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The effect of early renal replacement therapy guided by plasma neutrophil gelatinase associated lipocalin on outcome of acute kidney injury: A feasibility study

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ABSTRACT

Purpose: The optimal time and the parameter utilized for decision to initiate renal replacement therapy (RRT) in acute kidney injury (AKI) are still controversial. Recently, high levels of plasma NGAL (pNGAL) has been strongly correlated with poor AKI outcome. This is a feasibility study conducted to test whether early RRT initiation guided by pNGAL could improve AKI outcome.
Material and methods: The study comprised of triage trial and interventional trial running subsequently. As a guide for triage to RRT, we measured pNGAL at the enrollment time. Forty patients with pNGAL ≥ 400 ng/mL (high pNGAL group) were randomized to 'early' or 'standard' group. Patients with pNGAL < 400 ng/mL (n = 20) were defined as low pNGAL group.
Results: The triggering pNGAL selected AKI patients with more severity of illness and worse clinical outcome. However, in high pNGAL group, early RRT did not result in different 28-day mortality from the standard group. The median numbers of day free from mechanical ventilation were significantly higher in the early RRT group.
Conclusions: Our finding suggested that it was feasible to use pNGAL to triage severe AKI patients. However, early initiation of RRT in this high risk group did not affect the 28-day mortality.

1. Introduction

Acute kidney injury (AKI) is an independent risk factor for increased mortality in critically ill patients [1,2]. In severe AKI, renal replacement therapy (RRT) could confer benefits by removal of uremic and putative toxins, achieving volume and solute control, correcting electrolyte imbalances, and may help remove cytokines and provide nutritional supplements. It is still unestablished regarding the optimal time, early versus standard, and the reliable parameter for decision to initiate RRT in severe AKI.

As mentioned earlier that early RRT initiation could provide a number of benefits. On the contrary, initiating early RRT in every AKI patients would recruit several patients who may recover spontaneously. Moreover, RRT is not the benign procedure. There are certain risks for catheter insertions associated complications (e.g. hemorrhage, thrombosis, bacteremia, arterial puncture) and RRT related complications (e.g. hypotension, arrhythmia, electrolyte disturbances). A few randomized controlled trials have explored the optimal time of RRT initiation but yield inconclusive results [3-5]. Recent systematic reviews and meta-analysis of retrospective and observational studies have found a statistically significant reduction in mortality with early RRT with a relative risk of 0.72 [6-8]. However, the study designs were heterogeneous with different AKI definitions and RRT initiation criteria.

Blood urea nitrogen, serum creatinine, timing from AKI diagnosis, and timing since ICU admission have been proposed as the parameters for RRT initiation [9-11]. Indeed the values of these parameters used to decide initiation of RRT are subjective, resulting in inconclusive outcome of severe AKI in previous studies. Recently, plasma neutrophil gelatinase associated lipocalin (pNGAL), one of the novel AKI biomarkers, has been shown to be a reliable marker of AKI non-recovery in the setting of severe AKI [12]. pNGAL at the cut point of 400 ng/mL

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had the sensitivity of 0.47 and specificity of 0.90 for predicting AKI non-recovery.

The present study is the first feasibility study to test the role of pNGAL in triage severe AKI patients and subsequently explore whether early RRT initiation in AKI patients with pNGAL level of ≥400 ng/mL would improve AKI outcome as compared to standard RRT initiation.

2. Materials and methods

2.1. Study design

This feasibility study comprised a triage trial and intervention trial conducted subsequently at both medical and surgical ICUs at King Chulalongkorn Memorial Hospital, Bangkok, Thailand from November 2012 to November 2014. The intervention trial was a prospective randomized control trial (RCT) which recruited only patients who had pNGAL level of ≥400 ng/mL. From previous study, pNGAL at 400 ng/mL demonstrated the sensitivity and specificity of 0.47 and 0.90 in predicting renal non-recovery [12]. RRT is not a benign procedure; therefore, we selected the cut-off point which showed the high specificity.

This study was approved by the Medical Review Board, Faculty of Medicine, Chulalongkorn University, IRB No. 406/55 and registered on ClinicalTrials.gov (Identifier No. NCT01819038).

2.2. Participants

The inclusion criteria consisted of patients aged of 18 years or older diagnosed with AKI by RIFLE criteria [13]. The exclusion criteria was life expectancy < 24 h, end stage renal disease (ESRD), baseline serum creatinine > 2 mg/dL in male or >1.5 mg/dL in female, previous kidney transplantation, and pregnancy. All patients with AKI who met the inclusion criteria were recruited to participate in the trial. All participants provided written informed consent.

2.3. Randomization

Firstly, the blood samples were drawn from patients who met the initial eligibility criteria to measure pNGAL concentrations with a cut-off value at 400 ng/mL. Patients with pNGAL ≥ 400 ng/mL, representing high pNGAL group, were enrolled by blocked randomization with sequentially numbered containers into two groups, early or standard RRT initiation. We used computer software to generate the random allocation sequence and assign participants to study groups. In the early group, RRT was started within 12 h of randomization. Indications for standard RRT included refractory severe acidosis (pH < 7.2 or HCO_3 < 15 mEq/L), severe peripheral edema, pulmonary edema, no response to diuretics, refractory hyperkalemia (K > 6.2 mEq/L or the presence of electrocardiogram change: tall T wave, absent P wave, or wide QRS wave), anuria or oliguria, or high BUN level > 60 mg/dL. Patients with pNGAL < 400 ng/mL who did not triage to interventional trial.

2.4. Intervention trial

Patients received standard AKI care according to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for management of AKI [14]. Continuous RRT (CRRT) was chosen as the mode of RRT. A session of CRRT was run within 12 h after group assignment for early RRT group, whereas standard group patients started CRRT in the presence of any of the previously mentioned indications. The indication to stop RRT was followed by previous study [15]. A CRRT session comprised of continuous venovenous hemofiltration (CVVH) modality with a dose of 25 mL/kg/h. The blood flow rate was set at 150–200 mL/min. We used the AN69 membrane dialyzers (M100 Prismaflex set) during CRRT without using any anticoagulants.

We collected blood chemistry and measured urine output, ventilator use, dialysis, mortality on day 28 after randomization, treatment complications in consecutive time points including the initiation of CRRT session on daily basis in the 1st week and then a weekly basis after the 2nd week until 28 days after randomization. pNGAL was measured by quantitative NGAL measurement kit (Alere, San Diego, CA), a point-of-care, fluorescence immunoassay, expressed in ng/mL. Duration from presentation to the hospital and admission to ICU was recorded as well as time of AKI diagnosis and start of RRT.

2.5. Outcomes

The primary outcomes were death upon day 28 after enrollment. The secondary outcomes on day 28 were ventilator-free day, ICU-free day, proportion of dialysis-dependent patients, and balance of input and output fluid along those periods. The renal recovery status was defined as dialysis independent and survival on day 28.The adverse events (RRT-related complications) were monitored and recorded during and post RRT sessions.

2.6. Statistical analysis

Previous study demonstrated a mortality difference between early RRT and late RRT of 20% (early vs late RRT, 62% vs 82%) [11]. Therefore, we calculated the sample size of 262 patients and decided to conduct the pilot study of 40 patients. The baseline characteristics were compared by mean or median, standard deviation (SD), and interquartile range (IQR), IQR 1 and 3. Student's *t*-test was analysed for comparison of means, and Kaplan Meier survival analysis. *P* value < 0.05 was considered to be significant. SAS program 9.4 (Cary, NC) was used for the statistical analysis. All data were recorded in electronic format organized by BIOPHICS, Faculty of Tropical Medicine, Mahidol University.

3. Results

3.1. Baseline characteristics in triage trial

As shown in Fig. 1, 70 patients with AKI in the ICU were screened. Of these, 10 patients were excluded, some declined to sign the informed consent form ($n = 7$) and 3 died. Twenty patients had pNGAL < 400 ng/mL (defined as low pNGAL group). Of 40 remaining patients with pNGAL concentration ≥ 400 ng/mL (defined as high pNGAL group) were equally randomized into early RRT ($n = 20$) and standard RRT ($n = 20$) groups. All patients in the early RRT group received CRRT while 8 patients (40%) in the standard RRT group required CRRT. Interestingly, none of the low pNGAL group received RRT.

3.2. Risk stratification efficacy of pNGAL and AKI outcome in triage trial

We stratified participants based on pNGAL level. Patients with high pNGAL (≥400 ng/mL) had significantly higher severity scores (APACHE II and SOFA score) than low pNGAL group (pNGAL < 400 ng/mL), $p < 0.001$, both (Table 1). No patient in the low pNGAL group met the RRT initiation indication. In addition, the clinical outcomes including 28-day mortality, dialysis dependence rate, ventilator-free day, ICU-free day, and renal recovery status in high pNGAL group were significantly higher than the low pNGAL group: 47.5% vs 15%, $p = 0.022$; 33.3% vs 0%, $p = 0.011$; 18 vs 27 days, $p = 0.002$; 18 vs 26 days, $p < 0.001$; 35% vs 85%, $p < 0.001$, respectively (Table 2).

3.3. Baseline characteristics in intervention trial

The demographic data of early RRT group and standard RRT group was compared and analysed as shown in Supplement Table 1. Baseline characteristics including inotropic agents/vasopressors, causes of AKI,