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Perioperative risk factors of acute kidney injury after non-cardiac surgery: A multicenter, prospective, observational study in patients with low grade American Society of Anesthesiologists physical status

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A B S T R A C T

Background: The aim of this study was to determine the incidence and the perioperative risk factors of acute kidney injury (AKI) using “Kidney Disease: Improving Global Outcomes” (KDIGO) guidelines, in patients with low grade American Society of Anesthesiologists physical status (ASA-PS) undergoing non-cardiac surgery.
Methods: In this multicenter, prospective, observational study, 870 surgical patients older than 40 years with ASA-PS I-II who underwent noncardiac surgery, were included. The primary outcome of this study was perioperative AKI defined by the KDIGO criteria.
Results: AKI was detected in 49 (5.63%) of the patients. Multivariate analysis detected the presence of preoperative hypertension (aOR = 0.130; CI = 0.030–0.566; p = 0.007) and intraoperative transfusion of erythrocytes (aOR = 0.076; CI = 0.008–0.752; p = 0.028) as independent predictors of postoperative AKI development.
Conclusion: Approximately, 6% of patients with ASA I-II presenting for noncardiac surgery developed postoperative AKI. Preoperative hypertension and intraoperative erythrocyte transfusion are independent predictors of AKI after non-cardiac surgery in this patient population.

Introduction

Acute kidney injury (AKI) is a common complication after major surgery and is associated with increased risk for morbidity, mortality and the development of chronic renal dysfunction.[1–3] AKI is characterized as a sudden loss of kidney function, resulting in the accumulation of urea and other nitrogenous wastes in body with extracellular fluid volume and electrolyte imbalance.[4] This clinical phenomenon was first described in 1951 as “Acute Kidney Failure".[5] Later on, in 2004, the term of “Acute Kidney Injury” was proposed in RIFLE criteria (Risk, Injury, Failure, Loss of kidney function, End-stage renal failure) by the Acute Dialysis Quality Initiative (ADQI).[6] In 2007, RIFLE criteria have been modified to use a staging system for AKI as established by “Acute Kidney Injury Network (AKIN)".[7] Finally, in 2012, “KDIGO (Kidney Disease: Improving Global Outcomes)" guidelines were introduced in order to unify the previous definitions of the RIFLE and AKIN criteria.[8] KDIGO guidelines consider both changes in creatinine level and urine output as well as acute need for renal replacement therapy for AKI. Currently, besides the presence of some biomarkers tested for validity at the experimental stage, AKI diagnosis is based on KDIGO guidelines (Appendix 1).

The incidence of perioperative AKI varies from 1.9 to 18%[1–3] depending on the definition of renal dysfunction and the surgical field. Although most of these studies have been performed in the field of cardiovascular surgery, studies evaluating the epidemiology of AKI after non-cardiac surgery also exist, which could demonstrate the independent perioperative risk factors for AKI in this cohort. It is not surprising that high-grade American Society of Anesthesiologists physical status (ASA-PS) is likely to be an

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important predictor of AKI after noncardiac surgery.[9] On the other hand, it would be of great importance to know which risk factors for AKI exist in patients with low grade ASA-PS.

Currently, no literature is available about the epidemiology of AKI after noncardiac surgery in patients with low grade ASA classification. Therefore, in the current multicentre, prospective, observational study, we aimed to determine the incidence and the perioperative risk factors of AKI using KDIGO guidelines, in patients with low grade ASA classification undergoing noncardiac surgery.

Methods

Ethics

This multicenter, prospective, observational study was approved by the Ethics Committee of the School of Medicine at Acıbadem Mehmet Ali Aydınlar University (ATADEK 2015–6/19). The trial was conducted at 4 tertiary medical centers of Acıbadem Group Hospitals. All the procedures followed in the study were in accordance with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all participants.

Study population

The study population consisted of 870 surgical patients with ASA-PS I-II and older than 40 years who underwent noncardiac surgery between July 2015 and July 2017. Patients presenting for cardiovascular, urological and transplantation surgeries as well as surgeries requiring only local anesthesia or monitored anesthesia care and day case surgical procedures were excluded. Further exclusion criteria were emergency surgery, ASA physical status > II, previous renal surgery, pre-existing renal disease requiring renal replacement therapy or preoperative serum creatinine level higher than 1.4 mg/dl. Inclusion criteria are summarized in Table 1.

Outcome

The primary outcome of this study was perioperative AKI defined by the KDIGO criteria. The patients were determined as having AKI if they had an increase in serum creatinine level of 0.3 mg/dl or higher within 48 h, postoperatively.

Data collection

Preoperatively, patients' demographics were registered including age, gender, preoperative diseases [hypertension, diabetes and its regulation strategies with diet and/or oral antidiabetics (OAD) and/or insulin], history of smoking, preoperative medication [preoperative use of beta-blockers, angiotensin converting enzymes (ACE) inhibitors, angiotensin receptor blockers (ARB), statins, aspirin, non-steroidal anti-inflammatory drugs (NSAID)] and preoperative values of hemoglobin (Hb), hematocrit (Hct) and serum creatinine.

Intraoperative data recorded for each case, included nadir mean arterial pressure, nadir heart rate, type of anesthesia, type of surgery, duration of operation, administration of colloids and their amounts used, transfusion of erythrocytes, presence of intraoperative hypotension and corresponding use of a vasopressor, whereas a mean arterial pressure (MAP) decreased below 60 mmHg or systolic arterial pressure (SAP) decreased by more than 30% compared to the patients' SAP before anesthesia induction were accepted as hypotension and, ephedrine (5 mg, IV) was administered intravenously, as first step routine medication. Regarding type of anesthesia, regional anesthesia was performed as combined spinal-epidural anesthesia. Postoperatively, laboratory values of hemoglobin (Hb), the presence of respiratory and/or circulatory complications and/or bleeding were collected.

Table 1
Inclusion criteria.

ASA status	ASA I-II
Age	>40 years
Hospitalization	at least one night
Preoperative creatinine (mg/dl)	<1.4

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 18.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine whether the data were distributed normally. Mann-Whitney *U* test was used to compare nonparametric data among patients with and without AKI and the chi-square test was used to compare proportions between two groups of subjects. The results were expressed as mean ± standard deviation (SD), proportions were expressed as percentages. To determine the relationship between perioperative variables and development of AKI, univariate analysis was performed using binary logistic regression. Variables with significant correlations were evaluated using multivariate analysis to determine independent risk factors for postoperative AKI development. The results of logistic regression analyses were given by odds ratios (OR) or adjusted odds ratios (aOR) and 95% confidence intervals (CI). For all outcomes, $p < 0.05$ was considered statistically significant.

Results

Demographic characteristics of patients are shown in Table 2. Acute kidney injury was detected in 49 (5.63%) of 870 patients. Patients with AKI were older ($p = 0.0011$), had hypertension ($p = 0.0158$), and had more incidence of preoperative beta-blocker medication ($p = 0.0043$). Table 3 shows the intra- and postoperative characteristics of the patients. AKI incidence was found to be as 7.69% in patients operated under regional anesthesia, and 5.48% in patients submitted for general anesthesia (Table 3). The comparison of demographic characteristics between patients who underwent general and regional anesthesia (Appendix 2), showed that patients who developed AKI under regional anesthesia were older than patients who developed AKI under general anesthesia ($p = 0.0141$). However, no significant difference was noticed between two anesthesia methods ($p = 0.3745$). On the other hand, patients with AKI had longer operations ($p < 0.0001$) and had higher rate of intraoperative transfusion of erythrocytes. Though, the amount of erythrocyte transfusion had no impact on AKI development (Table 3).

Rates of surgery type and related postoperative AKI development are shown in Table 4. The majority of cases consisted of orthopedic or general surgery (44.6 and 37.6%, respectively). The incidence of AKI in patients who underwent gynecologic surgery was higher than in patients presenting for non-gynecologic surgery. The comparison of preoperative and intraoperative data between both groups showed that preoperative Hb and Hct values were lower and the duration of surgery was longer in patients who underwent gynecologic operations (Appendix 3). However, different surgery types with AKI development showed no statistical significance.

Univariate analysis of risk factors for AKI and their relevant p values are summarized in Table 5. A significant association of AKI occurrence was shown with age (OR = 1.042, CI = 1.016–1.068,

Table 2
Demographic characteristics of patients with and without AKI.

	Postoperative AKI (n = 49)	Postoperative normal renal function (n = 821)		p value
Age (years)	60.8 ± 1.6	55.4 ± 0.4		0.0011
Male (n, %)	23 (47.0)	382	(46.4)	0.9555
Female (n, %)	26 (53.0)	439	(53.6)	0.9555
Co-morbid diseases				
Diabetes mellitus (n, %)	9 (18.4)	148	(18.0)	0.3485
Regulated by diet (n)	1	9		0.6219
Use of OAD (n)	8	115		0.4322
Insulin dependent (n)	0	24		
History of smoking (n, %)	10 (20.4)	203	(24.7)	0.4953
Hypertension (n, %)	26 (53.1)	295	(35.9)	0.0158
Preoperative drug use				
ACE inhibitor/ARB (n, %)	12 (24.5)	121	(14.7)	0.0655
Beta blocker (n, %)	13 (26.5)	101	(12.3)	0.0043
Statin (n, %)	3 (6.1)	29	(3.5)	0.3500
Aspirin (n, %)	8 (16.3)	90	(10.9)	0.2505
NSAID (n, %)	4 (8.2)	53	(6.4)	0.6307
Preoperative hemoglobin (g/dl)	13.2 ± 0.40	13.6 ± 0.10		0.2976
Preoperative hematocrit (%)	38.9 ± 0.70	40.0 ± 0.20		0.0835
Preoperative creatinine (mg/dl)	0.86 ± 0.04	0.85 ± 0.00		0.8127

Values are presented as mean ± standard deviation (SD). Abbreviations: AKI, acute kidney injury; OAD, oral antidiabetic; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug.

p = 0.001), presence of preoperative hypertension (OR = 2.016, CI = 1.130–3.596, p = 0.018), use of beta-blocker (OR = 2.574, CI = 1.321–5.018, p = 0.005), duration of the operation (OR = 1.004, CI = 1.003–1.006, p = 0.000) and intraoperative transfusion of erythrocytes (OR = 3.134, CI = 1.446–6.789, p = 0.004) (Table 5).

A multivariate regression analysis was performed for the detection of perioperative independent risk factors for AKI (Table 5). The presence of preoperative hypertension (*a*OR = 0.130; CI = 0.030–0.566; p = 0.007) and intraoperative transfusion of erythrocytes (*a*OR = 0.076; CI = 0.008–0.752; p = 0.028) were found to independently predict postoperative AKI development.

Discussion

The aim of this study was to determine the incidence and the perioperative risk factors of AKI using KDIGO guidelines, in patients with low grade ASA-PS undergoing noncardiac surgery. Our results reported the incidence of AKI to be 5.63% among these patients. Additionally, we could show a significant association between age, presence of preoperative hypertension, use of beta blocker, duration of the operation, intraoperative transfusion of erythrocytes and AKI occurrence. Furthermore, we could demonstrate that hypertension and intraoperative transfusion of erythrocytes independently predicted postoperative AKI.

The epidemiology of AKI has been investigated and the incidence and the perioperative risk factors have been determined in various clinical studies.[10–14] Although most of these studies have been performed in the field of cardiovascular surgery, studies evaluating the epidemiology of postoperative AKI after noncardiac surgery also exist.[9,15–18] We are aware of four relevant studies

Table 3
Intra- and postoperative characteristics of patients with and without AKI.

	Postoperative AKI(n = 49)	Postoperative normal renal function(n = 821)	p value
Nadir MAP (mmHg)	68 ± 1	66 ± 2	0.368
Nadir heart rate (bpm)	60.1 ± 2	58.6 ± 2	0.502
Duration of surgery (min)	226.0 ± 27.7	147.6 ± 3.4	<0.0001
Type of anesthesia			
General (n, %)	46(93.9)	792(96.4)	0.3745
Regional (n, %)	3(6.1)	29(3.6)	0.3745
Hypotensive episode (n, %)	21(42.9)	380(46.5)	0.6187
Ephedrine use (n, %)	16(32.7)	212(26.0)	0.3132
Colloid use (n, %)	12(24.5)	141(17.1)	0.1917
HES (n, %)	6(12.2)	79(9.6)	0.6890
Gelofusine (n, %)	6(12.2)	62(7.5)	0.6890
Colloid amount (n, %):			
<500 ml (n, %)	11(22.4)	93(11.3)	0.0676
500–1000 ml (n, %)	1(2.0)	35(4.2)	0.1986
>1000 ml (n, %)	0(0)	12(1.4)	
Erythrocyte transfusion (n, %)	9(18.4)	55(6.7)	0.0023
1 unit	4(8.1)	28(3.4)	0.0360
2–4 units	4(8.1)	25(3.0)	0.9559
>5 units	1(2.0)	2(0.2)	0.3320
Postoperative hemoglobin (g/dl)	11.4 ± 0.5	12.4 ± 0.1	0.1385
Postoperative complications(n, %)	4(8.2)	55(6.7)	0.3475
None (n, %)	45(91.8)	766(93.3)	0.3475
Respiratory (n, %)	4(8.2)	17(2.1)	
Circulatory (n, %)	2(4.1)	9(1.1)	0.053
Bleeding (n, %)	3(6.1)	29(3.5)	0.3967

Values are presented as mean ± standard deviation (SD). Abbreviations: AKI, acute kidney injury; MAP, mean arterial pressure; HES, hydroxyethyl starch.

Table 4
Rates of surgery type and postoperative AKI.

	Number of patients		Postoperative AKI	
	n	(%)	n	(%)
Orthopedics	388	(44.6)	19	(4.89)
General surgery	327	(37.6)	16	(4.89)
Gynecologic surgery	52	(6.0)	8	(15.38)
Neurosurgery	52	(6.0)	5	(9.61)
Otorhinolaryngology surgery	36	(4.1)	1	(2.77)
Plastic surgery	9	(1.0)	0	(0.0)
Thoracic surgery	3	(0.3)	0	(0.0)
Peripheral vascular surgery	3	(0.3)	0	(0.0)
Total	870	(100)	49	(5.63)

Abbreviations: AKI, acute kidney injury.

which investigated the incidence and risk factors of AKI in this patient population. Kheterpal et al. studied the epidemiology of postoperative acute renal failure after noncardiac surgery among patients with previously normal renal function.[15] The authors determined a 0.8% incidence and 7 independent preoperative predictors (age, emergent surgery, liver disease, body mass index, high-risk surgery, peripheral vascular occlusive disease, and chronic obstructive pulmonary disease necessitating chronic bronchodilator therapy) of postoperative acute renal failure, which was defined as a calculated creatinine clearance of 50 ml/min or less within the first 7 postoperative days. A further study presented by the same investigators showed a 1% incidence of AKI defined as an increase in serum creatinine of at least 2 mg/dL or acute renal failure necessitating dialysis.[16] In this study, the authors could identify 11 independent preoperative predictors for postoperative AKI, including age 56 years or older, male gender, 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. Abelha et al. studied postoperative AKI using Acute Kidney Injury Network criteria.[17] 1166 patients with no previous renal insufficiency, who were admitted to the intensive care unit after noncardiac surgery, were investigated. ASA physical status, RCRI score, high-risk surgery, and congestive heart failure were shown as preoperative determinants for postoperative AKI, which was determined in 7.5% of the patients. Biteker et al. investigated incidence, risk factors, and outcomes of perioperative acute kidney injury after noncardiac and nonvascular surgery in 1200 adult patients using the RIFLE criteria.[9] The incidence of AKI was found to be 6.7% among these patients. Age, diabetes mellitus, RCRI score, and ASA physical status were demonstrated as independent predictors of perioperative AKI.

The multiple different definitions for AKI have long complicated the assessment of the epidemiology of AKI in various patient populations.[19] Thus, the incidence and the perioperative factors of AKI appear to depend on the definition of acute renal dysfunction and the patient population.[15,20] In our study, we aimed to determine the incidence and the perioperative risk factors of AKI using KDIGO guidelines, in patients with ASA I-II undergoing noncardiac surgery, which is a subgroup of patients presenting for noncardiac surgery. We considered, that it would be of great importance to know which risk factors for AKI exist in a low-risk patient population.

In our study, the incidence of AKI among patients with ASA I-II and normal preoperative function was found to be 5.63% which is in line with previous studies evaluating the epidemiology of AKI after noncardiac surgery.[9,17] Regarding the perioperative risk factors of AKI, we could demonstrate a significant association of AKI with age, presence of preoperative hypertension, use of beta-blockers, duration of the operation and intraoperative transfusion of erythrocytes. The association of age with AKI could be also indirectly demonstrated. The comparison of demographic characteristics between patients presenting for general and regional anesthesia showed that patients who developed AKI under regional anesthesia were older than patients who developed AKI under general anesthesia. In studies evaluating the epidemiology of postoperative AKI after noncardiac surgery, significant associations of postoperative AKI were shown with age, diabetes, ischemic heart disease, hypertension, ASA status, RCRI score, hemoglobin, left ventricle ejection fraction among the study population. It is not surprising that severe disease is an important predictor of AKI after noncardiac surgery. We purposely excluded high-risk patients from our study to evaluate the ASA I-II population. Beyond age we also found that AKI was significantly associated with the use of beta-blockers and duration of operation. The use of beta-blockers in patients undergoing cardiac surgery is common and supported by current guidelines.[21] However, recent studies suggest that the use of preoperative beta-blockers may not provide improved mortality rates and may even contribute to negative clinical outcomes.[21,22] The association between beta-blocker use and postoperative AKI have been shown in patients undergoing noncardiac surgery[23,24] which we could also verify in the current study. Additionally, the duration of operation was also found to be associated with postoperative AKI in our study. This conclusion is in line with previous studies investigating the incidence and risk factors of acute kidney injury after oesophageal cancer surgery.[25,26] As major surgery takes a long time and frequently involves large shifts of volume, renal blood flow can be compromised and renal dysfunction may occur.[27] The impact of surgery duration could be also indirectly demonstrated in patients presenting for gynecologic surgery. The incidence of AKI in patients who underwent gynecologic surgery was higher than in patients presenting for non-gynecologic surgery. The comparison of preoperative and intraoperative characteristics between both groups showed that the duration of surgery was longer and preoperative Hb and Hct values were lower in patients who underwent gynecologic operations.

Table 5
Univariate and multivariate analysis of risk factors for postoperative AKI development.

	Univariate analysis				Multivariate analysis			
	%95 CI				%95 CI			
	OR	Lower	Upper	p	aOR	Lower	Upper	p
Preoperative variables								
Age (years)	1.042	1.016	1.068	0.001	1.021	0.959	1.087	0.513
Hypertension	2.016	1.130	3.596	0.018	0.130	0.030	0.566	0.007
Beta-blocker use	2.574	1.321	5.018	0.005	1.308	0.246	6.966	0.753
Duration of surgery (min)	1.004	1.003	1.006	0.000	0.997	0.986	1.008	0.603
Erythrocyte transfusion	3.134	1.446	6.789	0.004	0.076	0.008	0.752	0.028

Values are presented as odds ratios (OR) or adjusted odds ratios (aOR) and 95% confidence intervals (CI). Abbreviations: AKI, acute kidney injury.

In studies evaluating the epidemiology of postoperative AKI after noncardiac surgery, age and hypertension appear to be common independent predictors of AKI after noncardiac surgery, if we exclude ASA and RCRI score according to our patient population. In our study, beyond hypertension, we also could show that erythrocyte transfusion is an independent risk factor for AKI development after noncardiac surgery in patients with low grade ASA-PS. The association between intraoperative anemia and postoperative AKI[28] provided the drive for studies evaluating the effects of correction of anemia by blood transfusion in order to improve the oxygen delivery. Available evidence from observational studies indicates that early transfusion to correct anemia may exacerbate, rather than ameliorate, the risk of AKI.[29] A possible explanation for this paradox, from a microcirculatory point of view is, that the altered hemorheological properties of the stored red blood cells in terms of increased stiffness, aggregability, and adhesiveness may severely impair the transfused cell to enter the microcirculation.[30] Furthermore, the higher viscosity seen with higher hematocrit can also decrease the rate of regional blood flow and subsequently the microvascular oxygen delivery. These changes result in accumulation of free iron which consequently leads to AKI.[31]

A limitation of the current study concerns the observational nature of the trial which did not allow specific data collection on patients' outcome. In addition, some intra- and postoperative data were not registered and could not be retrospectively acquired. These include intraoperative hematocrit measurements, fluid balance and urine output since the patients did not have a urinary catheter. Moreover, some surgery types such as vascular surgery, thoracic surgery or the cohort operated under regional anesthesia included a small number of patients. As a result, we were not able to determine the risk factors regarding anesthesia type, properly. We expect that further long-term studies will overcome these shortcomings.

Conclusion

Acute kidney injury is a common complication after noncardiac surgery and is associated with several risk factors. Using KDIGO guidelines, we could determine an incidence of 5.6% in patients with low grade ASA-PS. Additionally, hypertension and intraoperative erythrocyte transfusions appear to independently predict postoperative AKI development in this cohort. Further studies, identifying the risk factors of AKI in different patient populations, can bring more progress on postoperative care and thus improvement on outcome of these specific patient groups.

Conflict of interest

All authors declare that they have no conflicts of interests.

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Appendix A. Supplementary data

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