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Original Article / Özgün Makale

Serum interleukin-18 as an early marker of acute kidney injury following open heart surgery

Açık kalp cerrahisi sonrasında akut böbrek hasarının erken bir belirteci olarak serum interlökin-18

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Background: This study aims to investigate whether serum interleukin (IL)-18 is an early biomarker of acute kidney injury (AKI).

Methods: Thirty consecutive patients (22 males, 8 females; mean age 62.4±9.0 years; range 49 to 78 years) who underwent open-heart surgery were enrolled in this prospective study. Serum IL-18 concentrations were analyzed prior to induction of anesthesia, at weaning from cardiopulmonary bypass (CPB) and two hours after weaning from CPB. Serum creatinine levels were analyzed in the postoperative first, second, and third days. Acute kidney injury was defined as creatinine levels exceeding 50% of the basal value or exceeding the basal value by 0.3 mg/dl at 48 hours postoperatively. The patients were classified into two groups including AKI (n=12) and non-AKI (n=18). Serum IL-18 levels were compared between the groups.

Results: Twelve patients (40%) developed AKI. The diagnosis was able to be made using the serum creatinine levels at 24 to 48 hours postoperatively. Although IL-18 concentrations at weaning from CPB decreased slightly in the AKI group, the decrease in the non-AKI presenting group was higher. Using univariate analyses, IL-18 concentrations at two hours after weaning from CPB were found to be related to AKI (p=0.031). The difference in serum IL-18 concentrations between the preoperative period and two hours after weaning from CPB were found to be statistically significant (p=0.017). According to the Receiver operating characteristic curve analysis, the threshold value for AKI prediction of serum IL-18 concentrations at two hours after weaning from CPB was 353.7 pg/ml with a sensitivity of 58.3% and a specificity of 83.3% (AUC=0.736).

Conclusion: Serum IL-18 concentration may be used as a biochemical indicator for early detection of acute kidney injury following open heart surgery.

Keywords: Acute kidney injury; cardiac surgery; cardiopulmonary bypass; interleukin-18.

Amaç: Bu çalışmada serum interlökin (IL)-18'in akut böbrek hasarının (ABH) erken bir biyobelirteci olup olmadığı araştırıldı.

Çalışma planı: Bu prospektif çalışmaya açık kalp cerrahisi yapılan 30 ardışık hasta (22 erkek, 8 kadın; ort. yaş 62.4±9.0 yıl; dağılım 49-78 yıl) dahil edildi. Anestezi indüksiyonu öncesi, kardiyopulmoner baypas (KPB) çıkışı ve KPB çıkışı ikinci saatte serum IL-18 konsantrasyonları çalışıldı. Ameliyat sonrası birinci, ikinci ve üçüncü günlerde serum kreatinin konsantrasyonlarına bakıldı. Akut böbrek hasarı; ameliyat sonrası 48 saatlik dönemde kreatinin değerinin, bazal değerin %50'sinden daha fazla olması veya bazal değerin 0.3 mg/dl üzerinde olması olarak tanımlandı. Hastalar ABH gelişen (n=12) ve ABH gelişmeyen grup (n=18) olarak ikiye ayrıldı. Serum IL-18 değerleri iki grup arasında karşılaştırıldı.

Bulgular: On iki hastada (%40) ABH gelişti. Tanı ancak serum kreatinin konsantrasyonları ile ameliyat sonrası 24-48 saatlerde konulabildi. Serum IL-18 konsantrasyonları ABH gelişen grupta KPB çıkışı bir miktar azalsa da bu düşüş ABH olmayan grupta daha fazla idi. Tek değişkenli analizlerde KPB çıkışı sonrası ikinci saatte alınan IL-18 konsantrasyonları ABH ile ilişkili bulundu (p=0.031). Serum IL-18 konsantrasyonlarındaki ameliyat öncesi dönem ile KPB çıkışı sonrası ikinci saat arasındaki fark ise istatistiksel olarak anlamlı idi (p=0.017). Alıcı işletim karakteristiği eğrisi analizine göre, KPB çıkışı sonrası ikinci saat serum IL-18 konsantrasyonunun ABH'yi öngörmedeki eşik değeri %58.3 duyarlılık ve %83.3 özgüllük ile 353.7 pg/mL olarak hesaplandı (AUC=0.736).

Sonuç: Serum IL-18 konsantrasyonu açık kalp cerrahisi sonrası akut böbrek hasarını erken dönemde saptayabilen bir biyobelirteç olarak kullanılabilir.

Anahtar sözcükler: Akut böbrek hasarı; kalp cerrahisi; kardiyopulmoner baypas; interlökin-18.

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Acute kidney injury (AKI) is a common complication of cardiopulmonary bypass (CPB)[1] that occurs in up to 10-40% of adults and is a predictor of poor outcomes.[2] Diminished renal blood flow, loss of pulsatile flow, and hypothermia are among the mechanisms that contribute to renal injury after cardiac surgery.[1] In the present day, AKI is typically diagnosed by detecting increases in serum creatinine,[3] but this is an imperfect marker in an acute setting because serum creatinine concentrations may not increase until approximately 50% of kidney function has been lost, and they may be affected by several non-renal factors.[4] For these reasons, early diagnosis of AKI may be difficult. In addition, serum creatinine concentrations do not reflect the severity of AKI;[4] hence, there is a need for early and specific markers of kidney injury in order to provide more effective treatment strategies.

Interleukin-18 (IL-18) is a member of the IL-1 family of cytokines which are produced by renal tubular cells and macrophages. It was originally described as an interferon gamma-inducing factor,[5] it has now been proven that IL-18 plays an important role in renal injury induced by acute ischemia-reperfusion.[6] Moreover, it is also a potential mediator of tubular injury.[7] There are published results that indicate that urinary IL-18 is an early biomarker for the diagnosis of AKI.[8,9] In this study, our objective was to demonstrate that this is true when this type of injury takes place after CPB.

PATIENTS AND METHODS

This prospective study consisted of 30 patients (22 males, 8 females; mean age 62.4±9.0 years; range 49 to 78 years) who consecutively underwent open heart surgery using CPB. We excluded patients with pre-existing renal insufficiency and those who had undergone renal transplantation as well as those who had used nephrotoxic drugs before the operation. Acute kidney injury is defined as an increase in serum creatinine from the preoperative values by either more than 50% or more than 0.3 mg/dl within the first 48 hours after surgery (AKI classification stage 1).[10] Thereafter, study patients were classified into two groups as patients who developed AKI (n=12; 8 males, 4 females; mean age 66.3±8.5 years; range 52 to 78 years) and the others (n=18; 14 males, 4 females; mean age 59.7±8.6 years; range 49 to 77 years) according to postoperative serum creatinine levels.

The local institutional review board approved this study, and written informed consent was obtained from the patients. This study was also in compliance with the Declaration of Helsinki, and the clinical practice was not changed or modified for the purpose of the study.

We analyzed the serum IL-18 concentrations prior to the induction of anesthesia, immediately after CPB, and two hours after CPB, and the serum creatinine levels were analyzed the day before operation and at postoperative days one, two, and three. In addition, blood samples were collected in non-heparinized tubes, and the serum IL-18 was measured by a human IL-18 enzyme-linked immunosorbent assay (ELISA) kit (Medical and Biologic Laboratories Co., Ltd, Nagoya, Japan) according to manufacturer's instructions.

Statistical analysis

All statistical analyses were performed using the SPSS version 15.0 for Windows statistical software program (SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables were expressed as mean ± standard deviation (SD) or median values with the interquartile range if not normally distributed while categorical variables were expressed as numbers and percentages. The demographic characteristics, perioperative variables, and calculated values were compared using an independent samples t-test or the Mann-Whitney U test for continuous variables and a chi-square test or Fisher's exact test for categorical variables. The serum IL-18 levels over time were compared using the Wilcoxon signed-ranks test. A receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off levels of the serum IL-18 to predict AKI, and a general linear model was used to determine the course of serum IL-18 levels over time in the AKI and the control groups. A p value of <0.05 was considered to be statistically significant.

RESULTS

The baseline characteristics of the patients are listed in Table 1. It was only possible to make a diagnosis of AKI using the serum creatinine levels 24-48 hours postoperatively, and we identified 12 patients (40%) who had developed AKI, all of whom were at stage 1 according to the AKI classification system.[10] None of the patients required renal replacement therapy, and all of the preoperative factors were similar between the two groups based on the presence of AKI except for age, ejection fraction (EF), and the presence of chronic obstructive pulmonary disease (COPD). The mean age of the patients was significantly higher in the AKI group than the control group (66.3±8.5 vs. 59.7±8.6 years, respectively) (p=0.025), whereas the mean preoperative EF of the AKI patients was significantly lower (47.2±7.8% vs. 53.8±7.6%, p=0.025).

Table 1. Preoperative patient characteristics

Factor	Total			AKI (-) (n=18)			AKI (+) (n=12)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			62.4±9.0			59.7±8.6			66.3±8.5	0.025*
Preoperative LVEF (%)			51.1±8.2			53.8±7.6			47.2±7.8	0.025*
Preoperative interval of contrast agents (days)			16.9±34.6			23.5±45.8			8.7±5.2	0.768*
Creatinine (mg/dl)			0.87±0.16			0.90±0.19			0.84±0.10	0.524*
Creatinine clearance (ml/min)			94.2±35.0			89.9±26.9			100.6±45.1	0.799*
Urea (mg/dl)			39.2±12.9			36.3±8.6			43.5±17.0	0.610*
Hematocrit (%)			41.6±4.7			41.5±5.3			41.6±4.0	1.000*
Number of males	22	73.3		14	77.8		8	66.7		0.678†
Hypertension	19	63.3		13	72.2		6	50.0		0.266†
Diabetes mellitus	7	23.3		3	16.7		4	33.3		0.392†
Hyperlipidemia	6	20.0		4	22.2		2	16.7		1.000†
COPD/asthma	13	43.3		5	27.8		8	66.7		0.035§

SD: Standard deviation; AKI: Acute kidney injury; LVEF: Left ventricular ejection fraction; COPD: Chronic obstructive pulmonary disease; * Mann-Whitney U test; † Fisher's exact test; § Chi-square test.

The perioperative factors and serum IL-18 levels over time are summarized in Table 2, and we found no statistical significance between the groups regarding the operative and early postoperative variables. Although the IL-18 concentrations measured when the patients were being weaned from CPB revealed a slight decrease in the AKI group, there was a larger decrease in the control group (Figure 1). In addition, when the IL-18 concentrations were measured two hours after being weaned from CPB, they were significantly higher in the AKI group compared with the control group (417.3±174.3 pg/ml vs. 318.6±63.5 pg/ml, respectively) (p=0.031). Furthermore, the increase in the serum IL-18 concentrations between the preoperative period and two hours after weaning from CPB were statistically significant in the AKI group (p=0.017) (Figure 1).

According to the ROC curve analysis, we also determined that the threshold value for predicting AKI using serum IL-18 concentrations two hours after weaning from CPB was 353.7 pg/ml, with a sensitivity of 58.3% and a specificity of 83.3% [area under the curve (AUC)=0.736].

DISCUSSION

Acute kidney injury after cardiac surgery affects a considerable portion of adult patients.[1,10] Regrettably, serum creatinine is not a reliable marker for AKI, but an increase in creatinine may be measured after a considerable loss of glomerular filtration rate (GFR).[3] In a recent study, Stafford-Smith et al.[11] determined that the serum creatinine measurements on arrival at the intensive care unit (ICU) after cardiac surgery were not a useful predictor of AKI.

Identifying an early predictive marker for AKI could result in earlier treatment strategies to limit associated

Table 2. Operative and early-postoperative variables

Factor	Total	AKI (-) (n=18)	AKI (+) (n=12)	
	Mean±SD	Mean±SD	Mean±SD	*p**
Perioperative factors				
Cross-clamp time (min)	71.8±22.5	70.1±25.1	74.5±18.8	0.329
CPB time (min)	103.7±28.0	106.5±30.5	99.5±24.7	0.799
Ventilation time (hours)	11.3±4.4	11.5±5.1	11.0±3.4	0.652
Drainage (ml)	831.0±342.1	800.0±400.8	875.0±246.3	0.422
Duration of ICU stay (hours)	25.1±19.7	27.9±25.7	21.3±5.1	0.815
IL-18 levels (pg/ml)				
IL-18 (preoperative level)	349.4±92.3	344.5±101.6	356.9±80.3	0.439
IL-18 (CPB weaning)	314.4±78.8	295.5±75.1	342.7±78.8	0.072
IL-18 (post-CPB 2nd hour)	358.1±127.7	318.6±63.5	417.3±174.3	0.031

SD: Standard deviation; AKI: Acute kidney injury; CPB: Cardiopulmonary bypass; ICU: Intensive care unit; * Mann-Whitney U test.

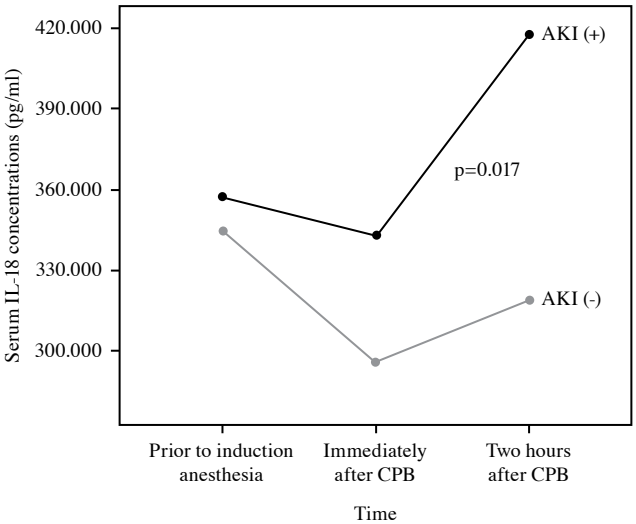

Figure 1. Serum IL-18 values over time in each group. AKI: Acute kidney injury; CPB: Cardiopulmonary bypass.

morbidity, and patients identified by these biomarkers may receive more prolonged invasive hemodynamic monitoring. Moreover, avoidance of nephrotoxic medications, hypotension, and hypovolemia may be enforced in these patients, and earlier intervention with renal replacement therapy should be considered in order to prevent further damage for patients for whom fluid overload is developing but no increase in serum creatinine levels is present.

Acute kidney injury is classified into three stages according to serum creatinine levels as follows:[10]

Stage 1: An increase in serum creatinine that is more than or equal to 0.3 mg/dl (≥26.4 μmol/l) or an increase which is more than or equal to 150-200% (1.5-two-fold) from the baseline

Stage 2: An increase in serum creatinine of more than 200-300% from the baseline

Stage 3: An increase in serum creatinine of more than 300% from the baseline (or serum creatinine more than or equal to 4.0 mg/dl [≥354 μmol/l] with an acute increase of at least 0.5 mg/dl [44 μmol/l])

All of the patients with AKI in this study were at stage 1, so none required renal replacement therapy.

Interleukin-18 is a novel biomarker that has been studied in detail in ischemia reperfusion models, and it has been demonstrated that it mediates ischemic acute renal failure in mice.[6,7] In a recent study by Parikh et al.,[8] urinary IL-18 levels displayed sensitivity and specificity of above 90% in patients who were diagnosed with AKI. Additionally, our findings showed that the specificity of serum IL-18 was over 80% for indicating AKI following cardiac surgery, and Lin et al.[12] discovered that the serum IL-18 levels had significantly better discriminatory power than any other method at the initiation of renal replacement therapy for hospital mortality prediction. Furthermore, Blankenberg et al.[13] determined that serum IL-18 concentration was an independent predictor of coronary events in their recent study. They also noted that interleukin-18 is an important regulator of both native and acquired immune responses and that it is present in human atherosclerotic lesions as well as at higher concentrations in unstable plaques. High serum IL-18 concentrations have been detected in many other inflammatory diseases, including diabetes mellitus (DM), metabolic syndrome,[14] and other renal tubulointerstitial diseases like immunoglobulin (Ig)A nephropathy[15] and contrast-induced nephropathy.[16]

In this study, we hypothesized that serum IL-18, when measured two hours after being weaned from CPB, could serve as an effective marker of renal injury after heart surgery. The serum IL-18 concentrations were decreased in the AKI and control groups immediately after being weaned from CPB, which may have been the result of the destruction of macrophages by the CPB. However, two hours later, the serum IL-18 levels were increased in both groups. This may be explained by the systemic inflammation caused by CPB.[1] In addition, the increase in the serum IL-18 levels were statistically significant in the AKI group, which was likely due to ischemia, hypotension, hypoperfusion, the release of cytokines, and the presence of atheroemboli, all of which have been previously identified as causing AKI development after CPB. Furthermore, Parikh et al.[17] stated that urinary IL-18 levels increase between four and six hours after CPB (peaking at 12 hours) can predict AKI, and Liangos et al.[18] suggested that urinary IL-18 levels at two hours post-CPB can also diagnose AKI. Both of those studies were performed by measuring urinary IL-18 levels, but we measured the serum IL-18 levels instead and had similar, consistent results.

Nowadays, multiple other novel biomarkers for AKI have been proposed,[19,20] including circulating cystatin C (CyC), neutrophil gelatinase-associated lipocalin (NGAL), and retinol-binding proteins (RBPs). Of these markers, some have been evaluated in patients who underwent CPB, and the results suggest that NGAL and CyC demonstrate excellent accuracy in the early diagnosis of AKI.[21,22] There are also studies showing that a combination of NGAL and IL-18 can prognosticate AKI better than one biomarker alone.[23,24] However, some controversy

still exists regarding these biomarkers. For example, Demirtaş et al.[25] stated that NGAL was not a relevant predictive factor for AKI in patients who underwent CABG, and Haase et al.[26] suggested that urinary IL-18 does not predict AKI after cardiac surgery.

Our study had several strengths. It was a prospective study with exclusion criteria that did not include confounding factors; therefore, cardiac surgery with CPB could be regarded as the only factor responsible for AKI. On the other hand, our study had some limitations as well. Our results were obtained from a relatively small number of patients from a single center. In addition, CPB itself can be a source of inflammation in the body. Furthermore, IL-18 is an inflammatory factor that should not be affected by CPB. We tried to overcome this limitation by including only patients who had undergone cardiac surgery with CPB in the study. We also made the measurements for longer intervals in order to detect the peak concentration value of serum IL-18 after CPB. The preoperative factors, such as EF, age, and the presence of COPD, occurred at different rates among the two groups, and since we know that these may influence the development of renal failure, we were not able to perform a further analysis regarding the predictive value of these variables on AKI development because the population of study was not adequate for logistic regression models.

Conclusion

Similar to urinary IL-18, our results indicated that serum IL-18 may also be an early predictive biomarker of AKI after CPB. Of course, the results of this study need to be confirmed in other settings where AKI is present, especially in patients with comorbid conditions where the etiology is multifactorial. Future studies are need in order to validate the sensitivity and specificity of serum IL-18 in clinical samples from larger cohorts and multiple clinical situations.

Declaration of conflicting interests

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