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REVIEW / *DERLEME*

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Perioperative Acute Kidney Injury

Perioperatif Akut Böbrek Hasarı

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ABSTRACT Acute kidney injury (AKI) is one of the important complications of the perioperative period, and associated with increased risk of chronic kidney disease, renal replacement therapy requirements, increased cost, and risk of mortality. In this overview, we summarized baseline confounders and surgical procedure related risk factors contributing to the perioperative AKI, which may serve as risk scores, improve early diagnosis, contribute to prevention, and early management of AKI. There are immediate needs for context specific clinical prediction scores and novel biomarkers to very early diagnose AKI. Preventive guidance provided by Kidney Disease: Improving Global Outcomes is a helpful practical tool for clinicians. Potential roles of novel biomarkers and their context specific contributions require further exploration and close attention. Perioperative hemodynamics and oxygenation appear to contribute to AKI. Therefore, while their optimization can be recommended, their detailed and context specific roles need further explored. Overall, decreased exposure to nephrotoxic agents is recommended to further decrease the impact of perioperative AKI.

Keywords: Perfusion, oxygen, oxygenation, hypoxia, oxygen delivery, blood pressure, hypotension, hemoglobin, acute kidney injury, creatinine, lipocalin (NGAL), hypoxia inducible factor, Kidney Disease: Improving Global Outcomes

ÖZ Akut böbrek hasarı (ABH), perioperatif dönemin önemli komplikasyonlarından birisidir. Perioperatif ABH kronik böbrek hastalığı riskini, diyaliz gereksinimini, periopeartif maliyeti ve mortalite şansını artırır. Hastalarımızın ameliyat öncesi riskleri ve cerrahi prosedürlerin ağırlığına bağlı risk faktörleri ABH oluşumuna katkıda bulunur. ABH'yi çok erken teşhis edebilecek yeni biyobelirteçlere ihtiyaç duyulmaktadır. Yeni biyobelirteçlerin potansiyel rolleri ve bunların tanıya ve prognostik değerlendirmeye katkıları detaylı araştırmalar gerektirmektedir. Böbrek Hastalığı: Küresel Sonuçların İyileştirilmesi tarafından sağlanan ABH'yi önlemeye yönelik öneriler klinisyenler için yararlı ve pratik bir rehber oluşturmaktadır. Perioperatif hemodinami ve oksijenasyonun ABH'yi önlemeye katkıda bulunduğu görülmektedir. Genel olarak, nefrotoksik ajanlara maruz kalmanın azaltılması, tedavinin etkisini daha da azaltmak için tavsiye edilir. Bu derlemede perioperatif dönemde ABH'ye yol açan risk faktörlerini özetlemeyi amaçladık. Ayrıca, erken tanının avantajlarını, ABH'nin önlenmesine katkısı olacak girişimleri ve erken yönetimini özetlemeye gayret ettik.

Anahtar Kelimeler: Perfüzyon, oksijen, oksijenasyon, hipoksi, oxygen delivery, kan basıncı, hipotansiyon, hemoglobin, akut böbrek hasarı, kreatinin, lipokalin (NGAL), hipoksi indükleyen faktör, Böbrek Hastalığı: Küresel Sonuçların İyileştirilmesi

Introduction

Perioperative management of surgical patients has been constantly improving within the past few decades. Improvements in safe anesthesia practices decreased intraoperative and immediate postoperative mortality to negligible levels, but when the perioperative focus expands to 30-day range, there's about a 2% mean mortality rate in non-cardiac and non-obstetric surgery (1). Interestingly, this relatively high mortality rate is strongly associated with end organ injuries, and myocardial and acute kidney injuries (AKIs) (1).

In this overview, we will focus on perioperative AKI. Although the importance of immediate perioperative factors in AKI formation is obvious, patients' age and baseline confounding factors play very significant roles as well (2,3).

Baseline Risk Factors for AKI

There are a few validated prediction scores for perioperative AKI including the frequently utilized "Dialysis

Risk After Cardiac Surgery" (Cleveland Clinic Score by Thakar) (4), "AKI risk after surgery" (Postop-MAKE by Woo) (5), and "Simple Postoperative AKI Risk Classification before Non-cardiac Surgery" (SPARK by Park) (Table 1a, b, c) (6). These scores were built from multicentric clinical databases including data from thousands of perioperative patients. Although there are specific confounders depending on the type of surgery and the environment, the following factors are commonly found in most of the risk scores: age, gender, baseline kidney functions, hypertension, congestive heart failure, type of surgery and acuity level of surgery, baseline laboratory values [specifically hemoglobin (Hb), sodium, albumin levels], history of diabetes (insulin dependent vs. non-dependent). Calculated value of each of these confounding factors are different depending on the context. Unfortunately, most of these risk factors are ever non-modifiable in the immediate perioperative period (e.g., age, baseline kidney functions, congestive heart failure), some of them are potentially modifiable within the immediate preoperative period (e.g., Hb, sodium levels, hypertension, duration of surgery).

Preventive role of modifiability of these factors is a good question on its own and requires testing in prospective interventional trials. On the other hand, confounding roles of these factors cannot be underestimated. Therefore, we strongly recommend using above mentioned perioperative AKI risk scores or any other institute-specific prediction system when approaching perioperative patients.

Table 1a. AKI risk prediction scores. Cleveland Clinic score (Thakar)

Risk factors	Points
Female gender	1
Congestive heart failure	1
Left ventricular ejection fraction <35%	1
Preoperative use of IABP	2
COPD	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only (reference to CABG)	1
CABG + valve (reference to CABG)	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to <2.1 mg/dL (reference to 1.2)	2
Preoperative creatinine ≥2.1 (reference to 1.2)	5

[1a]Minimum score, 0; maximum score, 17. AKI: Acute kidney injury, IABP: intra-aortic balloon pump, COPD: chronic obstructive pulmonary disease, CABG: coronary artery bypass graft

Definition of Acute Kidney Injury

There are multiple clinical definitions of AKI Kidney Disease: Improving Global Outcomes (KDIGO), Risk Injury Failure, Loss, End-stage, and Acute Kidney Injury Network. All 3 of these established criteria use changes in creatinine levels and urine output to assess and level the disease process of AKI (Table 2).

Within the definitions provided, KDIGO gained more interest, which may help in the means of communication of a common medical language.

Role of Perioperative Hypotension

Intraoperative hypotension is one of the factors which has recently gained a lot of interest due to its strong associations with perioperative AKI. Cumulative evidence suggests that on a population basis, intraoperative mean arterial pressures (MAP) less than 60 to 70 mmHg are associated with myocardial injury, AKI, and death in adults having non-cardiac surgery (7-10). The risk was moderately increased with exposures to MAP less than 65 to 60 mmHg for at least 5 min, or any exposure to MAP less than 55 to 50 mmHg (11). High risk of any end-organ injury was reported for exposures to MAP less than 65 mmHg for at least 20 min, MAP less than 50 mmHg for at least 5 min, or any exposure to MAP less than 40 mmHg (11).

Perioperative hypotension is a modifiable factor, one can test the hypothesis that whether optimization of perioperative blood pressure (BP) with various approaches prevent organ injuries and accordingly decrease perioperative mortality (12,13). Hypotension during and after non-cardiac surgery is multifactorial in origin, including baseline patient-specific confounders, anesthetic pharmacological effects, and surgical procedural factors (14,15). In non-cardiac and non-obstetric surgeries of adult patients, intraoperative hypotension is associated with >10% of AKI, which ~2% of these become persistent AKI extending beyond 90-day period (16). Postoperative hypotension is also common and may also impact organ injury. Mild vs. profound hypotension can be prolonged in the postoperative phase, but largely can be missed due to the conventional intermittent low-frequency vital sign monitoring (meaning hourly to once in every 8 hours) (12).

Table 1b. Postop-MAKE by Woo et al (5). Predictors of postoperative AKI requiring dialysis					
Characteristics	**Coefficient**	**SEM**	**p-value**	**Adjusted odds ratio (95% confidence interval)**	
Intercept	-9.228	0.122	<0.001		
Age, per yr	0.012	0.001	<0.001	1.01 (1.01 to 1.02)	
Ascites	0.971	0.089	<0.001	2.64 (2.22 to 3.14)	
Congestive heart failure	0.832	0.059	<0.001	2.30 (2.05 to 2.58)	
Emergency surgery	0.773	0.042	<0.001	2.17 (2.00 to 2.35)	
Hypertension requiring medication	0.440	0.038	<0.001	1.55 (1.44 to 1.67)	
Diabetes, reference: no diabetes					
Insulin dependent		0.667	0.04	<0.001	1.95 (1.79 to 2.12)
Non-insulin dependent		0.219	0.05	<0.001	1.25 (1.14 to 1.36)
Serum sodium, reference: 135.1-145, mEq/L					
0-130		0.328	0.07	<0.001	1.39 (1.21 to 1.60)
130.1-135		0.193	0.04	<0.001	1.21 (1.12 to 1.31)
>145		0.390	0.09	<0.001	1.48 (1.24 to 1.76)
Missing		-0.165	0.18	0.36	0.85 (0.59 to 1.21)
Serum hematocrit, reference: >30, %					
0-24		0.802	0.07	<0.001	2.23 (1.93 to 2.57)
24.1-30		0.688	0.04	<0.001	1.99 (1.83 to 2.16)
Missing		-0.582	0.16	<0.001	0.56 (0.40 to 0.78)
Preoperative sepsis, reference: no					
SIRS		0.959	0.06	<0.001	2.61 (2.34 to 2.91)
Sepsis		1.238	0.06	<0.001	3.5 (3.09 to 3.85)
Septic shock		2.116	0.06	<0.001	8.30 (7.35 to 9.38)
Surgery type, reference: anorectal, appendix					
ENT		0.255	0.37	0.49	1.29 (0.62 to 2.68)
Bariatric, stomach, esophagus		1.425	0.12	<0.001	4.16 (3.24 to 5.33)
Brain		0.872	0.21	<0.001	2.39 (1.58 to 3.61)
Cardiac		2.864	0.14	<0.001	17.53 (13.30 to 23.09)
Endocrine, thyroid, parathyroid, adrenal, breast		-0.427	0.20	0.04	0.65 (0.44 to 0.97)
Gallbladder, biliary tract		0.555	0.14	<0.001	1.74 (1.33 to 2.29)
Hernia, peritoneum, omentum, diverticul		0.920	0.12	<0.001	2.51 (1.98 to 3.18)
Intestine (not rectum)		1.690	0.11	<0.001	5.42 (4.36 to 6.73)
Liver, pancreas, spleen		2.565	0.13	<0.001	13.00 (10.16 to 16.64)
OBGYN		0.203	0.17	0.24	1.23 (0.87 to 1.72)
Orthopedic lower extremity, pelvis		0.732	0.11	<0.001	2.08 (1.7 to 2.62)
Orthopedic upper extremity, shoulder		0.020	0.26	0.94	1.02 (0.61 to 1.70)
Skin, subcutaneous, other musculoskeletal		0.909	0.12	<0.001	2.48 (1.93 to 3.20)
Spine		0.593	0.14	<0.001	1.81 (1.35 to 2.42)
Thoracic (non-esophageal)		1.913	0.15	<0.001	6.77 (5.06 to 9.07)
Urology		1.590	0.12	<0.001	4.90 (3.85 to 6.25)
Vascular (endovascular aneurysm repair)		2.310	0.15	<0.001	10.07 (7.50 to 13.53)
Vascular (open aorta surgery)		3.993	0.13	<0.001	54.20 (42.19 to 69.64)
Vascular (other)		1.709	0.12	<0.001	5.53 (4.37 to 6.98)
Preoperative serum creatinine per 1 mg/dL		0.449	0.01	<0.001	1.57 (1.54 to 1.59)

SIRS: Systemic inflammatory response syndrome, ENT: ear, nose, throat, OBGYN: obstetrics and gynecology, SEM: scanning electron microscopy, AKI: Acute kidney injury

Table 1c. SPARK by Park et al. (6)			
Perioperative risk factors		**Scores**	
Age (years)			
<40 y		0	
≥40 and <60 y		6	
≥60 and <80 y		9	
≥80 y		13	
eGFR (mL/min per 1.73 m^2)			
≥60		0	
≥45 and <60		8	
≥30 and <45		15	
≥15 and <30		22	
Dipstick albuminuria (urine alb ≥1+)		6	
Sex			
Female		0	
Male		8	
Expected surgical duration (hours)			
Expected duration		x5	
Emergency procedure		7	
Baseline confounders			
Diabetes mellitus		4	
RAAS blockade use		6	
Hypoalbuminemia (<3.5 g/dL)		8	
Anemia (<12 g/dL for female, <13 g/dL for male)		4	
Hyponatremia (<135 mEq/L)		3	
SPARK class	**Total score**	**AKI**	**Critical AKI**
A	<20	Less likely (<2%)	Less likely (<2%)
B	≥20 and <40	Possible (≥2%)	Less likely (<2%)
C	≥40 and <60	At risk (≥10%)	Possible (≥2%)
D	≥60	Definite risk (≥20%)	At risk (≥10%)

eGFR: Estimated glomerular filtration rate, RAAS: renin-angiotensin-aldosterone system, alb: albumin, AKI: Acute kidney injury

Perioperative Oxygen Delivery & Impact on Organ Injury

BP which is a product of cardiac output (CO) and systemic vascular resistance (SVR) is only one of the factors altering organ-tissue perfusion [BP = CO x SVR]. When considering tissue and organ oxygenation and perfusion, the first thing comes to mind is oxygen delivery.

The two components of oxygen delivery are 1) availability and transportability of oxygen (main substrate & carrier; oxygen & Hb), and 2) the flow needed to deliver oxygen (CO) (Table 3). Great majority of oxygen is being carried by Hb. In addition to oxygen's availability, its delivery also depends upon cardiac functionality. CO is the product of stroke volume and heart rate, and BP/SVR. When we adopt global oxygen delivery physiology to the tissue level, we realize that we need to stick with the same principles. In short, availability of oxygen to the tissues and blood flow which helps transportation of that oxygen. Therefore, tissue oxygenation and perfusion together assure the delivery of oxygen to the peripheral tissues and end organs.

We may consider giving a new spin to ischemia-based AKI. If ischemia can be explained by decreased DO_2 and

Table 2. AKI stages-KDIGO, RIFLE, and AKIN				
AKI stage	**KDIGO**	**RIFLE**	**AKIN**	**Urine output**
1. Risk	Increase ≥0.3 mg/dL within 48 h or ≥1.5- to 2x from baseline	Increase ×1.5 baseline or GFR decrease >25%	Increase 1.5-1.9x from baseline or ≥0.3 mg/dL increase within 48 h	<0.5 mL/kg/h for 6-12 h
2. Injury	2.0-2.9x from baseline	Increase ×2 from baseline or GFR decreased >50%	Increase >2- to 3-x from baseline	<0.5 mL/kg/h for 12 h
3. Failure	3.0x from baseline or increase in creatinine to ≥4.0 mg/dL or initiation of RRT or, in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	Increase ×3 from baseline, or creatinine >4 mg/dL) with an acute rise >0.5 mg/dL or GFR decreased >75%	Increased >300% (>3x) from baseline, or ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL or on RRT	<0.3 mL/kg/h for 24 h or anuria for 12 h

KDIGO: Kidney Disease: Improving Global Outcomes, RIFLE: The Risk, Injury, Failure, Loss, End-Stage, AKIN: Acute Kidney Injury Network, RRT: renal replacement therapy, GFR: glomerular filtration rate, eGFR: estimated glomerular filtration rate, AKI: acute kidney injury

Table 3. Blood pressure, cardiac output, & oxygen delivery
BP = CO x SVR
CO = BP / SVR
$DO_2 = CO \times CaO_2$
CO = HR x SV
$CaO_2 = (SO_2 \times 1.34 \times Hb) + (PaO_2 \times 0.003)$
If we adjust the relevant components of DO_2 and ignore the very small contribution of PaO_2 component, then we will end up with the following formula:
$DO_2 = [BP / SVR] \times [SO_2 \times 1.34 \times Hb]$

BP: Blood pressure, SVR: systemic vascular resistance, CO: cardiac output, SV: stroke volume, Hb: hemoglobin

if the main components of DO_2 are BP, SO_2, and Hb (also reversely by SVR), then we can extrapolate that directly positive effects of BP, SO_2, and Hb, and negative effects of SVR impacts oxygen delivery. In a recent post-hoc analysis, from these components, von Groote and Zarbock showed that hypotension and low CO contributed to 2-2.5x more AKI (17).

Another important component to consider in MINS is the total Hb level and decrease in Hb level in the perioperative period. MINS was associated with a hazard ratio of 1.29 [95% confidence interval (CI), 1.17-1.42] with each unit reduction of postoperative Hb after adjusting for iron deficiency anemia and anemia of chronic disease in the time-varying Cox model (18).

Role of Nephrotoxic Agents

Agent-induced nephropathy is a type of renal dysfunction, which occurs after exposure to nephrotoxic drugs. It is a relatively common pathology for patients with underlying renal dysfunction, or confounding cardiovascular disease, diabetes mellitus, and increased inflammatory diseases like sepsis. Nephrotoxic drugs can cause mild to moderate organ injury such as intrarenal obstruction, interstitial nephritis, acid-base changes, fluid-electrolyte disturbances, changes in intraglomerular hemodynamics, renal tubular inflammation, and persistent renal tissue injury leading to AKI and chronic kidney injury.

There are many nephrotoxic drugs and drug combinations: Beta-lactam antibiotics such as piperacillin-tazobactam (especially in combination with vancomycin), cephalosporin-aminoglycoside combinations, rifampin, polymyxins/colistin, non-steroidal anti-inflammatory drugs, acetaminophen, interferon, proton pump inhibitors, bisphosphonates, lithium, various chemotherapeutic agents (e.g. mitomycin, gemcitabine), cisplatin, cyclosporin A, methotrexate, ACE inhibitors, anabolic androgenic steroids, TNF-alpha inhibitors, amphotericin B, dextrans, and contrast dyes.

Following the early signs of adverse effects of drugs and reviewing a patient's baseline renal function, drug-related risk factors, and nephrotoxic drug combinations need to

be closely addressed to prevent nephrotoxicity and the progression of AKI.

Biomarkers of Organ Injury

In perioperative AKI, mechanisms of short-term volume depletion-triggered and ischemia-triggered injuries are likely different, but their clinical phenotypes are similar (i.e., creatinine increase and urine output decrease). Ischemic insult provokes cell injury and repair (which upregulates ERB, MAPK) and inflammatory genes (such as TLR, NFKB, JAK/STAT, chemokines) (19). Macrophages and CD4 T-cells' overexpression of Lcn2 could induce intrinsic resistance to ischemia, causing protection from kidney ischemia-reperfusion (I/R) injury (20,21). Lipocalin (NGAL), despite being a potential biomarker for renal injury, has been shown to have protective effects in ischemic AKI by inhibition of tubular cell death and induction of antioxidant genes (22).

Tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7) are released during cell cycle arrest, which makes them potentially sensitive and specific biomarker molecules for diagnosing AKI (23). During cell damage, cell cycle arrest serves as a protective mechanism to get around the replication of damaged DNA (24). Renal cells' cell cycle arrest is possibly an adaptive response due to tissue damage mediated by surrounding cells through the release of TIMP-2 and IGFBP-7 (24). Combined presence of TIMP-2 and IGFBP-7, along with a change in creatinine, could potentially predict renal adverse events with better sensitivity and specificity. NephroCheck (Astute Medical, USA), which tests presence of both TIMP-2 and IGFBP-7 was authorized by Food and Drug Administration in 2014 as a point-of-care urinary biomarker assay to evaluate AKI development (25). In spite of NephroCheck's predictive role in critically ill patients' AKI, it's role in distinguishing temporary injury from persistent AKI or acute kidney disease (AKD) is unclear (26).

Compared to ischemia or ischemic tissue damage triggered AKI, volume depletion-triggered AKI promotes adaptive appearing metabolic pathways (i.e. TCA, gluconeogenesis, oxidative phosphorylation, respiratory electron transport) (27). In volume depletion-triggered AKI, upregulated genes are typically localized to the cortex and inner stripe of the outer medulla, and this type of injury appears to cause more transient triggers such as *PAPPA2* gene (metalloproteinase secreted by the thick ascending loop of Henle) expression. However, in theory, an extended duration of volume depletion stimulus with or without a secondary injury (e.g., nephrotoxins) may impact the volume depletion injury to progress to ischemia-based injury, meaning temporary AKI to persistent AKI vs. AKD. Also, it's noteworthy that NGAL rapidly stimulated by ischemic injury, is in fact not responsive to the volume depletion injury despite the similar elevations in creatinine levels (28,29).

It looks like the absence of permanent injury in most AKI is due to volume depletion mechanisms and renal protective factors such as prostaglandins, NO, NGAL, and hypoxia inducible factor, but instead of being conclusive statements, these are likely testable hypotheses at this point. In the light of current evidence, NGAL and TIMP-2 & IGFBP-7 combination appears to be only available and somewhat guiding biomarkers.

Kidney Disease: Improving Global Outcomes Guidelines

These guidelines aimed to provide a bundle of potentially preventive strategies for the patients who are at high risk for developing AKI. The bundle includes avoidance of nephrotoxic agents, contrast dyes, maintenance of intravascular volume status and perfusion pressure, maintenance of normoglycemia, monitoring of creatinine and urine output, and functional hemodynamic monitoring (Table 4) (30).

A recent randomized controlled clinical trial (PrevAKI) showed that biomarker-guided implementation of the KDIGO guidelines as compared with standard care significantly reduced the occurrence of AKI in cardiac surgery patients [absolute risk reduction, 16.6% (95 CI, 5.5-27.9%)]; p=0.004 (31).

Other Preventive Measures of Perioperative AKI

As previously mentioned, the application of nephrotoxic agents is associated with AKI. Surgical patients are frequently exposed to contrast agents or anti-inflammatory drugs. Avoidance of these agents are recommended. As stated before, prevention of hypotension and related blood flow decreases in kidneys need to be prevented, and intravascular volume status needs to be optimized. The choice of intravenous fluids plays an important role in the development of AKI. Isotonic saline 0.9% has high chloride content, which may cause hyperchloremic acidosis and renal vasoconstriction, resulting in a reduced glomerular filtration rate (32) and a higher incidence of AKI (33). Therefore, balanced crystalloid solutions with electrolyte compositions compared with plasma should be preferred for volume resuscitation.

Table 4. Summary of KDIGO guidelines
Recommendations of the KDIGO guidelines can be summarized as follows:
1) Discontinuation of nephrotoxic agents
2) Optimization of volume status and hemodynamics [stroke volume (SV), SV based cardiac output monitor use suggested)
a) If stroke volume variation (SVV) ≥11, then give 500 to 1000 mL of crystalloid
b) If SVV <11, but cardiac index (CI) <3 L/min/m^2, then consider starting dobutamine (or epinephrine)
c) If SVV <11, CI >3 L/min/m^2, but MAP <65 mmHg, then consider starting norepinephrine
d) Repeat following above volume state and hemodynamic parameters in frequent intervals
3) Consideration of functional hemodynamic monitoring
4) Close monitoring of serum creatinine and urine output
5) Avoidance of hyperglycemia
6) Consideration of alternatives of radiocontrastagents
KDIGO: Kidney Disease: Improving Global Outcomes, MAP: mean arterial pressures

Arterial hypotension is a frequent result of hypovolemia, but also occurs in association with multiple other etiologies. AKI is associated with intraoperative hypotension in a graded fashion. Therefore, all efforts needed to prevent decreasing MAP levels <65 mmHg, and if/when BP drops treated depending on the cause is strongly recommended.

Tight glycemic control has been shown to significantly reduce AKI in critically ill patients (34). Subsequently, it has been ruled out in cardiac surgery patients that tight glycemic control is superior to continuous perioperative insulin therapy in terms of AKI incidence and mortality. This has been underlined by several well-conducted clinical trials (35,36).

Active Areas for Future Research

In this review we have highlighted the risk factors that appear to be both unmodifiable and potentially modifiable. Much of the work highlighting the association of these confounding risk factors has been done in retrospective fashion. Their prospective can be graded and assessed prospectively.

Given the perioperative importance of AKI, there appear to be multiple areas for future research. Hemodynamic management to prevent hypotension and improve perfusion & oxygen delivery appear to be important in prior studies and these are potentially modifiable factors. This would be one important target of priority, especially given the recent advances in bioinformatics that make new studies possible that before were not.

Additionally, plasma and urinary biomarkers of renal injury overcome the limitations of the current gold standard definitions of serum creatinine and may offer significant future clinical utility to diagnose and treat kidney injury. Perioperative diagnostic, mechanistic, and even therapeutic potentials of biomarkers require further attention.

Conclusion

AKI is a relatively common complication of the perioperative period. It is associated with increased risk of chronic kidney disease, hemodialysis requirements after discharge, increased cost, and risk of mortality. Better understanding of baseline and procedure related risk factors, which contribute to perioperative AKI may improve early diagnosis, prevention, and early management of AKI. There are still needs for detailed context specific clinical prediction scores and novel biomarkers to improve the chances of early diagnosis. Improved imaging techniques with decreased exposure to contrast dyes, avoiding nephrotoxic agents, and improved perioperative care focusing on prevention of hypotension, diminished CO and oxygen delivery will further decrease the impact of perioperative AKI.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: L.G., O.A., Analysis or Interpretation: L.G., O.A., Literature Search: L.G., O.A., Writing: L.G., O.A.

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References

1. Nepogodiev D, Martin J, Biccard B, Makupe A, Bhangu A; National Institute for Health Research Global Health Research Unit on Global Surgery. Global burden of postoperative death. Lancet 2019;393:401.
2. Mathis MR, Naik BI, Freundlich RE, Shanks AM, Heung M, Kim M, et al. Preoperative Risk and the Association between Hypotension and Postoperative Acute Kidney Injury. Anesthesiology 2020;132:461-75.
3. Ahuja S, Mascha EJ, Yang D, Maheshwari K, Cohen B, Khanna AK, et al. Associations of Intraoperative Radial Arterial Systolic, Diastolic, Mean, and Pulse Pressures with Myocardial and Acute Kidney Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. Anesthesiology 2020;132:291-306.
4. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 2005;16:162-8.
5. Woo SH, Zavodnick J, Ackermann L, Maarouf OH, Zhang J, Cowan SW. Development and Validation of a Web-Based Prediction Model for AKI after Surgery. Kidney360 2021;2:215-23.
6. Park S, Cho H, Park S, Lee S, Kim K, Yoon HJ, et al. Simple Postoperative AKI Risk (SPARK) Classification before Noncardiac Surgery: A Prediction Index Development Study with External Validation. J Am Soc Nephrol 2019;30:170-81.
7. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. Anesthesiology 2017;126:47-65.
8. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015;123:515-23.
9. Sessler DI, Meyhoff CS, Zimmerman NM, Mao G, Leslie K, Vásquez SM, et al. Period-dependent Associations between Hypotension during and for Four Days after Noncardiac Surgery and a Composite of Myocardial Infarction and Death: A Substudy of the POISE-2 Trial. Anesthesiology 2018;128:317-27.
10. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, Bentt DR, et al. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology 2015;123:307-19.
11. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth 2018;121:706-21.
12. Turan A, Chang C, Cohen B, Saasouh W, Essber H, Yang D, et al. Incidence, Severity, and Detection of Blood Pressure Perturbations after Abdominal Surgery: A Prospective Blinded Observational Study. Anesthesiology 2019;130:550-9.
13. Saugel B, Sessler DI. Perioperative Blood Pressure Management. Anesthesiology 2021;134:250-61.
14. Reich DL, Hossain S, Krol M, Baez B, Patel P, Bernstein A, et al. Predictors of hypotension after induction of general anesthesia. Anesth Analg 2005;101:622-8.
15. Cheung CC, Martyn A, Campbell N, Frost S, Gilbert K, Michota F, et al. Predictors of intraoperative hypotension and bradycardia. Am J Med 2015;128:532-8.
16. Shaw AD, Khanna AK, Smischney NJ, Shenoy AV, Boero IJ, Bershad M, et al. Intraoperative hypotension is associated with persistent acute kidney disease after noncardiac surgery: a multicentre cohort study. Br J Anaesth 2022;129:13-21.
17. von Groote TC, Ostermann M, Forni LG, Meersch-Dini M, Zarbock A; PrevAKI Investigators. The AKI care bundle: all bundle components are created equal-are they? Intensive Care Med 2022;48:242-5.
18. Turan A, Cohen B, Rivas E, Liu L, Pu X, Maheshwari K, et al. Association between postoperative haemoglobin and myocardial injury after noncardiac surgery: a retrospective cohort analysis. Br J Anaesth 2021;126:94-101.
19. Xu K, Rosenstiel P, Paragas N, Hinze C, Gao X, Huai Shen T, et al. Unique Transcriptional Programs Identify Subtypes of AKI. J Am Soc Nephrol 2017;28:1729-40.
20. Jung M, Brüne B, Hotter G, Sola A. Macrophage-derived Lipocalin-2 contributes to ischemic resistance mechanisms by protecting from renal injury. Sci Rep 2016;6:21950.
21. Lee SA, Noel S, Kurzhagen JT, Sadasivam M, Pierorazio PM, Arend LJ, et al. CD4(+) T Cell-Derived NGAL Modifies the Outcome of Ischemic Acute Kidney Injury. J Immunol 2020;204:586-95.
22. Mishra J, Mori K, Ma Q, Kelly C, Yang J, Mitsnefes M, et al. Amelioration of ischemic acute renal injury by neutrophil gelatinase-associated lipocalin. J Am Soc Nephrol 2004;15:3073-82.
23. Koyner JL, Shaw AD, Chawla LS, Hoste EA, Bihorac A, Kashani K, et al. Tissue Inhibitor Metalloproteinase-2 (TIMP-2) IGF-Binding Protein-7 (IGFBP7) Levels Are Associated with Adverse Long-Term Outcomes in Patients with AKI. J Am Soc Nephrol 2015;26:1747-54.
24. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013;17:25.
25. Lameire N, Vanmassenhove J, Van Biesen W, Vanholder R. The cell cycle biomarkers: promising research, but do not oversell them. Clin Kidney J 2016;9:353-8.
26. Daubin D, Cristol JP, Dupuy AM, Kuster N, Besnard N, Platon L, et al. Urinary Biomarkers IGFBP7 and TIMP-2 for the Diagnostic Assessment of Transient and Persistent Acute Kidney Injury in Critically Ill Patients. PLoS One 2017;12:e0169674
27. Neuhofer W, Beck FX. Response of renal medullary cells to osmotic stress. Contrib Nephrol 2005;148:21-34.
28. Belcher JM, Sanyal AJ, Peixoto AJ, Perazella MA, Lim J, Thiessen-Philbrook H, et al. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. Hepatology 2014;60:622-32.
29. Paragas N, Qiu A, Zhang Q, Samstein B, Deng SX, Schmidt-Ott KM, et al. The Ngal reporter mouse detects the response of the kidney to injury in real time. Nat Med 2011;17:216-22.
30. Nephrology ISo: KDIGO Clinical Practice Guideline for Acute Kidney Injury. Available at: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf. Accessed 08/22/2022
31. Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med 2017;43:1749.
32. Bullivant EM, Wilcox CS, Welch WJ. Intrarenal vasoconstriction during

hyperchloremia: role of thromboxane. Am J Physiol 1989;256:152-7.
33. McCluskey SA, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. Anesth Analg 2013;117:412-21.
34. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.
35. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med 2007;146:233-43.
36. Bhamidipati CM, LaPar DJ, Stukenborg GJ, Morrison CC, Kern JA, Kron IL, et al. Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2011;141:543-51.