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Clinical paper

Plasma neutrophil gelatinase-associated lipocalin as an early predicting biomarker of acute kidney injury and clinical outcomes after recovery of spontaneous circulation in out-of-hospital cardiac arrest patients☆

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ABSTRACT

Aims: To determine whether the level of plasma neutrophil gelatinase-associated lipocalin (NGAL) can predict acute kidney injury (AKI) and clinical outcomes after recovery of spontaneous circulation (ROSC) in patients with out-of-hospital cardiac arrest (OHCA).
Methods: We conducted a prospective observational study of consecutive admitted patients with ROSC after OHCA between January 2013 and March 2015. Plasma was collected within 4 h of ROSC to determine the level of NGAL. Outcome variables were AKI, 30-day survival, and good neurological outcome (GNO). We evaluated the association between NGAL and outcomes.
Results: Fifty-four patients were included. AKI occurred in 26 (48.0%); 15 (27.7%) survived over 30 days and 8 had GNO (14.8%). NGAL was significantly lower in the group with non-AKI, 30-day survival, and GNO. To predict AKI, 30-day survival, and GNO, the area under the receiver operating characteristic curve for NGAL was 0.810, 0.728, and 0.875, respectively. In a logistic regression model, NGAL >189 ng ml^{-1} was strongly associated with AKI (odds ratio [OR] 7.01, 95% confidence interval [CI]: 1.89–26.01) in a multivariate model. A lower level of NGAL was strongly associated with 30-day survival (OR 6.12, 95% CI: 1.64–23.42 at NGAL <153.5 ng ml^{-1}) and GNO (OR 19.83, 95% CI: 2.21–178.32 at NGAL <129.5 ng ml^{-1}) in a univariate model, but was not significantly associated with outcomes in a multivariate model.
Conclusions: Plasma NGAL is a strong predictor of AKI in patients exhibiting OHCA at ICU admission. Lower levels of NGAL are associated with greater chance of 30-day survival and GNO.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major health problem because it is associated with high rates of mortality and disability. Despite considerable efforts to improve the treatment of cardiac arrest, most reported survival outcome figures are poor,[1] and 29.4% die from multiple organ failure after intensive care unit (ICU) admission.[2] Cardiac arrest causes general ischaemia/hypoxia, which can affect the kidneys. Renal dysfunction is common after OHCA and causes adverse effects and poor outcomes.[3] The serum creatinine concentration is an indicator of the glomerular filtration rate (GFR) and reduced kidney function.[4] Therefore, the serum creatinine concentration is used in many criteria to assess acute kidney injury (AKI), such as the Risk, Injury, Failure, Loss, and End-stage Kidney classification, Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[5,6] Serum creatinine concentration can vary widely with age, sex, muscle mass, muscle metabolism, medications and hydration status. However, the increase in serum creatinine concentration in

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response to kidney injury can be delayed by several days and may not occur until kidney function is already impaired.[7,8]

Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein that is stored in granules within mature neutrophils and is produced in the kidney after ischaemic or nephrotoxic injury.[9–12] NGAL is an early and specific marker of tubular damage and may predict a poor outcome of AKI.[13] Previous results suggested that plasma and urine NGAL concentrations represent predictive biomarkers of AKI in the ICU setting and may predict this complication about 2 days before the increase in serum creatinine concentration.[14] NGAL is emerging as a centre-stage player in the AKI field as a predictive biomarker in coronary artery disease (CAD), acute myocardial infarction (AMI), cardiac surgery, sepsis and major burn patients.[15–20] For patients with cardiac arrest, AKI is not typically a direct cause of death from multiple organ failure. However, the presence of AKI might be related to high mortality rates and poor outcomes in patients after cardiac arrest. For these patients, kidney damage may be influenced by primarily global ischaemia resulting from the lack of systemic flow during the arrest phase, and reperfusion injury and the systemic inflammatory reaction after recovery of spontaneous circulation.[21,22] We speculated that plasma NGAL may be a strong biomarker for early prediction of AKI in patients after cardiac arrest, and associated with patient survival and neurological outcomes. The first aim of the study was to determine whether plasma NGAL levels at admission are a reliable predictor of AKI in patients with OHCA admitted to the ICU after recovery of spontaneous circulation (ROSC). We also sought to evaluate the relationship between plasma NGAL and 30-day survival and neurological outcomes in patients after cardiac arrest.

Methods

Study design or patient selection

This prospective, observational study was performed in the emergency department and ICU of our medical centre (Anyang, Republic of Korea) between January 2013 and March 2015. The protocol of this study was approved by the Institutional Review Board of our hospital, and written informed consent was obtained from the closest relatives. The emergency centre is in a tertiary care hospital, and the annual emergency department (ED) volume was about 79,000 in 2014.

All consecutive patients aged 18 years or older with ROSC after OHCA who were admitted to the ICU were included in the study. The exclusion criteria were age <18 years, experiencing trauma, pregnant, pre-injury chronic renal failure requiring haemodialysis and no informed consent.

The following variables were recorded for each patient: age, sex, witnessed arrest, bystander cardiopulmonary resuscitation (CPR), initial identified ECG rhythm, collapse to ROSC time, therapeutic hypothermia, survival and neurological outcome at the time of 1 month later. Neurological outcome was defined using the Cerebral Performance Category Scale (CPC) as follows: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; and category 5, death.[1] CPC 1–2 was defined as good, and CPC 3–5 as poor.

Measurement of the concentrations of NGAL

Blood samples were collected when the patient was admitted to the ICU. Whole venous blood was collected in tubes containing the anticoagulant ethylene diamine tetra acetic acid. Plasma NGAL concentration was measured using a Triage NGAL Test Kit and the Triage Meter (Alere Inc., Waltham, MA). The lower limit of detection of plasma NGAL was 60 ng ml^{-1} and the upper limit of the assay range was 1300 ng ml^{-1}.

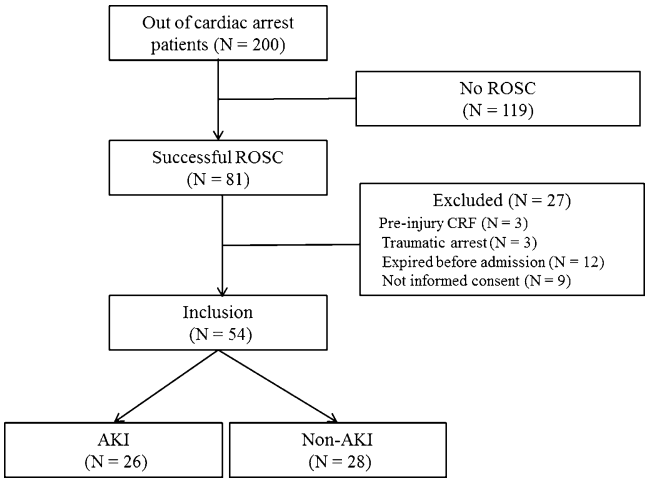

Fig. 1. Flow chart of the study.

AKI definition

AKI was defined according to the AKIN definition and KDIGO guidelines, based on the serum creatinine concentration or urine output.[6] Patients who met any of the criteria for the AKIN definition were classified as AKI patients (Table 1). The initial serum creatinine concentration measurement on ICU admission was used as the baseline value. The severity of AKI was staged according to the KDIGO guideline using the highest serum creatinine concentration recorded during the hospitalization period.

Sample size

A pilot study was performed before this study to determine the appropriate sample size. Five patients from each group were recruited and the mean and standard deviation (SD) of NGAL concentration were calculated. The mean NGAL concentration were 395 ng ml^{-1} (SD 360 ng ml^{-1}) in the AKI group and 170 ng ml^{-1} (SD 150 ng ml^{-1}) in the non-AKI group. We estimated that 26 patients would be needed to differentiate NGAL concentrations between the two groups at an alpha error of 5% (two-sided test) and a power of 80% in a prospective observational study design.

Assessment and data analysis

Outcome variables for the study analysis were presence of AKI, 30-day survival and good neurologic outcomes. The significance of differences between two groups was tested using an independent two-sample *t* test, Mann–Whitney *U* test, chi-square test of Fisher's exact test. Continuous variables were dichotomized according to cut-off points from the analysis of receiver-operating characteristic (ROC) curves before being incorporated into the logistic model. Univariate and multivariate logistic regression testing model were used to determine the factors associated with outcome variables. The adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were calculated to assess the relationship between covariates and outcomes. We used the SPSS statistical software package 18.0 (SPSS, Inc., Chicago, IL), MedCalc 15.2.2 (MedCalc Ltd., Mariakerke, Belgium) or SAS 9.1 (SAS Institute, Inc., Cary, NC) for the statistical analyses. A two sided *p*-value of <0.05 was considered significant.