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Plasma NGAL predicts early acute kidney injury no earlier than s-creatinine or cystatin C in severely burned patients

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ABSTRACT

Introduction: Neutrophil gelatinase-associated lipocalin (NGAL) is a novel biomarker used in acute kidney injury (AKI) diagnostics. Studies on burn patients have highlighted it as a promising biomarker for early detection of AKI. This study was designed to discover whether plasma NGAL is as a biomarker superior to serum creatinine and cystatin C in detecting AKI in severely burned patients.

Methods: Nineteen subjects were enrolled from March 2013 to September 2014 in the Helsinki Burn Centre. Serum creatinine, cystatin C, and plasma NGAL were collected from the patients at admission and every 12 h during the first 48 h and thereafter daily until seven days following admission. AKI was defined by acute kidney injury network criteria.

Results: Nine (47%) developed AKI during their intensive care unit stay and two (11%) underwent renal replacement therapy. All biomarkers were significantly higher in the AKI group but serum creatinine- and cystatin C values reacted more rapidly to changes in kidney function than did plasma NGAL. Plasma NGAL tended to rise on average 72 h ± 29 h (95% CI) later in patients with early AKI than did serum creatinine. Area-under-the-curve values calculated for each biomarker were 0.92 for serum creatinine, 0.87 for cystatin C, and 0.62 for plasma NGAL predicting AKI by the receiver-operating-characteristic method.

Conclusion: This study demonstrated serum creatinine and cystatin C as faster and more reliable biomarkers than plasma NGAL in detecting early AKI within one week of injury in patients with severe burns.

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1. Introduction

Acute kidney injury (AKI) is common in severely burned patients and is associated with high mortality. Risk factors for AKI are high total burned surface area (%TBSA), use of nephrotoxic drugs, sepsis, and prolonged need for ventilation [1].

Serum creatinine (SCr) and urine output are the main means to diagnose AKI. More than 50% of renal function must be lost before elevated SCr levels in blood are detectable and levels depend on age, gender body mass, and ethnicity [2].

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Another test sometimes used in AKI diagnosis, involves cystatin C (CysC), a 13 kD protease inhibitor located in nucleated cells; that is freely filtered through human glomeruli, but it is not actively secreted into urine. Impairment of glomerular filtration rate (GFR) leads to its increased levels in plasma. Normal plasma concentrations neither depend on age, gender or muscle mass, and CysC may be a better indicator for kidney function than is SCr in patients with severe burns [3–5].

Of the other biomarkers studied so far, none has gained widespread use in AKI diagnostics [6].

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein bound to gelatinase from neutrophils. It is, in normal conditions, expressed in the human epithelia of kidney, stomach, colon, trachea, and lungs. Concentrations rise in inflammatory processes and after epithelial injury. Elevated concentrations of NGAL are detectable in patients with rheumatoid arthritis, chronic obstructive pulmonary disease, or severe peritonitis [7]. Professional swimmers constantly exposed to chlorinated water may also show high NGAL levels [8].

NGAL has been considered as an excellent biomarker predicting AKI after cardio-pulmonary bypass in children [9]. It can be rapidly measured from plasma or urine by using enzyme-linked immunosorbent assay (ELISA). The role of NGAL in burn related injuries has so far not been clearly defined and the purpose of this study was to evaluate whether plasma NGAL (p-NGAL) is superior in detecting AKI at an earlier phase than is CysC or SCr in severely burned patients.

2. Materials and methods

We enrolled 19 consecutive patients at Helsinki Burn Centre between March 2013 and September 2014, all with a %TBSA of at least 20%—or for those aged over 60, a lower 15%TBSA. Grading of AKI was based on acute kidney injury network (AKIN) criteria [10] (See Table 1). AKI was diagnosed when grade I AKIN criteria were fulfilled. Since SCr is one of the AKIN criteria it sets limitation to the interpretation of the results.

The following parameters were included: Age, gender body mass index (BMI), %TBSA, burn mechanism, need for intubation or ventilation, escharotomies, abbreviated burn severity index (ABSI) [11], sequential organ failure assessment score (SOFA) [12], co-morbidities, need for renal replacement therapy (RRT), duration of intensive care, and outcome. Measurements of SCr, CysC, and p-NGAL values continued from the week after arrival at 12-h intervals during the first 48 h and thereafter daily at 6–8 a.m. Measurements of SCr and urine output (UOP) continued through out the intensive care to detect AKI at any time point. SCr at arrival set the baseline for AKIN criteria determination.

SCr and CysC were analyzed by hospital laboratory services and p-NGAL by Triage®, a point-of-care device (Alere Inc., Waltham, MA, USA). It detects p-NGAL values between 15 and 1300 ng/ml by an ELISA-based immunoassay. Quality control was run for each set of test kits by the manufacturer's orders. Cut-off points were chosen 100 μmol/l (1.14 mg/dl) for SCr, 1.4 mg/l for CysC, and 400 ng/ml for p-NGAL, all generally accepted values indicating AKI.

Table 1 – AKIN classification of acute kidney injury (10).

Stage	Creatinine criteria	Urine output criteria
AKIN 1	Increase in serum creatinine at least 0.3 mg/dl (26.4 μmol/l) or increase at least to 150–200% (1.5- to 2-fold) from baseline.	Less than 0.5 ml/kg per hour for more than 6 h.
AKIN 2	Increase in serum creatinine more than 200–300% (2- to 3-fold) from baseline.	Less than 0.5 ml/kg per hour for more than 12 h.
AKIN 3	Increase in serum creatinine more than 300% (>3-fold) from baseline or serum creatinine at least 4.0 mg/dl (354 μmol/l) with an acute increase at least 0.5 mg/dl. (44 μmol/l).	Less than 0.3 ml/kg per hour for more than 24 h or anuria for 12 h or need for RRT.

AKIN, acute kidney injury network; RRT, renal replacement therapy.

Patients were resuscitated by our standard fluid protocol (Parkland formula, no colloids during the first 8 h, urine output target 0.5 ml/kg h). When necessary, vasoactive agents maintained adequate hemodynamics. Statistical analysis was run by IBM SPSS Statistics for Macintosh, Version 22.0 (Armonk, NY, USA, IBM Corp.). Student's *t*-test and chi-square test analysis were performed between groups when appropriate. Area under the curve (AUC) was defined for each biomarker by the receiver operating characteristics (ROC) method.

The Research Ethics Board at our institution approved the study protocol and informed consent was obtained from all subjects.

3. Results

The treatment in the ICU began on average 3.6 h (1.5–8 h) after burn injury. Nine patients (47%) developed AKI during their intensive care. Eight patients (42%) developed early AKI during the seven days' study time, all within five days after burn. Five patients were diagnosed by Scr criterion, three by UOP criterion and one patient fulfilled both criteria. SCr and UOP were recorded also after the study time and one patient (5%) developed late AKI on the 14th day after burn. Two patients (11%) underwent RRT with subsequent recovery of renal function. Two patients (11%) succumbed during their intensive care unit (ICU) stay within 48 h after admission.

Patients with AKI had longer ICU stay time, higher BMI, greater number of co-morbidities, higher %TBSA, and higher ABSI and SOFA score during ICU stay but only BMI ($p = 0.011$), SOFA-score on admission ($p = 0.015$), and highest SOFA score ($p = 0.018$) were statistically significant in predicting AKI. Demographic data is presented in Table 2.

Patients who developed AKI had on days four and five significantly higher ($p < 0.05$) p-NGAL values than did the

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