommended (22).

Other Pharmacological Interventions

Several other pharmacological agents have been studied in the perioperative period. N-acetylcysteine (NAC) is a potent antioxidant with vasodilatory effects as a result of increased nitric oxide availability. The use of NAC in cardiac surgery has been extensively examined with no benefit found (25). HMG Co reductase inhibitors (statins) have been studied in retrospective cohorts with conflicting results. A recent large randomised controlled trial of patients undergoing cardiac surgery, high dose perioperative atorvastatin did not reduce the

risk of post-operative AKI (26). Aspirin and clonidine have been examined in a randomised controlled trial of patients undergoing non-cardiac surgery. Neither reduced the risk of post-operative AKI (27).

Non-pharmacological Interventions

The importance of achieving the balance of adequate resuscitation without causing fluid overload is becoming clear in the management of AKI(28).

Maintaining renal perfusion through perioperative haemodynamic optimization is arguably the most effective means of preventing post-operative AKI. This is the use of perioperative monitoring and volume expansion through the use of fluid, blood transfusion and inotropes to improve cardiac output and improve oxygen delivery A meta-analysis of 20 studies showed that post-operative AKI was significantly reduced by perioperative haemodynamic optimisation compared with a control group (OR 0.64 95%CI 0.50 to 0.83, $p<0.001$)(29). A retrospective cohort study of 5,127 patients undergoing non-cardiac surgery found that risk of AKI was associated with intraoperative sustained periods of mean arterial pressure less than 60mm Hg (30). It would therefore follow that fluid therapy in the perioperative period may be an effective means of reducing AKI. However, a recent study examining the use of 0.9% saline at a rate of 1.5 ml per kg per hour for 12 hours before major open abdominal surgery showed no reduction in rates of AKI (31). This lack of difference may have been due to the type of fluid used or the lack of a tailored regime based on volume assessment. It is also important to note that fluid overload can be detrimental leading to a reduction in GFR through increased subcapsular pressure and abdominal compartment syndrome (sustained intra-abdominal pressure greater than 20 mmHg with associated new organ dysfunction).

Choice of intravenous fluids in the perioperative period remains controversial. The high chloride content of 0.9% saline has been shown to be associated with AKI compared with balanced solutions (32). More recently, randomised controlled trial comparing balanced crystalloid to 0.9% saline in the ICU setting showed no reduction in risk of AKI(33). Use of

hydroxyethyl starches (HES) are no longer recommended due to concerns regarding nephrotoxicity (34).

While there are no randomised controlled trials to support avoidance of NSAIDs, aminoglycosides, inhibitors of the renin-angiotensin system and contrast media in the perioperative period there is certainly ample evidence that nephrotoxins can cause significant kidney injury in other settings. Minimising exposure to nephrotoxins would therefore seem a logical approach, particularly in high risk patients.

Remote ischaemic preconditioning is thought to protect the kidney from subsequent injury through eliciting brief periods of ischaemia and reperfusion in distant tissues. This has recently been shown to reduce rates of AKI in a randomised controlled trial of 240 high risk patients undergoing cardiac surgery (35). However, other studies have shown no benefit (36, 37). It remains unclear whether general anaesthesia is associated with AKI compared with a combination of general anaesthesia and neuraxial anaesthesia with a meta-analysis suggesting reduced rates of AKI in the combined group but a large cohort study showing no difference(38, 39).

Timing of the initiation of RRT for AKI remains controversial. Two recently published randomised controlled trials have shown conflicting result with the latter showing reduced ninety day mortality following early initiation (40, 41).

In conclusion, post-operative AKI is common and associated with significant adverse events. It remains unclear whether these are caused by the kidney injury itself or whether AKI is simply a marker of underlying disease severity. Awareness of the risk factors for AKI in patients undergoing surgery improves preoperative assessment and allows closer monitoring of patients deemed high risk in the post-operative period. There is no evidence to support the use of pharmacological interventions perioperatively while haemodynamic optimization, avoidance of potential nephrotoxins and closer monitoring are all likely to prevent AKI. Further prospective clinical studies are required.

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Table 1: RIFLE, AKIN and KDIGO definitions for AKI

Stage/Class	Serum Creatinine or GFR	Urine Output
RIFLE (over 7 day window)		
Risk	↑ SCr × 1.5 or ↓ GFR >25%	<0.5 mL/kg/h × 6 h
Injury	↑ SCr × 2 or ↓ GFR >50%	<0.5 mL/kg/h × 12 h
Failure	↑ SCr × 3 or ↓ GFR >75% or SCr ≥ 353.6μmol/l with an acute rise of > 44.2 μmol/l	<0.3 mL/kg/h × 24 h or anuria × 12 h
Loss of kidney Function	AKI requiring RRT >4 weeks	
ESKD	RRT dependent >3 month	
AKIN (over 48 hours)		
1	↑ SCr ≥ 26.5 μmol/l or ↑SCr >=1.5 to 1.9 x baseline	<0.5 mL/kg/h (>6 h)
2	↑ SCr >2 to 3 x baseline	<0.5 mL/kg/h (>12 h)
3	↑ SCr >3 x baseline or SCr ≥ 353.6 μmol/l with acute rise of ≥ 44.2 μmol/l or requiring RRT	<0.3 mL/kg/h (24 h) or anuria (12 h)
KDIGO		
1	↑ SCr ≥ 26.5 μmol/l within 48 hours or ↑SCr >1.5 to 1.9 x baseline over 7 days	<0.5 mL/kg/h (>6 h)
2	↑ SCr >2 to 3 x baseline	<0.5 mL/kg/h (>12 h)
3	↑ SCr >3 x baseline or SCr ≥ 353.6 μmol/l with acute rise of ≥ 44.2μmol/l or initiation of RRT	<0.3 mL/kg/h (24 h) or anuria (12 h)

Table 2: Incidence of AKI according to surgical specialty

Author & Year	Type of Surgery	Definition for AKI	Cohort Size	Incidence
Abdullah 2016(42)	Bariatric Surgery	KDIGO	1230	2.9%
Cabezuelo 2006 (43)	Liver Transplant	≥50% of baseline	184	30.9%
Kimmel 2014 (44)	Orthopaedic (Total joint arthroplasty)	RIFLE	425	14.8%
Grams 2015 (3)	Overall Cardiac Ear Nose &Throat General Orthopaedic Thoracic Urology Vascular	KDIGO	161185 22179 4741 44597 33564 11779 17704 26621	11.8% 8.7% 4.1% 13.2% 10.2% 12% 8.6% 9.2%
Bell 2015 (4)	Orthopaedic Urology Vascular Gastroenterology Gynaecology	KDIGO	7666 823 720 3271 403	7-11% 11.6-15.7% 23.2-25.1% 7.4%-12.2% 4.0-4.5%
Huber 2015 (45)	Vascular	KDIGO	3646	49%
Vaught 2015 (46)	Gynaecology	RIFLE	2341	13%
O'Connor (5)	Major abdominal Surgery (systematic review of 19 studies)	RIFLE AKIN KDIGO	82,514	13.4%

Table 3: Risk Factors for Post-operative AKI

Patient	**Surgery**
Age	Emergency Surgery
Male Sex	Cardiac surgery
ASA grade	Perioperative use of nephrotoxins (ACEI/ARB inhibitor/ NSAIDs/aminoglycosides)
Chronic Kidney Disease	Use of Intra-arterial Balloon Pump (IABP)
Diabetes	Use of CPB
Liver disease	Intraperitoneal Surgery
Congestive Cardiac Failure	Perioperative use of contrast media
Hypertension	

Appendix

Biomarkers

Serum creatinine does not rise until approximately 48 hours after the initial tubular insult and is affected by factors such as age, gender and muscle mass therefore focus has turned to developing more sensitive and specific biomarkers for AKI. The optimum biomarker would detect tissue injury rather than functional damage correlating with severity as well as easy, cheap and quick to measure. This could potentially play an important future role in pre-operative risk stratification allowing earlier detection of AKI and implementation of earlier interventions. The search for biomarkers has led to a number of promising developments. The majority of these studies examine patients undergoing cardiac surgery. The Translational Research Investigating Biomarker Endpoints (TRIBE) Consortium has examined a number of biomarkers in cardiac surgery with the aim of improving pre-operative and post-operative risk stratification of AKI. Promising biomarkers include urine interleukin-18 (IL-18) and plasma neutrophil gelatinase associated lipocalin (NGAL) which have both been found to improve risk stratification (1, 2). Urinary kidney injury molecule-1 (KIM-1) has also found to show promise in early detection of AKI particularly in those undergoing cardiac surgery(3). A recent meta-analysis of 28 studies in adult patients undergoing cardiac surgery examining a number of biomarkers concluded that current biomarkers have generally poor and at best moderate discrimination for AKI when measured within the first 24 hours post cardiac surgery(4). Kashini et al performed a two stage multi-centre study in which they tested 340 proteins including previously described AKI biomarkers. They developed a panel of the top 2 performing biomarkers tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7 [TIMP-2]x[IGFBP7] and validated their ability to predict moderate to severe AKI in 744 Intensive Care Unit (ICU) patients which included post cardiac surgery patients (Sapphire study)(5).This panel has also been tested in non-cardiac surgery with an area under receiving operating characteristic curve (AUC) for the risk of any AKI of 0.85, for early use of RRT 0.83 and 0.77 for 28-day mortality. The investigators found

that [TIMP-2]x[IGFBP7] was the strongest predictor for AKI significantly improving the risk assessment(6). A further study examined this panel in high risk surgical patients. They found that a single urinary [TIMP2]x[IGFBP7] test accurately identified patients at risk for developing AKI within the ensuing 12 hours with an AUC of 0.84 (95% confidence interval, 0.76-0.90; $p < 0.0001$)(7).

Whilst these studies show promising results, biomarkers are not currently used routinely worldwide in post-operative patients. It is likely that it in the future a panel of biomarkers will be developed to facilitate earlier detection of AKI rather than an individual biomarker.

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AKI	Acute Kidney Injury
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
AKIN	Acute Kidney Injury Network
KDIGO	Kidney Disease Improving Global Outcomes
RRT	Renal replacement therapy
NSAID	Nonsteroidal anti-inflammatory drug
CPB	Cardiopulmonary bypass
AUC	Area under receiving operating characteristic curve
ESRD	End stage renal disease
ANP	Atrial natriuretic peptide
NAC	N-acetylcysteine
HES	Hydroxyethyl starches
CABG	Coronary artery bypass graft
ASA	American Society of Anesthesiologists
TRIBE	Translational Research Investigating Biomarker Endpoints
NGAL	Neutrophil gelatinase associated lipocalin
[TIMP-2]x[IGFBP7]	Tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7