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Can urinary neutrophil gelatinase-associated lipocalin have a role in the early diagnosis of acute kidney injury after coronary artery bypass graft?

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ABSTRACT

Introduction: The role of urinary neutrophil gelatinase-associated lipocalin (NGAL) as a prognostic biomarker in acute kidney injury (AKI) associated with coronary bypass graft has been suggested in some studies. However, the results have been inconclusive in different studies.

Objectives: In the present research, we investigated the diagnostic and prognostic roles of NGAL in Iranian patients who developed AKI after coronary bypass surgery.

Patients and Methods: This study was cross-sectional conducted on adult patients undergoing coronary artery bypass graft (CABG) surgery. Postoperative AKI was defined based on the RIFLE (risk, injury, failure, loss and end-stage kidney disease) criteria. Patients were divided into AKI and non-AKI groups. The urinary NGAL and serum creatinine levels were measured at different times after surgery.

Results: Out of 29 patients, men constituted 75.9% of cases. Mean age of the patients was 61.4±7.7 years old and the mean duration of surgery was 4.9±0.6 hours. Based on serum creatinine, AKI was diagnosed in 37.9%, 17.25%, and 13.8% of patients at first, second, and third day post-surgery, respectively. The urine NGAL increased by 48.35% and 34.5% at 2 and 6 hours after surgery, respectively. However, there was no significant association between the urinary NGAL level and the incidence of post-surgery AKI.

Conclusion: This study showed that urinary NGAL was inapplicable to independently diagnose or predict the outcome of transient AKI associated with CABG.

Implication for health policy/practice/research/medical education:
Urinary neutrophil gelatinase-associated lipocalin is not an independent diagnostic or prognostic biomarker in transient acute kidney injury associated with coronary artery bypass graft.

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Introduction

Coronary bypass graft is one of the most common surgeries worldwide. Transient acute kidney injury (AKI) is known as one of the major devastating complications of this surgical procedure. In addition to financial costs, AKI may lead to multi-organ dysfunctions and higher rate of mortality in this condition. The coronary artery bypass grafting (CABG) is annually conducted in around 1 000 000 patients (1) which up to 30% of them develop AKI. About 3% of the patients developing AKI following CABG will require dialysis, of whom more than 60% may be expired (2). The reported incidence of AKI after CABG varies based on the diagnostic criteria applied for this condition. The CABG-associated renal injury is generally defined as an increase in serum creatinine either 0.3 mg/dL (≥26.4 μmol/L) or 50% of the baseline value (i.e. 1.5 folds from the baseline) within 48 hours post-operation (3).

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The risk factors of AKI following cardiopulmonary bypass surgery are generally related to a reduced renal perfusion and the blood supply. Based on such risk factors, scoring systems have been suggested to predict the prognosis of AKI (4,5). However, these scoring systems have been mainly indicated in high-risk and hemodialysis-dependent patients. In recent years, our understanding of the pathogenesis and therapeutic approaches of AKI has been improved by studies on animal models (6). On the other hand, most of the human studies have not resulted in successful treatment approaches (7). One of the important factors limiting the effectiveness of these therapeutic approaches is the lake of reliable diagnostic biomarkers to early diagnose of AKI which precludes advanced renal injury (8). In the current clinical practice, serum creatinine is the gold standard for diagnosis and classification of AKI (9). Nevertheless, serum creatinine level is not a reliable marker for monitoring the acute alternations in renal function (7,8).

Neutrophil gelatinase-associated lipocalin (NGAL) belongs to the lipocalin genes superfamily and is produced by neutrophils, renal tubular, and epithelial cells in response to inflammation or renal tubular ischemic injury (8). The serum level of NGAL is low in conditions with normal renal function. On the other hand, urinary and plasma levels of NGAL are quickly increased in AKI. Therefore, it may be a useful biomarker to early diagnose this condition in patients undergoing kidney transplantation (10) as well as in hemolytic uremic syndrome (11), gentamycin induced renal damage (12), lupus nephritis (13) and contrast induced AKI (14). NGAL can be detected in urine samples approximately two hours after ischemia, and therefore can be a valuable predictor of AKI in clinical settings (15).

The role of NGAL as a diagnostic marker in AKI following the CABG is uncertain. Comprehensive knowledge on this issue can pave the way to early diagnose of AKI in this condition and to prevent its progression to end-stage kidney failure.

Objectives

Since the role of NGAL as a prognostic biomarker of AKI has been documented in numerous studies, the results have been inconclusive in different populations. Regarding the genetic diversity among populations, the present research aimed to assess the diagnostic validity of this biomarker in Iranian patients developing AKI after CABG.

Patients and Method

Study population

The present study was a cross-sectional research. The research population included all adult patients undergoing CABG surgery in Musavi hospital of Zanjan (Iran). The patients were enrolled in the study from December 2016 until May 2017.

Patients with clinical conditions that might affect renal function were excluded from the study. The exclusion criteria were history of renal or hepatic failure, acute or chronic pulmonary diseases, pulmonary artery hypertension, previous cardiac surgery, malignancies, infectious disease, massive proteinuria (>3.5 g/day), evidences of ongoing inflammation (e.g. leukocytosis), and preoperative treatment with steroids or nephrotoxic drugs (e.g. aminoglycoside).

The required clinical and demographic information was initially gathered. The demographic data (age and gender), as well as the history of cardiac surgery or myocardial infarction, diabetes, vascular or respiratory diseases, renal dysfunction, smoking and finally the type and intensity of coronary artery stenosis were recorded by a questionnaire. In addition, the duration of operation and anesthesia, hemodynamic parameters, urine output and the total volume of drainage were also recorded.

Blood samples were taken for measuring baseline serum creatinine level before the induction of anesthesia. Then serum creatinine levels were measured for three consecutive days. Additionally, spot urine samples were obtained preoperatively, and at 2 and 6 hours after the CABG procedure. The blood samples were immediately centrifuged at ≥400 RCF (relative centrifugal force) for 5 minutes. Then, all the centrifuged samples were transferred to microtubes, appropriately labeled and stored at -70°C till examination. Urinary NGAL level was measured by fluorescence-based immunoassay using a specific ELISA kit (Cristal Day Biotech Kit, China).

The postoperative AKI was diagnosed based on the RIFLE (risk, injury, failure, loss, end-stage kidney disease) criteria [i.e. either 25% (or higher) or ≥0.3 mg/dL increases in serum creatinine level within 48 hours, or urine volume <0.5 mL/kg/h for 6 hours].

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all the patients. This study was approved by the Ethics Committee of Zanjan University of Medical Sciences (IR.ZUMS.REC.1392.82). Accordingly, all the participants were informed about the objectives of the study and assured that their information will remain confidential.

Data analysis

The collected data were analyzed by SPSS 22 software using descriptive and analytical tests. Mean ± SD, frequency and percentage were used to present the data. To compare quantitative variables, independent samples, student t-test and repeated measures ANOVA were applied. Kolmogorov-Smirnov test was used for checking the normality of the variables. The *P* value less than 0.05 was considered as statistically significant.

Results

Among patients undergoing CABG procedure, 29 fulfilled the inclusion criteria and entered into the study.

Men comprised 75.9% of the subjects. The patients' mean age was 61.4±7.7 (median; 61, minimum; 49, and maximum; 78) years. There was no significant difference between the mean age of men (61.1 ±8.8 years) and women (62.6±4.2 years; p=0.657). Overall, 27.6% and 75.9% of the patients had diabetes and hypertension respectively without evidence of renal dysfunction.

The mean duration of the surgery was 4.9±.6 (median; 5, minimum; 4, and maximum; 6.5) hours. The mean serum creatinine level before the surgery was 1.19 ±0.21 (median; 1, minimum; 0.8, and maximum; 1.7) mg/dL. Only, two patients (6.9%) had a serum creatinine level >1.5 mg/dL. There was no significant correlation between serum creatinine level and the duration of surgery (p> 0.05). Table 1 shows the means of serum creatinine level at different times during the study.

Overall, AKI was identified in 44.8% of the participants. Based on serum creatinine values, AKI was diagnosed in 37.9%, 17.25%, and 13.8% of the patients at the first, second and third days, post-surgery, respectively.

The urine NGAL level increased by 48.35% and 34.5% at 2 hours and 6 hours after surgery respectively. There was no significant difference in the urine NGAL levels before surgery, within 2 hours, and 6 hours after surgery (Table 2). There was no significant difference comparing the urine NGAL level between the patients who developed AKI after the surgery and those without post-surgery AKI at any time (Table 2). No significant association of at least one-unit increase in urine NGAL at any time after surgery with the incidence of AKI was observed (Table 3).

In patients who developed AKI, the urinary level of NGAL increased by averages of 53.8% and 45.5% at 2 and 6 hours after surgery, respectively. In patients with no evidence of AKI, the mean urinary NGAL was not changing. In total, there was no association between urinary level of NGAL and the incidence of AKI after CABG (Table 4).

Discussion

Our findings showed that urinary NGAL level was not a reliable diagnostic or prognostic marker to diagnose or predict transient AKI associated with CABG within the first six hours after the procedure in adults.

Although urinary NGAL has been suggested as a promising biomarker for early diagnosis of AKI, some recent studies have suggested that this marker has only moderate diagnostic validity in patients undergoing cardiac surgery (16, 17). Parameters such as patient's age, serum creatinine level, ejection fraction and probably

Table 1. The mean serum creatinine levels in patients undergoing coronary artery bypass graft at baseline and different time-points post-surgery

Time	Mean± SD	Comparison with preoperative serum creatinine level (mg/dL) [*P* value]	Comparison with peri- surgery serum creatinine level (mg/dL) [*P* value]	Comparison with day 1st serum creatinine level (mg/dL) [*P* value]	Comparison with day 2nd serum creatinine level (mg/dL) [*P* value]
Preoperative	1.19±0.04	-	0.05 [1]	-0.21 [0.001]	-0.06 [1]
Peri- surgery	1.14±0.04	-0.05 [1]	-	-0.26 [0]	-0.11 [0.085]
Day 1st after surgery	1.40±0.05	0.21 [0.001]	0.26 [0]	-	0.15 [0.040]
Day 2nd after surgery	1.25±0.05	0.06 [1]	0.11 [0.08]	-0.15 [0.04]	-
Day 3rd after surgery	1.17±0.05	-0.01 [1]	-0.03 [1]	-0.022 [0.002]	-0.08 [0.36]

Table 2. Comparison of urine neutrophil gelatinase-associated lipocalin at various time points between patients with and without acute kidney injury after coronary artery bypass graft

Time points	Urinary NGAL (ng/mL)			*P* value
	Patients with AKI (Mean±SD)	Patients without AKI (Mean±SD)	Total (Mean±SD)	
Preoperative	382.5±11.7	391.3±40.5	386.6±81.9	0.812
2 hours postoperative	375.9±49.9	377.3±67.3	374.8±60.9	0.951
6 hours postoperative	365.9±84.9	356.9±84.8	360.6±83.3	0.789

NGAL, Neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury; SD, standard deviation.

Table 3. The association between elevated urinary NGAL at 2 and 6 hours after surgery and the incidence of acute kidney injury post coronary artery bypass graft

Elevated urinary NGAL	Patients with AKI No. (%)	Patients without AKI No. (%)	Total No. (%)	*P* value
2 hours postoperative	7 (53.8)	7 (43.8)	14 (43.8)	0.5
6 hours postoperative	5 (45.5)	5 (31.3)	10 (37)	0.4

Table 4. The mean alternations of urinary NGAL in patients with and without acute kidney injury at 2 and 6 hours post coronary artery bypass graft

Variations in urinary NGAL at different time points respective to baseline (preoperative)	Urinary NGAL (ng/mL)	
	Patients with AKI	Patients without AKI
2 hours postoperative	4.2±25.3	2.2±22.1
6 hours postoperative	2.8±34.9	-7.9±22.7

other unknown mediators may influence the diagnostic accuracy of this marker in AKI associated with cardiac surgery. In the present study, our sample size was 29 which is comparable with some other studies on the subject (16). We assessed the diagnostic predictability of urinary NGAL concentration in adults within the first six hours after cardiac surgery. In other studies, different periods of time have been investigated in patients with different age spectrums. For example; one study showed that urinary NGAL was significantly increased in pediatric patients with AKI within 15 hours after cardiac surgery. In a recent report, urinary NGAL also correlated with surgical variables and clinical outcomes. In addition, the normalization of urinary NGAL respective to serum creatinine improved the validity of NGAL for predicting the severity of AKI; however, the diagnostic validity of this marker remained unclear (18). It seems that this biomarker delivers superior diagnostic applicability in younger patients; however, this needs to be further investigated.

Sargentini et al declared that urinary NGAL was able to detect AKI earlier than serum creatinine in adults undergoing cardiac surgery; nevertheless, the sensitivity and specificity of this marker were not superior compared with other biomarkers (19). Wagener et al also noted that urinary NGAL level significantly correlated with the duration of cardiopulmonary bypass and aortic cross-clamp procedures; however, its prognostic value was limited in patients with AKI (20).

In the study by Wan et al, the incidence of AKI after cardiac surgery was reported as 27% (21). They found that the urinary level of NGAL and NGAL/creatinine ratio were strong and were the independent predictors of AKI at two hours post-cardiac surgery.

Our understanding regarding the role of urinary NGAL in the postoperative management of AKI is currently limited. Therefore, more studies are needed to ascertain the potential application of this marker in prevention and treatment of ischemia-reperfusion renal injury in this condition. Urinary NGAL has been able to effectively and independently predict the AKI after cardiopulmonary bypass.

Conclusion

Contrary to the previous studies, the present research showed no significant associations between urinary NGAL levels at neither two hours nor six hours of post-surgery and also the incidence of AKI. This finding suggested that urinary NGAL level is not an independent predictor of AKI post-CABG surgery. We, therefore, concluded that urinary NGAL level is an unreliable marker in predicting AKI post-CABG surgery.

Recommendations

It is suggested to interpret the urinary level of NGAL with respect to serum creatinine level. It is better to consider longer intervals to determine this parameter after surgery, and to incorporate patient's hydration and urine output to more precisely scrutinize the applicability of this biomarker in predicting AKI. In fact, hydration after cardiac surgery can dilute urine and reduce the urinary concentration of this biomarker. Furthermore, the ratio of urinary NGAL to either creatinine or total NGAL may be more reliable in this regard.

Limitations of the study

Our sample size was low, which limited the power of the study. We suggest investigating the urine NGAL levels in a large group of patients in future studies.

Acknowledgments

This study has been presented as a lecture at 15th International Congress of Nephrology, Dialysis and Transplantation, on Mashhad (2015).

Authors' contribution

AP and AB designed the study. AE consulted on the procedure. HC contributed in clinical study. KK performed statistical analysis, MH and AP, prepared the manuscript, since MH corresponded to the journal. All authors read and signed the final draft.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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