Southern African Journal of Anaesthesia and Analgesia 2015; 21(2):5-8
http://dx.doi.org/10.1080/22201181.2015.959342

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

REVIEW

A review of renal protection strategies

Erna Meyer*

Northland District Health Board, Whangarei Base Hospital, Whangarei, New Zealand
**Corresponding author, email: erna.meyer@northlanddhb.org.nz*

Globally, more than 10 million people are affected every year by acute kidney injury (AKI) and approximately 6% of hospital patients sustain some degree of kidney injury during their hospital event. Reducing perioperative kidney injury may significantly improve patient outcomes. As perioperative physicians, we are in a position to have some influence on renal outcomes.This article is a review of the current literature on the relevance of renal protection, definitions, mechanisms and new biomarkers of AKI, as well as improved renal perfusion strategies. It specifically considers the renal effects of general and regional anaesthesia, intra-abdominal pressure and abdominal compartment syndrome. The usefulness of certain drugs is investigated. Mechanisms of injury by nephrotoxins, as well as strategies to minimise these injuries, are discussed. Intravenous fluids are briefly mentioned as they relate to renal function.

Keywords: acute kidney injury, chloride, chronic kidney disease, glomerular filtration rate, goal-directed therapies, N-acetyl-cysteine, nephrotoxins, perioperative urine output, postoperative kidney injury, renal failure, renal perfusion, renal protection, sodium bicarbonate

Introduction

The kidneys are uniquely vulnerable to injury. They make up 1% of the body weight, but receive approximately 20% of the cardiac output. The medulla receives only 1-2% of the renal blood flow (RBF) and this portion decreases with reduced RBF. Autoregulation occurs from 80-180 mmHg, which is significantly higher than that in most other organs. It should be kept in mind that renal perfusion is pressure, as well as flow, dependent.

Patients with acute kidney injury (AKI) who need renal replacement therapy (RRT) have a 33% risk of dying in the first 90 days and a 32% risk of dying in the next 3.5 years. This is a higher mortality rate than that for acute respiratory distress syndrome. Although few patients who need RRT for AKI require dialysis afterwards, they have a high (> 40%) incidence of developing albuminuria and an 8.8-fold increased risk of developing chronic kidney disease (CKD).[1] Chronic proteinuria, independent of estimated glomerular filtration rate (GFR), and CKD, have repeatedly been demonstrated to be risk factors for death, cardiovascular disease and end-stage renal disease.

Acute renal failure is not "acute renal success".[2] It was shown that renal oxygen consumption remained constant in patients with AKI, even though sodium resorption was reduced by 60%. The overall net resorption of sodium consumed 2.4 times more oxygen in injured than in healthy kidneys, possibly owing to loss of tight junctional integrity between the tubular cells. On average, the RBF decreased by 40% in AKI and renal oxygen extraction increased to 68%, a very narrow safety limit.

Definitions of acute kidney injury

The USA National Surgical Quality Improvement Program (NSQIP) defines AKI as a > 177 mmol/l (2 mg/dl) rise in serum creatinine which gives a prevalence of AKI of 7% in surgical patients in the USA. A recent article demonstrated that the optimal discrimination levels for a change in serum creatinine associated with adverse postoperative outcomes may be as low as 18 mmol/l (0.2 mg/dl).[3]

RIFLE criteria (risk, injury, failure, loss and end-stage renal disease) define AKI as more than a 50% decrease in creatinine clearance. This provides a prevalence of AKI of 37% in postoperative patients in the USA, significantly higher than that outlined by the NSQIP.

The Kidney Disease Improving Global Outcomes guideline defines AKI as an increase of 27 mmol/l (0.3 mg/dl) within 48 hours or a 50% increase from baseline creatinine; very similar to the RIFLE criteria and is easy to use in clinical practice.

Biomarkers of renal function

Cystatin C is produced by nucleated cells and is freely filtered, but not reabsorbed by the kidneys. It is independent of gender, age, muscle mass and diet, and may be a better indicator of GFR than creatinine.

Glutatione S-transferase-alpha (GSTA) is a sensitive (but non-specific) biomarker for oxidative stress in liver and kidney cells.

Neutrophil gelatinase-associated lipocalin (NGAL) is probably the most useful of the new biomarkers for AKI. It is produced by renal tubular cells, and becomes elevated within hours of the onset of AKI, rather than days, as is the case with creatinine. NGAL identified more cases of subclinical kidney injury than creatinine alone in recent studies, and suggested that these patients were at greater risk of death than control patients.

Mechanisms of perioperative AKI include:

- Hypotension, regardless of the cause.
- Hypovolaemia.
- Fluid overload with raised intra-abdominal pressure (IAP).
- Low cardiac output states.
- High cardiac output states, with profound vasodilatation and capillary leak. Vasodilatation lowers mean arterial pressure (MAP) and causes dilatation of the efferent arteriole, both of which reduce GFR.
- Direct trauma or embolism to the kidneys or renal arteries, e.g. during surgery.

- Metabolic derangement, e.g. liver failure or hyperthermia.
- Nephrotoxic drugs and dyes, including haemoglobin and myoglobin.

Renal protection strategies include:

- Identifying patients at risk of AKI. These include patients with pre-existing renal disease, those undergoing major thoracic or abdominal surgery, elderly patients, patients with significant co-morbidities (diabetes, hypertension, heart failure, peripheral vascular disease or liver dysfunction), patients with any condition causing an ongoing capillary leak, e.g. multi-trauma, major burns, sepsis, systemic inflammatory response syndrome (SIRS), multiorgan dysfunction, those with sustained intra-abdominal hypertension (IAH) and those exposed to internal or external nephrotoxins.
- Maintaining adequate intravascular volume, cardiac output and MAP. A recent meta-analysis[4] found that protocolised therapies with specific haemodynamic goals can reduce the incidence of AKI. Studies varied significantly in their approach to timing, type of intervention, monitoring, targets and patient populations. The conclusion was that the adoption of any haemodynamic protocol to prevent AKI appears to be better than no protocol at all. Conventional haemodynamic monitoring may be appropriate if basic targets are met, but a shift to higher monitoring levels may be necessary if the patient fails to improve after initial fluid loading. Patients with hypotension-induced renal impairment may need a higher MAP (70-80 mmHg), rather than the usual 65 mmHg, to prevent secondary renal injury.
- Preventing hypoxia – The deadly duo of hypoxia and ischemia may be synergistic.[5]
- Preventing hyperthermia.
- Monitoring IAP and preventing fluid overload.
- Carefully managing nephrotoxic factors.
- Recognising that some drugs may be useful in specific clinical situations.

The effects of anaesthesia

Fluid loading is the mainstay of perioperative haemodynamic optimisation. It should be kept in mind that renal handling of intravenous (IV) fluid loads during anaesthesia is very different to that in the awake patient. A fluid load rapidly excreted when awake, may remain unexcreted when the same patient is anaesthetised.[6] It is important to aim for euvolaemia, and to avoid hypovolaemia and excessive fluid loading as this may contribute to gut oedema and IAH.

The effect of volatile anaesthetic-associated hypotension on renal function, and particularly on urine output, is not well documented. Volatile agents probably dilate the efferent arteriole non-selectively, thus causing a decrease in GFR and urine output, without causing AKI. There is some evidence that volatile agents may also interfere with vasopressin V2 aquaporin receptors in the kidneys, thereby increasing fluid retention. Total IV anaesthesia may have less effect on urine output owing to less pronounced vasodilatation. The effect of sympathetic activation on the kidneys is a balance between the systemic circulatory effects, renal hormonal effects and intra-renal vascular effects. Fluid retention during surgery is usually the overall effect.[6]

It may not be useful to chase urine output during anaesthesia for low-risk surgery. Anaesthetised patients who are euvolaemic or slightly hypervolaemic often produce small volumes of dilute-looking urine. The urine of these patients has high Na (50-100 mmol/l) and normal or near-normal osmolality. Hypovolaemic patients, in contrast, produce small volumes of concentrated dark urine with low Na (< 20 mmol/l) and high osmolality. They obviously need to receive appropriate IV fluid resuscitation. The clinical picture should confirm hypovolaemia.[6]

Mild hypotension during anaesthesia is common, generally well tolerated and seldom aggressively treated. During anaesthesia, GFR and urine output seem to be passively dependent on MAP. Impressive polyuria often results if blood pressure is maintained with vasopressors above the kidneys' autoregulatory limit. Paradoxically, this can sometimes be so pronounced that a negative fluid balance is produced, which may then precipitate AKI.[6]

Intra-abdominal hypertension and abdominal compartment syndrome

IAH is the sustained pathological elevation of IAP. It is usually determined by standardised measurement of the bladder pressure, with the patient relaxed in a horizontal position. Normal IAP is 2-5 mmHg, but can be as high as 12 mmHg in obese patients. IAP is elevated in critically unwell patients to 5 mmHg or higher. Organ dysfunction usually sets in at levels above 20 mmHG. Vigorous fluid resuscitation during a phase of capillary leak, regardless of the cause, alters normal hydrostatic and oncotic pressure gradients, resulting in interstitial gut oedema that impairs splanchnic perfusion. Increasing IAP exerts upward pressure on the diaphragm, which increases venous congestion and impairs lymphatic drainage. This leads to a self-perpetuating vicious circle, with ever-increasing IAP.[7]

The renal effects of increasing IAP are significant. Oliguria and worsening creatinine clearance are among the earliest signs of abdominal compartment syndrome (ACS) developing, e.g. a SIRS patient progressively developing a tighter abdomen, followed by decreasing urine output (UOP), despite ongoing fluid resuscitation. Increasing IAP directly compresses the renal veins and cortical arterioles, which increases renal venous, as well as arterial, resistance. Renal vascular resistance increases up to fivefold. The overall effect is reduced renal arterial flow and reduced GFR (GFR decreases to less than 25% when IAP is above 20 mmHg). At the same time, the antidiuretic hormone (ADH) and the aldosterone, renin and angiotensin systems are upregulated, resulting in even more sodium and water retention. It is important to maintain adequate abdominal perfusion pressure (APP) at all times. APP = MAP–IAP, and should be maintained at 60 mmHg or higher.[7]

ACS is defined as sustained IAP above 20 mmHg, associated with new-onset organ failure.

The management of ACS consists of prevention, conservative management and possibly surgery, as follows:

- Anaesthetic management – Anaesthetic management reduces the risk of ACS developing by avoiding excessive fluid loading in critically unwell patients.
- Critical care – It is important to sedate and paralyse to relax the abdominal wall. Optimise APP with inotropic support and careful fluid therapy. Correct a gross positive fluid balance by moderate fluid restriction and judicial use of diuretics or continuous haemofiltration with fluid removal. Consider plasma exchange to decrease inflammatory cytokine levels. This may reduce an ongoing capillary leak in patients with extensive burn injury. Evacuate the intraluminal contents with a nasogastric tube, colonoscopic decompression and/or prokinetic agents. Large abdominal fluid collections can be drained at the bedside under ultrasound guidance.[7]
- Surgical management – Decompressive laparotomy is the definitive treatment for ACS.

Useful drug therapies to prevent acute kidney injury

The only drug treatment that has been proven to be renal protective is high-dose N-acetyl-cysteine (1 200 mg twice daily for 48 hours) to prevent contrast-induced AKI.There is no convincing evidence of any benefit provided by mannitol in preventing secondary kidney injury above aggressive hydration alone. However, a recent single-centre, randomised controlled trial demonstrated improved RBF and increased GFR with mannitol in the setting of complicated cardiac surgery.[8] Mannitol is still recommended for use in adults with pigment-associated AKI.

There is also no convincing evidence of the benefit of loop diuretics in preventing secondary kidney injury. Nonetheless, loop diuretics are still recommended in children with pigment-induced AKI if urine output becomes inadequate. Synthetic vasopressins (terlipressin or ornipressin), combined with albumin, may be useful in patients with hepatorenal syndrome.

Nephrotoxins

Nephrotoxic drugs are contributing factors in 20–25% of AKI. Radiocontrast-induced AKI is associated with threefold increased mortality in critically unwell patients.

Mechanisms of drug-induced renal injury include

- A direct toxic effect on the renal tubules, causing cellular injury.
- Crystal-induced tubular injury with luminal obstruction.
- Renal interstitial flogosis with acute interstitial nephritis.
- Indirect nephrotoxicity – Impaired renal perfusion.
- Impaired pharmacokinetics in critically unwell patients, leading to overdose secondary to delayed clearance or decreased protein binding.
- Drug interactions – Clarithromycin may lead to severe hypotension and AKI in patients treated with calcium-channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors or angiotensin II-receptor blockers (ARBs).

Strategies to protect the kidneys against nephrotoxic drugs include:

- Ensuring adequate hydration before each dose.
- Avoiding concomitant nephrotoxins and monitoring drug efficacy and toxicity.
- Avoiding perioperative NSAIDs in hypovolaemic, hypotensive, elderly and diabetic patients, those with CKD, as well as those on ACE inhibitors and ARBs.
- Withholding antihypertensive drugs from postoperative patients who are normotensive or slightly hypotensive, including patients with epidurals, sepsis and SIRS, immediately after major trauma and surgery and from patients with an existing AKI.
- Tailoring antibiotic dosing to the drug class – Recommendations include a once-daily administration of an aminoglycoside antibiotic, the continuous infusion of vancomycin, the prolonged infusion of acyclovir and sulpha drugs, and a high-dose of, with an extended interval for, colistin.
- Minimising radiocontrast-induced kidney injury – It is important to prehydrate, using hypo- or iso-osmotic contrast at the lowest possible volumes, withholding other nephrotoxins whenever possible, and considering pre-emptive N-acetyl-cysteine, preferably the day before and on the day of imaging.

Intravenous fluids

An in-depth discussion of IV fluids is beyond the scope of this article. A short summary is warranted as some IV fluids may influence kidney function. We gained significant knowledge from the famous randomised controlled trials [A comparison of albumin and saline for fluid resuscitation in the intensive care unit (SAFE), 2004,[9] Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP), 2008,[10] Assessment of haemodynamic efficacy and safety of 6% hydroxyethel starch 130/0.4 vs 0.9% NaCl fluid replacement in patients with severe sepsis (CRYSTMAS), 2012,[11] CRYSTMAS letter,[12] 6S, 2012[13] and Hydroxyethel starch or saline for fluid resuscitation in intensive care (CHEST), 2012],[14] and more recently, from a prospective sequential analysis of perioperative fluid therapy with tetrastarch and gelatin in cardiac surgery,[15] together with editorial comment,[16] published in November 2013. This allows us to conclude that balanced crystalloids, blood products and albumin are probably safe, and that synthetic colloids can potentially cause kidney injury if used in large volumes or in septic patients. High chloride loads and supraphysiological doses of bicarbonate should also be avoided.

The effects of "abnormal saline" on renal perfusion and GFR were clearly demonstrated in a recent randomised controlled, double-blind crossover study on 12 healthy volunteers.[17] The infusion of normal saline, but not Plasma-Lyte®, caused a progressive decline in renal cortical perfusion, as well as in renal blood flow velocity. Compared to Plasma-Lyte®, there was a statistically significant longer time to first micturition ($p < 0.006$), reduced urinary volume ($p < 0.002$), higher urine Na ($p < 0.025$), increased weight gain ($p < 0.022$), and greater expansion of extravascular fluid compartment ($p < 0.031$) with saline. NGAL was not increased after either infusion. It must be taken into account that this study was performed on healthy volunteers, and that only two litres of fluid were used. It is conceivable that kidney injury could result in patients with existing kidney dysfunction, or if a huge volume of saline was used for resuscitation.

Chloride was described as the "forgotten electrode" in a recent review.[18] Chloride is the dominant negative ion, contributing to a third of plasma tonicity, and is also a key contributor to the strong ion difference. The Stewart approach to acid base balance highlights the role of strong ion difference and chloride in the pathogenesis of metabolic acidosis. Hyperchloraemic acidosis has been shown to be proinflammatory in rats, inducing nitric oxide, increasing the interleukin (IL)-6:IL-10 ratio, and increasing tumour necrosis factor DNA binding and cytokine expression. The effect of chloride on the kidneys includes renal vasoconstriction secondary to increased tubular chloride resorption and thromboxane-mediated renal vasospasm. Hyperchloraemia increases renal vascular responsiveness to angiotensin II, and the increased osmolality associated with hyperchloraemia may stimulate secretion of the ADH, leading to further fluid retention. GSTA and NGAL were significantly higher in older postoperative cardiac surgery patients receiving normal saline, compared to those receiving balanced solutions.

A recent multicentre randomised controlled trial investigated the possible benefit of prophylactic perioperative sodium bicarbonate infusions to prevent postoperative AKI in high-risk cardiac surgery patients.[19] The trial was terminated at interim analysis because more patients receiving bicarbonate developed AKI and a greater proportion of these patients died in hospital. The authors concluded that alkalinisation of urine with sodium bicarbonate after cardiac surgery is ineffective and possibly harmful.

Recommendations

Recommendations include the following:

- Follow the first Hippocratic principle: Do no harm!
- Realise that there is no "magic bullet". There is no single evidence-based intervention for the prevention of AKI.

- Note that recommendations for the prevention of AKI are mostly "negative".
- Be aware that management should be guided by protocolised haemodynamic optimisation.
- Remember that the correct type and dose of resuscitation fluid should be used.
- Optimise the intra-abdominal perfusion pressure.
- Minimise secondary renal injury owing to nephrotoxins and other systemic factors.

References

1. Gallagher M, Cass A, Bellomo R, et al. POST-RENAL study investigators and the ANZICS clinical trials group. Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized controlled trial. PLOS Med. 2014 Feb;11(2):1–13.
2. Redfors B, Bragadottir G, Sellgren J, Sward K, Rickson S. Acute renal failure is NOT an "acute renal success" – a clinical study on the renal oxygen supply/demand relationship in acute kidney injury. Critic Care Med. 2010;38(8):1695–701. http://dx.doi.org/10.1097/CCM.0b013e3181e61911
3. Bihorac A, Brennan M, Ozrazgat-Baslanti T, Bozorgmehri S, Efron P, Moore F, et al. National surgical quality improvement program underestimates the risk associated with mild and moderate postoperative acute kidney injury. Critic Care Med. 2013;41(11):2570–83. http://dx.doi.org/10.1097/CCM.0b013e31829860fc
4. Brienza N, Giglio M, Dalfino L. Protocoled resuscitation and the prevention of acute kidney injury. Curr Opinion Critic Care. 2012;18:613–22. http://dx.doi.org/10.1097/MCC.0b013e32835944d6
5. Dubin A. The lethal duo of hypoxemia and ischemia. Critic Care Med. 2013;41 (11):2664–5. http://dx.doi.org/10.1097/CCM.0b013e3182982507
6. McLoughlin P. Urine output: to chase or not to chase? Australasian anaesthesia (ANZCA Blue Book). 2013:23–26. Available from ANZCA website: http://www.anzca.edu.au/resources/college-publications: with login: http://asp-au.secure-zone.net/v2/index.jsp?id=522/576/4135&lng=en
7. Carr JA. Abdominal compartment syndrome: a decade of progress. J Am College Surg. 2012;9(4): 135–46. Available from: http://dx.doi.org/10.1016/j.jamcollsurg.2012.09.004
8. Bragadottir G, Redfors B, Ricksten S. Mannitol increases renal blood flow and maintains filtration fraction and oxygenation in postoperative acute kidney injury: a prospective interventional study. Critic Care Med. 2012;16:R159. http://dx.doi.org/10.1186/cc11480
9. Finfer S, Bellomo R, Boyce N, French J, Myburgh JA, Norton R. The SAFE study investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56.
10. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125–39. http://dx.doi.org/10.1056/NEJMoa070716
11. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Critic Care Med. 2012;16(3):R94. Available from: http://ccforum.com/content/16/3/R94 http://dx.doi.org/10.1186/cc11358
12. Hartog CS, Reinhart K. Letter: CRYSTMAS study adds to concerns about renal safety and increased mortality in sepsis patients. Critic Care Med. 2012;16(6):350, 2247–56. Available from: http://ccforum.com/content/16/6/454
13. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124–34. http://dx.doi.org/10.1056/NEJMoa1204242
14. Myburgh JA, Finfer S, Bellomo R, et al. The CHEST trial investigators. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012 Oct;10:1056, 1–11.
15. Bayer O, Schwarzkopf D, Doenst T, et al. Perioperative fluid therapy with tetrastarch and gelatin in cardiac surgery – a prospective sequential analysis. Critic Care Med. 2013;41(11):2532–42. http://dx.doi.org/10.1097/CCM.0b013e3182978fb6
16. Hall R. Artificial colloids Critic Care Med. 2013;41(11):2651–3. http://dx.doi.org/10.1097/CCM.0b013e31829cb24d
17. Chowdhury A, Cox E, Francis S, Lobo D. A randomised controlled double-blind crossover study on the effects of 2L infusions of 0.9% saline and plasma-lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Anal Surg. 2012;256:18–24. http://dx.doi.org/10.1097/SLA.0b013e318256be72
18. Yunos N, Bellomo R, Story D, Kellum J Bench-to-bedside review: chloride in critical illness. Critic Care Med. 2010;14:226. Available from: http://ccforum.com/content/14/4/226 http://dx.doi.org/10.1186/cc9052
19. Haase M, Haase-Fielitz A, Plass M, et al. Prophylactic perioperative sodium bicarbonate to prevent acute kidney injury following open heart surgery: a multicentre double-blinded randomized controlled trial. PLoS Med. 2013;10(4):e1001426. Available from: www.plosmedicine.org http://dx.doi.org/10.1371/journal.pmed.1001426

Received: 25-04-2014 Accepted: 03-07-2014