JOURNAL OF SURGICAL RESEARCH 196 (2015) 382–387

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Whole blood neutrophil gelatinase–associated lipocalin predicts acute kidney injury in burn patients

Soman Sen, MD, FACS,[a,*] *Zack R. Godwin, BS,*[b] *Tina Palmieri, MD, FACS, FCCM,*[a] *David Greenhalgh, MD, FACS,*[a] *Amanda N. Steele, BS,*[b] *and Nam K. Tran, PhD, MS, FACB*[b]

[a] *Division of Burn Surgery, Department of Surgery, University of California Davis, Sacramento, California*
[b] *Department of Pathology, University of California Davis, Sacramento, California*

ARTICLE INFO

Article history:
Received 30 July 2014
Received in revised form
16 January 2015
Accepted 13 March 2015
Available online 20 March 2015

Keywords:
Acute renal injury
Burn injury
NGAL
Resuscitation

ABSTRACT

Background: Early detection of acute kidney injury (AKI) in severely burn-injured patients can help alter treatment to prevent progression to acute failure and reduce the need for renal replacement therapy. We hypothesized that whole blood neutrophil gelatinase–associated lipocalin (NGAL) will be increased in severely burn-injured patients who develop AKI during acute resuscitation.

Materials and methods: We performed a prospective observation study of adult burn patients with a 20% total body surface area (TBSA) burned or greater burn injury. Two-hour serial measurements of NGAL, serum creatinine (Cr), and hourly urine output (UO) were collected for 48 h after admission. Our primary goal was to correlate the risk of AKI in the first week after burn injury with serial NGAL levels in the first 48 h after admission. Our secondary goal was to determine if NGAL was an earlier independent predictor of AKI compared with Cr and UO.

Results: We enrolled 30 adult (age $\geq$ 18 y) burn patients with the mean $\pm$ standard deviation age of 40.9 $\pm$ 15.4 and mean TBSA of 46.4 $\pm$ 22.4. Fourteen patients developed AKI within the first 7 d after burn injury. There were no differences in age, TBSA, fluid administration, mean arterial pressure, UO, and Cr between AKI and no-AKI patients. NGAL was significantly increased as early as 4 h after injury (182.67 $\pm$ 83.3 *versus* 107.37 $\pm$ 46.15) in the AKI group. Controlling for age, TBSA, and inhalation injury, NGAL was a predictor of AKI at 4 h after injury (odds ratio, 1.02) and remained predictive of AKI for the period of more than the first 24 h after admission. UO and Cr were not predictive of AKI in the first 24 h after admission.

Conclusions: Whole blood NGAL is markedly increased in burn patients who develop AKI in the first week after injury. In addition, NGAL is an early independent predictor of AKI during acute resuscitation for severe burn injury. UO and Cr are not predictive of AKI during this time period.

* *Corresponding author*. Department of Surgery, University of California Davis, 2425 Stockton Boulevard, Suite 718, Sacramento, CA 95817. Tel./fax: +1 916 453 2050.
E-mail address: soman.sen@gmail.com (S. Sen).
0022-4804/$ – see front matter
http://dx.doi.org/10.1016/j.jss.2015.03.033

1. Introduction

Acute kidney injury (AKI) in critically ill burn patients is a morbid and often fatal complication. The prevalence of AKI in severely burn-injured patients is reported to be as high as 53% with a mortality rate >30% [1]. Current methods of evaluating renal function rely on serum creatinine (Cr) measurements and hourly urine output (UO). However, these measurements are often insensitive to rapid changes in renal function because of acute injury [2]. Serum Cr has a long half-life (3.85 h) and is subject to variations because of muscle mass, age, and gender, thus limiting its effectiveness as a sensitive marker of rapid changes in renal function [3]. Decreasing UO may reflect AKI because of reduced glomerular filtration; however, neurohormonal and functional changes influence diuresis and thus UO may be normal despite ongoing renal injury [4].

Neutrophil gelatinase–associated lipocalin (NGAL) is a molecule that is released by polymorphonuclear granulocytes during inflammation and is uniquely produced by endothelial cells of nephrons for urinary secretion and subsequent reabsorption into bloodstream [5]. Under normal conditions, low amounts of NGAL circulate in the bloodstream and are freely filtered by the glomerulus. Normal reference intervals have been suggested of 40–100 ng/mL [6]. During AKI, NGAL rapidly accumulates in the serum because of an increase in secretion by the nephrons and reduction in glomerular filtration rate [7]. This, coupled with a short half-life (10 min) makes whole blood NGAL a potential sensitive and early marker of AKI.

In adult critically ill medical patients, increased serum NGAL levels (155 nmol/L) showed high sensitivity and specificity for AKI. Moreover, NGAL was increased 48 h before significant changes in Cr and UO [8]. In addition, serum NGAL improves the accuracy of AKI predictions compared with Cr alone [9,10]. NGAL also may be a more sensitive predictor of risk for AKI compared with standard methods. A large pooled study of more than 1200 critically ill patients indicates that NGAL is able to detect patients with AKI before any changes in Cr occur [11]. Serum NGAL may also be a marker of renal recovery. A study of 181 patients showed that NGAL levels decreased in the plasma in patients who recovered from AKI [12].

In burn patients, NGAL is also an early marker for AKI. In a study of 45 adult burn-injured patients, NGAL was measured three times after admission (on admission, day 3, and day 7 after burn injury) and found that NGAL levels at days 3 and 7 were significantly higher in patients who developed AKI [13]. Of note, 27% of the patients in this study developed AKI in the second week after injury. In a study of 22 pediatric burn patients, both urine and serum NGAL levels were increased both on admission and on the fifth day after burn injury in patients with AKI. However, Cr was not different at either time point [14].

We hypothesized that after severe burn injury, an increased NGAL level within the first 12 h after injury would be associated with the development of AKI in the first week after burn injury. Our primary aim was to prospectively measure serial serum NGAL, serum Cr, and hourly UO during the first 48 h after burn injury and correlate these measurements to the development of RIFLE (risk, injury, failure, loss, end-stage)-based criteria for AKI in the first 7 d after injury [15]. Our secondary aim was to determine if NGAL was a more rapid and responsive marker of AKI compared with serum Cr and hourly UO.

2. Methods

A prospective observational study was conducted for adult burn-injured patients who were admitted to our regional burn center. Inclusion criteria included age 18 y or older, 20% or greater total body surface area (TBSA) second and third degree burn injury, and admission to our burn center within 2 h of burn injury. Patients were excluded from the study if they had a nonsurvivable burn injury or a history of preinjury renal disease. A nonsurvivable burn injury was determined at the time of admission by the attending burn surgeon and determination of preinjury renal disease was made through interrogation of the patient's past medical history. All patients were admitted to the burn intensive care unit and standard burn resuscitation protocol was started under the direction of the attending burn surgeon. The University of California Davis Institutional Review Board approved all protocols for the study.

After enrollment, serial whole blood NGAL and Cr measurements were collected every 2 h for the first 48 h after admission. NGAL and Cr were measured from 1.5 mL blood samples using the point of care Triage System (Alere, San Diego, CA) and The StatSensor Creatinine meter (Nova Biomedical, Waltham, MA). Both the Triage System NGAL and The StatSensor Creatinine results were calibrated to the central hospital clinical laboratory's UniCel DxC 800 Synchron chemistry analyzer (Beckman Coulter, Brea, CA) before the initiation of the study. In addition to serial measurements of Cr and NGAL, hourly heart rate, respiratory rate, mean arterial pressure, central venous pressure, fluid intake, and UO were recorded for 48 h. Research personnel recorded all point of care assays and results. The treating burn care team, including the physicians and nurses, was blinded to the results of the serial NGAL and Cr measurements. AKI was diagnosed based on renal RIFLE criteria [16]. Patients were considered as having AKI if they met the "Injury" level of the RIFLE criteria in the first 7 d after burn injury. Injury is defined as UO of 0.3 to <0.5 mL/kg/h for at least 12 h, a doubling of the serum Cr from baseline, or a decrease in glomerular filtration rate of >50% but <75%. Failure is defined as a serum Cr rise three times of baseline or a UO <0.3 mg/kg/h.

R statistical package (www.r-project.org) was used to analyze the data. Continuous variable comparisons between two groups were performed using the two-sample Student *t*-test for continuous data. Times series data (e.g., serial measurements) were analyzed using repeated measures analysis of variance. *Post hoc* analysis was performed using pairwise comparisons with a Bonferroni adjustment for significant repeated measures analysis of variance results. The Fisher's Exact test was used to assess association between discrete categorical variables. Multivariate logistic regression analysis was performed to determine associations between