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ORIGINAL STUDIES

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University of Novi Sad, Faculty of Medicine, Novi Sad
Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica

PREOPERATIVE HEMOGLOBIN AND URIC ACID LEVELS AS RISK FACTORS FOR ACUTE KIDNEY INJURY IN CARDIAC SURGERY PATIENTS

PREOPERATIVNE VREDNOSTI HEMOGLOBINA I MOKRAĆNE KISELINE KAOFAKTORI RIZIKA ZA AKUTNO OŠTEĆENJE BUBREGA KOD KARDIOHIRURŠKIH PACIJENATA

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Summary

Introduction. Acute kidney injury associated with cardiac surgery is a common and significant postoperative complication. With a frequency of 9–39% according to different studies, it is the second most common cause of acute kidney injury in intensive care units, and an independent predictor of mortality. This study aimed to investigate the importance of preoperative hemoglobin and uric acid levels as risk factors for acute kidney injury in the postoperative period in cardiac surgery patients. Material and Methods. The study included a total of 118 patients who were divided into two groups. Each group included 59 patients; the fist group included patients who developed acute kidney injury and required renal replacement therapy, and the second included patients without acute kidney injury. Types of cardiac surgery included coronary, valvular, combined, aortic dissection, and others. All necessary data were collected from patient medical records and the electronic database. Results. A statistically significant difference was found between the groups in preoperative hemoglobin levels (108.0 vs. 143.0 g/l, p = 0.0005); postoperative urea (26.4 vs. 5.8 mmol/l, p = 0.0005) and creatinine (371.0 vs. 95.0 μmol/l, p = 0.0005), acute phase inflammatory reactants C-reactive protein (119.4 vs. 78.9 mg/l, p = 0.002) and procalcitonin (7.0 vs. 0.2 ng/ml, p = 0.0005), creatine kinase myocardial band isoenzyme (1045.0 vs. 647.0 μmol/l, p = 0.014); duration of extracorporeal circulation (103.5 vs. 76.0 min, p = 0.0005) and ascending aortic clamp during cardiac surgery (89.0 vs. 67.0 min, p = 0.0005). The exception was the preoperative uric acid level, where there was no statistically significant difference (382.0 vs. 364.0 μmol/l, p = 0.068). There was the preoperative uric acid level, where there was no statistically significant difference (382.0 vs. 364.0 μmol/l, p = 0.068). There was a statistically significant correlation between the use of inotropic agents and acute kidney injury development. Conclusion. There is a correlation between the preoperative low hemoglobin levels and postoperative acute kidney injury. There is no statistically significant correlation between the preoperative levels of uric acid and postoperative acute kidney injury.

Key words: Acute Kidney Injury; Cardiac Surgical Procedures; Preoperative Care; Hemoglobins; Uric Acid; Risk Factors; Renal Replacement Therapy; Postoperative Complications

Sažetak

Uvod. Akutno oštećenje bubrega udruženo sa kardiohirurškom operacijom česta je i značajna postoperativna komplikacija i sa učestalošću 9–39%, prema različitim studijama, predstavlja drugi najčešći uzrok akutnog zatajivanja bubrega u jedinicama intenzivne nege i nezavisan prediktor mortaliteta. Cilj ovog rada bio je da se ispitaju značaj preoperativnih vrednosti hemoglobin i mokraćne kiseline kao faktora rizika za razvoj akutnog oštećenja bubrega u postoperativnom periodu kod kardiohirurških pacijenata. Materijal i metode. Istraživanjem je obuhvaćeno ukupno 118 pacijenata, koji su podeljeni u dve grupe. Prvu grupu činilo je 59 pacijenata koji su razvili akutno oštećenje bubrega i koji su zahtevali terapiju zamene bubrežne funkcije, a drugu grupu je činilo 59 pacijenata bez akutnog oštećenja bubrega. Tipovi hirurških procedura su bili koronarna, valvularna, kombinovana, aortni disekcija i druge. Svi potrebni podaci o pacijentima su uzeti iz medicinske dokumentacije i iz elektronske medicinske baze podataka. Rezultati. Pronađena je statistički značajna razlika između grupa u odnosu na vrednosti preoperativnog hemoglobin (108 vs 143 g/l, p = 0.0005); postoperativnih vrednosti uree (26.4 vs. 5.8 mmol/l, p = 0.0005) i creatinina (371 vs 95 μmol/l, p = 0.0005), reakcije akutne fazne zapaljenja – C-reaktivni protein (119.4 vs. 78.9 mg/l, p = 0.002) i prokalcitonina (7 vs. 0.2 ng/ml, p = 0.0005), dometa ekstrakorporalne cirkulacije (103.5 vs. 76.0 min, p = 0.0005) i kretanja aortne klape tokom kardiohirurške operacije (89 vs. 67 min, p = 0.0005). Otkrivena je statistički značajna korelacija između upotrebe inotropnih lekova i razvoja akutnog oštećenja bubrega. Zatvoren je postoji visok stepen korelacija između preoperativnih niskih vrednosti hemoglobin i posleoperativne pojave akutnog oštećenja bubrega. Ne postoji statistički značajna korelacija između preoperativnih vrednosti mokraće kiseline i posleoperativne pojave akutnog oštećenja bubrega.

Ključne reči: akutno oštećenje bubrega; kardiohirurške procedure; preoperativna priprema; hemoglobin; mokraćne kiseline; faktori rizika; sustitucijska terapija bubrežne funkcije; postoperativne komplikacije

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Introduction

Cardiac surgery, including coronary artery bypass grafting and valvular surgery, are among the most common surgical procedures, with over 2 million procedures performed annually throughout the world [1]. Postoperative mortality after cardiac surgery has declined significantly over the last two decades [2]. However, despite the advancement in operative techniques, peri- and postoperative care, postoperative complications have remained a significant problem. This is mainly due to an always-increasing number of older and high risk patients who are being selected for surgery [3], which is associated with a higher multiorgan dysfunction and extensive vascular disease. Postoperative complications affect the length of postoperative recovery, require greater staff engagement and significantly increase the overall treatment cost. Cardiac disorders, respiratory, neurological and hemorrhagic/thromboembolic complications, and liver and kidney failure are the most common complications [4, 5]. Furthermore, intra-hospital infections are also becoming increasingly reported as important complications [6].

Acute kidney injury and its poorly understood etiopathogenesis represents a significant problem in the treatment of cardiac surgery patients. The etiology is most likely influenced by multiple factors and depends on both the patient’s general condition and the operative and postoperative treatment factors, including pharmacological therapy. Possible specific risk factors for the development of acute kidney injury include anesthesia-related problems, type of surgery and use of cardiopulmonary bypass, treatment in intensive care unit using nephrotoxic drugs and contrast agents, sepsis development and prolonged hemodynamic instability followed by hypotension [7]. The persistent risk factors associated with acute kidney injury are chronic kidney disease, albuminuria, hypertension, diabetes mellitus, advanced life age, and obesity.

The primary objective of this study was to investigate the significance of preoperative hemoglobin and uric acid levels as risk factors for the development of acute kidney injury after cardiac surgery. The secondary objectives of the study were to test the hypothesis that certain postoperative values of renal function parameters (urea, creatinine), acute-phase inflammatory reactants (procalcitonin, C-reactive protein (CRP)), creatine kinase myocardial band (CK-MB) isoenzyme, as well as application of specific pharmacological therapy (inotropic and vasopressor agents) and extracorporeal circulation and ascending aortic clamps duration may represent risk factors for the development of acute kidney injury.

Material and Methods

A retrospective study was conducted at the Institute of Cardiovascular Diseases of Vojvodina using the medical records and hospital information system. A total of 118 patients, who underwent open heart surgery between January 2014 and December 2018, were included in the study. The first group included patients who developed acute kidney injury and required renal replacement therapy (group I, n = 59), while the patients without acute kidney injury in the postoperative period were in the second group (group II, n = 59). The patients were matched by age, gender, type of surgery and operative risk calculated by EuroSCORE II.

The diagnosis of acute kidney injury in group I was established according to Kidney Disease Improving Global Outcomes (KDIGO) criteria. Indications for continuous renal replacement therapy in the first group included uremia, circulatory blood volume overload, biochemical abnormalities, and acute kidney injury resistant to diuretics. Other indications for continuous renal replacement therapy were severe hemodynamic instability, severe systemic inflammatory response, cardiac decompensation, and any other organic disorder followed by acute kidney injury.

The main exclusion criteria for participation were:
- patients with incomplete medical history data;
- patients undergoing another type of cardiac surgery that did not require the use of extracorporeal circulation;
- patients who died intraoperatively.

Data analysis included:
- Medical history data:
  - demographic characteristics (age and gender);
  - cardiovascular risk factors (positive family history, smoking, arterial hypertension, hyperlipoproteinemia, diabetes mellitus);
- Physical examination:
  - body height (cm); body weight (kg); body mass index (BMI) (kg/m²);
- Laboratory blood tests:
  - preoperative hemoglobin and uric acid levels;
  - parameters of renal function after surgery (urea, creatinine, uric acid), with the highest serum values measured before the start of renal replacement therapy;
- postoperative values of procalcitonin, CRP, CK-MB isoenzyme;
- Surgery related parameters:
  - type of cardiac surgery (coronary, valvular, combined, aortic dissection, and others);
  - the urgency of the performed surgery (emergency or elective);
  - duration of the extracorporeal circulation and ascending aortic clamp during surgery;
  - use of inotropes and vasopressors, as well as their doses after surgery;
  - outcome, i.e. mortality during hospital treatment.

Descriptive statistical methods, methods for testing statistical hypotheses, and methods for testing
dependence were used to analyze the primary data. Descriptive statistical methods included measures of central tendency (arithmetic mean, median), measures of variability (standard deviation), and relative numbers (indicators of structure). To test the statistical hypotheses the following methods were used: t-test for two independent samples, and χ² test. From dependence analysis methods the following were used: Pearson’s linear correlation coefficient and Spearman’s rank correlation coefficient. Statistical hypotheses were tested at the level of statistical significance of 0.05.

**Results**

The study included 82 (69%) male and 36 (31%) female patients. The gender distribution in groups was as follows: in group I, there were 35 male (59%) and 24 female patients (41%), while in group II there were 47 male (80%) and 12 female patients (20%). The average age of all participants was 64 years, while in the groups it was 65 (45–80) in group I, and 63 (35–78) in group II. There were 57 (48%) patients younger than 65 years, and 61 (52%) older than 65.

The following preoperative risk factors for the development of cardiovascular diseases were identified in group I: 30.5% of patients had a positive family history; 74.6% hypertension; 30.5% were smokers; 28.8% had hyperlipoproteinemia; while 42.4% of patients had diabetes mellitus. There were 39% of patients who underwent an emergency operation and 61% of patients underwent an elective surgery. The average BMI in this group was 28.63 kg/m².

In group II, the prevalence of these risk factors was: 40.7% of patients had a positive family history; 71.2% hypertension; 37.3% were smokers; 35.6% had hyperlipoproteinemia; 20.3% of patients had diabetes mellitus. There were only 11.9% of emergency operations versus 88.1% of elective. The average BMI in this group was 28.73 kg/m².

None of the patients from group II developed acute kidney injury (Table 1).

**Table 2** shows the mean values of the numerical variables in both groups of the participants. There

| Group I/Grupa I | Group II/Grupa II | p value/p vrednost |
|----------------|------------------|--------------------|
| Preoperative hemoglobin (g/l) | 108.0 (97.5 - 125.5) | 143.0 (138.0 - 153.0) | 0.0005 |
| Preoperatni hemoglobin (g/l) | 382.0 (304.5 - 469.5) | 364.0 (302.5 - 415.5) | 0.068 |
| Uric acid (μmol/l)/Mokraćna kiselina (μmol/l) | 103.5 (86.0 - 143.0) | 76.0 (60.5 - 100.5) | 0.0005 |
| Extracorporeal circulation (min) | 89.0 (73.0 - 119.0) | 67.0 (52.0 - 86.5) | 0.0005 |
| Ascending aortic clamp (min) | 26.45 (19.0 - 37.6) | 5.8 (4.5 - 7.3) | 0.0005 |
| Creatinine (μmol/l)/Kreatinin (μmol/l) | 371.0 (256.0 - 485.0) | 95.0 (81.0 - 119.0) | 0.0005 |
| Procalcitonin (ng/ml)/Prokalcitonin (ng/ml) | 6.98 (1.95 - 22.33) | 0.22 (0.11 - 0.63) | 0.0005 |
| CK-MB (mg/l)/CK-MB (mg/l) | 1045.0 (498.0 - 2783.0) | 647.0 (377.5 - 1275.0) | 0.014 |
| CRP (mg/l)/CRP (mg/l) | 119.4 (69.9 - 213.0) | 78.9 (43.8 - 108.15) | 0.002 |

Legenda: CK-MB – kreatin kinaza MB frakcija, CRP – C-reaktivni protein
was a statistically significant difference between the mean values of preoperative hemoglobin, the postoperative values of renal function parameters (urea, creatinine), acute-phase inflammatory reactants (CRP and procalcitonin), CK-MB isoenzyme as well as the duration of both extracorporeal circulation and ascending aortic clamp during cardiac surgery (p < 0.05). The exception was the preoperative mean value of uric acid, where there was no statistically significant difference between the studied groups (p = 0.068).

The area under the receiver operating characteristic (ROC) curve showed that preoperative hemoglobin represents a good marker of postoperative acute kidney injury, with a cut-off value of 131.5 g/l with sensitivity and specificity of 83.1% and 94.9%, respectively.

Out of 118 participants, 66.8% received vasopressor medications and 74.6% inotropic medications. Using the χ² test for nonparametric data testing, an association between acute kidney injury after the postoperative therapeutic administration of vasopressor and inotropic drugs was investigated in both study groups (Table 3).

In group I, 67.8% of patients received vasopressors, but there was no statistically significant association between vasopressor use and the occurrence of acute kidney injury. In the second group, 66.1% (p = 1.000) received vasopressors.

In group I, there was an association between the use of inotropes and the onset of acute kidney injury (p = 0.001). The percentage of patients who did not receive inotropes and developed acute kidney injury was 11.9%, while there were 88.1% of patients who developed acute kidney injury after receiving inotropes. The use of inotropes in group II was 61%.

Table 4 shows whether there was a statistically significant correlation of the listed numerical variables in the examined groups with the occurrence of acute kidney injury in the postoperative period. By calculating the Pearson's correlation coefficient, the following results were obtained:

- There is a statistically significant strong negative correlation of preoperative hemoglobin levels with the occurrence of acute kidney injury (r = -0.740; p = 0.0005), meaning that participants with lower preoperative hemoglobin levels were more likely to experience acute kidney injury after cardiac surgery.
- Acute kidney injury development was in a slight positive correlation with preoperative uric acid values (r = 0.244; p = 0.008), where higher uric acid values were a possible indicator of the development of acute kidney injury.
- There was a moderate positive correlation between the extracorporeal circulation and ascending aortic clamps time during cardiac surgery with acute kidney injury (r = 0.339; r = 0.328; p = 0.0005).
- Postoperative values of renal function parameters, urea and creatinine, are strongly positively correlated.

### Table 3. Frequency of inotrope and vasopressor drugs use and acute renal failure development

|                   | Group I | Group II | Total/UKupno |
|-------------------|---------|----------|--------------|
| **Vasopressors**  |         |          |              |
| Yes               | 40      | 39       | 79           |
| Da                | 67.8%   | 66.1%    | 66.8%        |
| No                | 19      | 20       | 39           |
| Ne                | 32.2%   | 33.9%    | 33.2%        |
| **Inotropes**     |         |          |              |
| Yes               | 52      | 36       | 88           |
| Da                | 88.1%   | 61%      | 74.6%        |
| No                | 7       | 23       | 30           |
| Ne                | 11.9%   | 39%      | 25.4%        |

### Table 4. Correlation between numerical variations within the group II

| Variable                        | Pearson's correlation coefficient | p value |
|---------------------------------|----------------------------------|---------|
| Hemoglobin/Hemoglobin           | -0.740                           | 0.0005  |
| Uric acid/Mokračna kiselina      | 0.244                            | 0.008   |
| Extracorporeal circulation time/Trajanje vantelesnog krvotoka | 0.339 | 0.0005 |
| Ascending aortic clamps/Kleme ascendentne aorte     | 0.328                           | 0.0005  |
| Urea/Urea                       | 0.828                            | 0.0005  |
| Creatinine/Kreatinin            | 0.708                            | 0.0005  |
| Procalcitonin/Prokalcitonin      | 0.416                            | 0.0005  |
| CK-MB/CK-MB                     | 0.230                            | 0.012   |
| CRP/CRP                         | 0.334                            | 0.0005  |

Legenda: CK-MB – kreatin kinaza MB frakcija, CRP – C-reaktivni protein
correlated with the occurrence of acute kidney injury \( (r = 0.828; r = 0.708; p = 0.0005) \).

- Acute-phase inflammatory reactants values, procalcitonin and CRP, measured postoperatively, were moderately positively correlated with the development of kidney injury \( (r = 0.416; r = 0.334; p = 0.0005) \).

- Finally, there is a small positive correlation between the measured postoperative values of CK-MB isoenzyme and the development of acute kidney injury \( (r = 0.230; p = 0.012) \).

In Group I, 25 (42.4%) of all participants had a fatal outcome within 60 days after surgery.

**Discussion**

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common and significant postoperative complication, with an incidence that varies between 9 – 39% \[8, 9\]. Among the causes of acute kidney injury in intensive care units, cardiac surgery is in the second place, just behind sepsis \[10\]. On the other hand, acute kidney injury represents one of the most common severe complications that occur after cardiac surgery and leads to a significant increase in morbidity and mortality, prolongs the length of stay in the intensive care and significantly increases the treatment cost \[11, 12\].

Studies have shown an association between acute kidney injury and subsequent development of chronic kidney disease, even though many cases of acute kidney injury are reversible within days or weeks after the onset. Although CSA-AKI is more common in patients with clearly diagnosed preoperative kidney disease, patients with preserved renal function are also at high risk \[13\]. Patients requiring some form of renal replacement therapy are at three times higher risk of developing end-stage chronic renal failure compared with those who do not require renal replacement therapy \[14, 15\]. The mortality rate in patients with renal replacement therapy is as high as 40–70% and is directly dependent on the number of episodes of acute renal failure during hospital treatment \[16\].

Although many different diagnostic algorithms and criteria have been used so far for the diagnosis of acute kidney injury, determining the actual incidence is difficult. Most of the existing criteria for the diagnosis of acute kidney injury are considered not sensitive enough, and therefore this significant entity remains under-recognized \[17\]. In clinical practice, the most commonly used algorithms for the diagnosis of acute kidney injury are Acute Kidney Injury Network, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease, and KDIGO \[18\].

In cardiac surgery patients, KDIGO criteria are recommended for the diagnosis of acute kidney injury \[19\]:

- Increase in serum creatinine ≥ 26.5 μmol/l within 48 hours;
- Increase in serum creatinine ≥ 1.5–1.9 times baseline within 7 days;
- Diuresis < 0.5 ml/kg/h for 6 hours.

The optimal moment for the initiation of renal replacement therapy in CSA-AKI is not clearly defined. The decision is based on patient’s clinical characteristics, primarily hemodynamic status, volume overload, and biochemistry findings (azotemia, hyperkalemia, and acidosis). In our center, renal replacement therapy was used in patients with severe kidney injury (KDIGO stages 2 and 3).

The exact pathophysiology of CSA-AKI has not been clearly understood yet. It encompasses multiple factors that, through different mechanisms and to varying degrees, lead to damage. Factors related to cardiac surgery include kidney hypoperfusion, reperfusion injury after ischemia, neurohumoral activation, inflammation, oxidative stress, as well
as exposure to exogenous (nephrotoxic drugs) and endogenous (hemoglobin) nephrotoxins [10, 12].

Renal hypoperfusion is one of the most important factors responsible for the damage. The use of extracorporeal circulation during cardiac surgery uses non-pulsatile blood flow with low blood pressure and poor tissue perfusion and is also associated with hemodilution and sudden changes in body temperature. All these conditions have a cumulative negative effect on renal tissue and lead to structural damage to the renal tubules [20]. After extracorporeal circulation is stopped and normal circulation is established, after a period of ischemia, the kidneys regain increased blood volume, which may lead to reperfusion cell injury and cell death [21].

The use of extracorporeal circulation is associated with intravascular hemolysis, leading to an acute increase in the concentration of free hemoglobin in the blood, which can cause injury to the tubular epithelium [22]. Patients undergoing cardiac surgery are most often exposed to nephrotoxic drugs such as antibiotics (aminoglycosides and glycopeptides), non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors [23] and angiotensin receptor blockers.

In addition to all the above mechanisms of renal parenchyma injury, it was found that risk factors were contributing to the degree and severity of CSA-AKI (Table 5). These factors can be divided into preoperative, intraoperative and postoperative, and each of them contributes differently to the damage. Preoperative risk factors mostly depend on the patient and cannot be modified. On the other hand, intraoperative and postoperative risk factors are variable and can be influenced. Altering the surgical procedure and type of surgery, avoiding nephrotoxic agents and blood transfusions can reduce the incidence of acute kidney injury [24].

Anemia is one of the most significant risk factors for the development of acute kidney injury. Anemia has negative effects on kidneys through several different mechanisms. The decreased oxygenation of the renal parenchyma, especially tubular epithelium, is the most important mechanism. Anemia, on the other hand, is associated with the use of erythrocyte transfusion, which itself is associated with several complications, including kidney injury [25]. The results of our study showed that there was a statistically significant difference in hemoglobin levels between patients with kidney injury and patients with preserved renal function. Such results are consistent with other studies [26, 27], which found that anemia significantly increases the incidence of acute kidney injury, and also prolongs the time spent in the intensive care and increases morbidity and mortality.

The association between low hematocrit and low hemoglobin levels during extracorporeal circulation with the development of kidney injury during the postoperative course has also been established [27]. Although anemia increases the risk of kidney injury in patients undergoing heart surgery, erythrocyte transfusion has been shown not to lead to improvement, but in some cases even to worsening of the clinical outcome [28, 29]. Khan and et al. [30] have concluded that both anemia and erythrocyte transfusions represent independent risk factors that increase the incidence of CSA-AKI. A study conducted by Karkouti et al. [31] showed that the optimal hemoglobin concentration during extracorporeal circulation, which maintains a balance between the benefits of hemodilution and lower release of free hemoglobin which is nephrotoxic on one hand and the risk of inadequate renal parenchyma oxygenation on the other, is 85 g/l.

The results of our study show that after cardiac surgery there is no statistically significant difference in uric acid levels between patients with kidney injury and patients with preserved renal function. This is in disagreement with previous studies [32, 33] which showed that uric acid represents a risk factor for worsening of renal function after coronary surgery and that this parameter can be used as a predictor of acute renal impairment after surgery. Lee et al. [34] came to the same conclusions and confirmed uric acid to be a risk factor and predictor of acute renal impairment after coronary surgery. The limit value for uric acid concentration above which a significant increase in the incidence of acute renal impairment was observed to be 330 μmol/l in males and 300 μmol/l in females.

Conclusion

There is a high degree of correlation between preoperative low hemoglobin levels and the postoperative onset of acute kidney injury. There is no statistically significant correlation between preoperative uric acid levels and the postoperative onset of acute kidney injury.

There is a moderate to a strong positive correlation between the postoperative levels of urea, creatinine, C-reactive protein, and procalcitonin with the occurrence of acute kidney injury after cardiac surgery.

The duration of the aortic clamp and extracorporeal blood pump, as well as the administration of inotropic drugs, also correlate with the onset of acute kidney injury in the postoperative period.

The results of this study indicate that measures should be taken to prevent acute kidney injury after cardiac surgery by adequate selection and preparation of patients needing surgery.
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