PERIOPERATIVE RENAL DYSFUNCTION
ANAESTHESIA TUTORIAL OF THE WEEK 227

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Dr Charlotte Battle, Dr Alistair Hellewell
Royal Devon & Exeter Hospital
Correspondence to: cabattle@doctors.org.uk

QUESTIONS

1) A 58 year old man with a past medical history of hypertension and type 2 diabetes mellitus was admitted for an emergency appendicectomy. On admission he had a creatinine of 110 and a urea of 7.8. Other than raised inflammatory markers, other routine blood results were normal. How many risk factors does this patient have for developing AKI perioperatively?

2) Which of the below medications impair renal autoregulation?
   a. Isoflurane
   b. Ibuprofen
   c. Ramipril
   d. Gentamicin
   e. Penicillin
   f. Suxemethonium

3) True or false?
   a. Normal Adult GFR is 180L/day.
   b. Acute kidney injury in patients with multiorgan failure is associated with a 30% mortality rate.
   c. Serum creatinine levels will generally not rise until GFR has fallen to 50% normal.
   d. Anaemic patient with CKD should receive routine pre-operative blood transfusions to restore haemoglobin concentrations to normal levels.
   e. Renal reabsorption of urea is increased in dehydration states.
INTRODUCTION

Acute Kidney Injury (AKI) in the peri-operative period, previously known as acute renal failure (ARF), is a common clinical complication, however its diagnosis is often delayed and it is frequently managed sub-optimally causing a significant effect on morbidity and mortality. Evidence shows that even small, transient rises in creatinine are associated with an increased risk of death. AKI needs prompt early diagnosis in order to prevent a decline in renal function. There is no standard classification but AKI is defined as an abrupt (within 48 hours) reduction in kidney function.

The AKI network defines the reduction in kidney function as the presence of any one of the following:

- An absolute increase in serum creatinine of ≥ 0.3 mg/dL (≥ 26.4 μmol)
- A percentage increase in serum creatinine of ≥ 150% (>1.5 fold from baseline)
- A reduction in urine output (< 0.5 ml/kg/hour for > 6 hours)

WHY IS IT RELEVANT?

- NCEPOD
In 2009, a report titled “Adding insult to injury” was published by the UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD). This report highlighted the deficiencies in healthcare services in identifying and managing patients with AKI, where cases were lacking basic medical care. It examined the care of patients who died as a result of a diagnosis of AKI and concluded that only 50% of patients received good care as judged by fellow clinicians. The report has prompted guidelines to be developed by the National Institute for Health and Clinical Excellence (NICE) and has highlighted the need to emphasise the importance of risk stratifying patients to identify those at risk of AKI.

- BMJ
In 2010 a clinical review was published in the BMJ emphasising the prevalence of peri-operative AKI. It recognises that peri-operative kidney injury is poorly recognised and increases surgical morbidity and mortality, as well as presenting a significant financial burden to healthcare. This case review recognises the complex nature of such patients and recommends seeking early senior advice with regards to renal replacement therapy (RRT) and critical care support. It also highlights the need to risk stratify patients pre-operatively with the aim to manage them more appropriately with respect to medications management and fluid status in the peri-operative period.

- The Renal Association
The UK Renal Association guidelines report the prevalence of AKI in hospital inpatients as between 1-7%. It has a mortality of between 10% in uncomplicated patients to as high as 80% in high risk populations if renal replacement therapy is required. It is evident that AKI is common and even for the previously well can lead to significant morbidity.

- AKIN
The Acute Kidney Injury Network represents an international group of nephrologists and critical care physicians who are working together to support the development of evidence based recommendations for the management of AKI and a standard definition for classification. This organisation is a development of the Acute Dialysis Quality Initiative who devised the RIFLE definition for staging kidney disease. It has further modified this staging system to reflect the clinical significance of small increments in creatinine, given its reported association with adverse outcomes.
CLASSIFICATION

Table 1: AKIN Staging for Acute Kidney Injury

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SERUM CREATININE CRITERIA</th>
<th>URINE OUTPUT CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase in serum creatinine &gt;0.3 mg/dl (≥26.4μmol/l); or Increase &gt;150-200% (1.5–2x) from baseline</td>
<td>&lt;0.5 ml/kg/hr for &gt;6 hours</td>
</tr>
<tr>
<td>2</td>
<td>Increase in serum creatinine &gt;200-300% from baseline</td>
<td>&lt;0.5ml/kg/hr for &gt;12 hours</td>
</tr>
<tr>
<td>3</td>
<td>Increase in serum creatinine &gt;300% from baseline; or Serum creatinine ≥ 4.0mg/dL (≥354 μmol/l) with an acute increase ≥0.5mg/dL (44 μmol/l); or Receiving renal replacement therapy (RRT)</td>
<td>&lt;0.3ml/kg/hr for &gt;24hrs Or anuria for 12 hours</td>
</tr>
</tbody>
</table>

*Source: AKI Network*

The AKIN staging for AKI reflects the importance of a raise in serum creatinine with regards to adverse outcomes. A raise in creatinine is a red flag, which should prompt urgent investigation and management.

PATHOPHYSIOLOGY

Along with maintaining fluid homeostasis, one of the main functions of the kidney is to excrete waste products, water soluble medications and water soluble products of metabolism. It does this by filtering the blood via its functional units, the nephrons, utilising active and passive processes including ultrafiltration, followed by reabsorption and tubular secretion, depending on the solute.

The GFR is the volume of plasma filtered per unit time by all the glomeruli of the kidneys. This is normally 125ml/min in adults. Renal autoregulation is an intrinsic property of the kidney independent of neurohumoral stimulation which allows GFR to be preserved at a constant rate at mean arterial blood pressures of between 70-170mmHg. This is possible due to changes in local vascular resistance of the afferent and efferent arterioles secondary to renal vasoactive substances such as norepinephrine, epinephrine, acetylcholine, angiotensin, prostaglandins and kinins. This protective mechanism of the kidney can be altered with medications, as described below, which may therefore exacerbate AKI.

Creatinine is an end product of skeletal muscle metabolism and is present at a fairly constant concentration in the plasma. It is freely filtered, not reabsorbed and small amounts can be secreted. When GFR decreases by more than 50%, creatinine exceeds its ability to be filtered and levels will rise in the plasma. Therefore a rising serum creatinine is indicative of renal dysfunction. It must be remembered that the trend of serum creatinine is important, as concentration is related to body skeletal muscle mass. Therefore, where it is diminished, for example in the elderly patient, a “normal range” laboratory creatinine may indicate AKI. Other factors that may affect serum creatinine concentration include drugs, diet, BMI, other organ dysfunction and ethnicity.
Pre-operative creatinine is a sensitive marker of existing renal dysfunction and a small rise reflects a significant deterioration in renal function. The below graph demonstrates the relationship between creatinine and GFR. This graph demonstrates that creatinine only begins to increase after more than 50% of renal nephron function has been lost signifying that a rise in creatinine is critically important.

**Figure 1:** Relationship between plasma creatinine and GFR

Urea, a waste product produced in the liver, is a less reliable indicator of renal function. It is freely filtered, but also reabsorbed. Being a product of protein metabolism, it’s production also varies greatly depending on protein intake, protein catabolism and variable rates of renal reabsorption. Urea reabsorption is increased in states of dehydration as it is taken up via aquaporins in response to increased vasopressin secretion.

**AKI**

AKI can occur in normal or diseased kidneys. A biochemical disturbance occurs when more than 50% of renal function is lost. Therefore with a rise in creatinine, especially in Chronic Kidney Disease (CKD), there is little functional reserve. It is important to optimise these patients pre-operatively to avoid further deterioration in renal function.

AKI can be classified as pre-renal, renal or post renal dysfunction. Pre-renal dysfunction is the most common in surgical patients. Surgery itself involves many risk factors contributing to this (see table 2). Patients who are shocked, or with probable atheromatous disease are at high risk of developing AKI.

A diagnosis of AKI in the peri-operative period should prompt the consideration of other causes such as intrinsic renal dysfunction, post renal obstruction, and crucially, iatrogenic causes – including recently administered drugs.

Whatever the cause, AKI is a condition that needs prompt recognition and management. Management comprises a history combined with clinical examination and specific blood tests, looking in detail at fluid status and serum biochemistry. Blood tests looking specifically for metabolic imbalance and complications of renal dysfunction including hyperkalaemia and acidosis should be performed. If renal tract obstruction is suspected then investigation of the renal tract should be performed, e.g. renal ultrasound imaging.
**Table 2: Fluid losses in the peri-operative patient**

<table>
<thead>
<tr>
<th>PERI-OPERATIVE FASTING</th>
<th>INSENSIBLE LOSSES</th>
<th>THIRD SPACE LOSSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency frequently worse than elective</td>
<td>Sweat</td>
<td>Oedema secondary to inflammation</td>
</tr>
<tr>
<td></td>
<td>Ventilation</td>
<td>Haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
<td>Nasogastric tube losses</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drains</td>
</tr>
</tbody>
</table>

**PRE-OPERATIVE MANAGEMENT**

- Risk stratification
- Optimising the patient
- Medication review
- Need for nephrology / HDU / ICU

**Risk Stratification for perioperative AKI**

**Table 3: Risk index for developing AKI in the peri-operative patient**

<table>
<thead>
<tr>
<th>RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;56</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Active Congestive cardiac failure</td>
</tr>
<tr>
<td>Presence of ascites</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Emergency Surgery</td>
</tr>
<tr>
<td>Intra-peritoneal surgery</td>
</tr>
<tr>
<td>pre-renal dysfunction</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
</tr>
</tbody>
</table>

By recognising the above risk factors, patients at risk of AKI peri-operatively can be identified. A combination of more than six of the above risk factors have a greater than 10% incidence of developing AKI. Factors which should also be considered are shown in table 4.
Table 4: Other risk factors for AKI

<table>
<thead>
<tr>
<th>PATIENT FACTORS</th>
<th>ANAESTHETIC FACTORS</th>
<th>SURGICAL FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Peri-operative hypotension</td>
<td>Prolonged surgery</td>
</tr>
<tr>
<td>Gender</td>
<td>Blood product administration</td>
<td>Major surgery</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>Drugs</td>
<td>Cardiothoracic surgery</td>
</tr>
<tr>
<td>Hypovolaemia</td>
<td></td>
<td>Transplant surgery</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td>Immunosuppressant therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aortic clamping</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significant 3rd space losses</td>
</tr>
</tbody>
</table>

Patients with the above risk factors or existing CKD should prompt the need for further assessment of renal function including serum biochemistry, full blood count and liver function tests.

Optimising Management
Patients with known CKD or AKI should be optimised prior to going to theatre. Measures include optimising blood pressure and fluid balance, correcting acidosis or hyperkalaemia. Drugs that are excreted solely via the kidney should be used cautiously and with appropriate dose adjustment. Those with anaemia secondary to CKD should not be transfused pre-operatively unless there is evidence for ongoing blood losses as this may precipitate fluid overload.

Medicines Management
Patients may already be taking drugs that put them at risk of AKI. On admission, those with known or previous renal dysfunction, or those susceptible to peri-operative renal dysfunction should have a medications review. Medications may need to be stopped or used with caution during the peri-operative period and care should be taken with prescribing peri-operatively, especially with regards to certain analgesics and antibiotics, e.g. NSAIDs and gentamicin:

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)
- This ubiquitous group of analgesic drugs can have significant effects on renal function, especially in those with reduced renal reserve. They impair renal autoregulation by inhibiting prostaglandin mediated dilatation of the afferent glomerular arteriole, the purpose of which is to maintain renal blood flow in the face of systemic vasoconstriction, e.g. in hypovolaemia.
- They are also known to cause acute interstitial nephritis.
- These drugs should be used with caution in the peri-operative period in patients at significant risk of AKI. The benefits and risks to the patient have to be balanced and monitoring of renal function is advised.

Angiotensin Converting Enzyme Inhibitors (ACEi) & Angiotensin Receptor Blockers (ARB)
- These prevent the local action of bradykinins, which are responsible for constriction of the efferent glomerular arteriole, the purpose of which is to maintain glomerular perfusion pressure in renal autoregulation.
- It is suggested that ACEi or ARBs be stopped on the day of surgery for renal protection and to minimise the risk of hypotension with anaesthetic agents.

Antibiotics
- Renal tubular toxicity may occur at high concentration in aminoglycosides e.g. gentamicin.
- Acute interstitial nephritis (AIN) can occur with certain antibiotics e.g. penicillins, cephalosporins and fluoroquinolones. This accounts for one third of all drug induced AIN.
IV Contrast Agents
- These may cause pathological vasoconstriction in a vulnerable kidney.
- In susceptible patients, pre-hydration with IV crystalloid may be of benefit and where possible, the use of lower volumes of contrast.

Senior Support
Doctors managing patients at risk of significant peri-operative kidney injury should liaise with support services for peri-operative management, including nephrology services and high dependency or critical care units where increased monitoring or RRT can be offered.

INDUCTION OF ANAESTHESIA

With the exception of ketamine, all commonly used anaesthetic agents decrease systemic vascular resistance, reduce both cardiac contractility and cardiac output and attenuate the normal response to hypovolaemia. The haemodynamically unstable patient is therefore at risk of cardiovascular collapse.

Measures to prevent AKI are simple and an essential part of good peri-operative care. In the anaesthetic room adequate IV access should be obtained, the patient’s intravascular volume should be adequately restored and if necessary an arterial line inserted and other invasive monitoring techniques considered.

Induction Agents
The dose of induction agent should be carefully considered. Many patients at risk of AKI will need a reduced dose. Prior to renal excretion, induction agents undergo redistribution and biotransformation into inactive products. However in hypovolaemia there is a diversion of blood to essential organs and across the blood brain barrier, therefore effects of induction agents may be exacerbated.
Volatile anaesthetic agents such as isoflurane and sevoflurane contain nephrotoxic fluoride, which poses a theoretical risk for AKI although there is little evidence for avoidance of these agents.

Opioids
AKI prolongs the action of opioids as they are renally excreted. The administration of lower doses is recommended in these patients.

Muscle relaxants
Suxamethonium should be avoided in AKI patients with documented raised potassium levels as it increases potassium efflux from muscle cells and its administration can lead to life-threatening hyperkalaemia. Non depolarising muscle relaxants have an altered duration of action, especially in acidosis; in particular pancuronium and vecuronium should be avoided as they may remain unchanged in urine.

INTRA-OPERATIVE MANAGEMENT

The aim of intra-operative management in those at risk of AKI is to maintain adequate renal perfusion pressure. The following may allow optimal intra-operative care:
- Appropriate intravascular volume replacement
- Avoidance of nephrotoxic drugs
- Urinary catheter aiming for a urine output >0.5ml/kg/hr
- Maintenance of a suitable Mean Arterial Pressure (MAP) for the patient and operation
- Monitoring of central venous pressure (CVP)
- Monitoring of cardiac output
- Vasopressors (there is no evidence supporting the use of “renal dose” dopamine)
- Anticipation of anaesthetic and surgically induced haemodynamic perturbations both intra and post operatively.

Intra-operatively the neurohumoral response to surgery causes a sympathetic response, releasing vasopressin, aldosterone and cortisol in the “fight or flight” response. One of the aims of this is to aid salt and water retention protecting the renal vasculature. Anaesthetic agents, ACE inhibitors and NSAIDs will alter this protective response.
THE POST-OPERATIVE PERIOD

Post operatively, patients may remain at risk of AKI due to relative hypotension caused by ongoing 3rd space fluid loss, pharmacological causes (NSAIDs and ACEi/ARBs) and residual effects of anaesthesia. Epidural anaesthesia has been cited as being a particular culprit by causing hypotension secondary to sympathetic blockade. The risk of AKI will be exacerbated if there is inadequate intra-operative fluid replacement. Post-operative fluid therapy is of utmost importance. This is guided by clinical examination, monitoring of urine output and monitoring renal function and electrolytes. It has been shown that 80% of patients with post op AKI respond to fluid therapy alone - ‘Optimise fluid and defend pressure’.

Those with significant metabolic disturbance e.g. acidosis, hyperkalaemia, uraemia or fluid overload not responsive to simple measures may need RRT in an appropriate setting.

Anaesthetists are often responsible for prescribing post-operative analgesia including NSAIDs. This should be done with extreme caution if the patient is at increased risk of developing AKI.

Patients who do develop AKI post-operatively should have this documented, and if possible highlighted on the anaesthetic charts to inform future anaesthetists.

MORBIDITY AND MORTALITY

Peri-operative AKI carries significant morbidity and mortality. Those at risk need to be identified early and managed accordingly. AKI has 3 possible outcomes

1. Return to baseline renal function
2. Development of CKD in previously normal kidneys
3. Accelerated progression of disease in patients with pre-existing CKD (5 fold increased risk for end stage disease)

The 2010 Bothwick clinical review highlighted the following points with regards with morbidity and mortality:

- AKI after major surgery worsens long term survival with normal baseline renal function. The mechanisms involved were:
  o Renal insult causing metabolic imbalance causing death
  o Distant organ injury causing dysfunction and death
  o AKI after non-cardiac surgery is an independent predictor for hospital mortality 26.4% vs 2.5%
  o Patients who completely recover after postoperative AKI still have increased adjusted hazard ratio for death of 1.20 over longer term

- Prolonged hospital admission
  o Organ dysfunction, metabolic disturbance and fluid overload
  o Post op immobility, poor wound healing, infection

- Progression to Chronic Kidney Disease (CKD)
  o Develop CKD in previously normal kidneys
  o Worsening of existing CKD, and a 5 fold increase in the risk of developing ESRF

ADVANCES IN EARLY DETECTION OF AKI

As explained earlier, an increase in creatinine signifies a loss of more than 50% of glomerular filtration, therefore several biomarkers of AKI are currently being researched in an attempt to detect AKI in its earlier stages:

- Neutrophil Gelatinase Associated Lipocalin (NGAL) – a protein found excess in the plasma and urine of patients with AKI up to 48hrs prior to a rise in creatinine concentration.
- Serum Cystatin C – a protease inhibitor less affected than creatinine by age, sex, muscle mass and diet.
SUMMARY
AKI is common peri-operatively. With good initial assessment and simple measures including fluid management and avoidance of nephrotoxic drugs, it is preventable. Delays in recognising and treating AKI lead to longer inpatient stay, increased mortality and significantly increased healthcare costs. Those who recover may have a lasting deterioration in renal function or distant organ damage and are more likely to have complications in the future.

Patients who develop AKI and have complications such has hyperkalaemia, electrolyte imbalance, acidosis or volume overload are likely to die unless RRT is provided. Liaison with nephrology and critical care services is recommended in such cases to allow optimal patient management.

ANSWERS TO QUESTIONS

1) This patient has 7 risk factors for AKI (table 3) and has >10% risk of developing AKI.
2) F T T F F F
3) T F T F T

REFERENCES AND FURTHER READING


http://www.renal.org/Clinical/GuidelinesSection/AcuteKidneyInjury.aspx


Abelha FJ et al Outcome and quality of life of patients with AKI after major surgery Nefrologica 2009;29:404-14