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Renal failure as a risk factor for venous thromboembolism in critically Ill patients: A cohort study

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ABSTRACT

Rationale: The relationship between kidney function and venous thromboembolism (VTE) in critically ill patients is not well studied. The main objective of this study was to evaluate this relationship in patients admitted to a medical-surgical intensive care unit (ICU).
Methods: This was a retrospective study of 798 patients admitted to a tertiary-care ICU and prospectively followed for the development of clinically suspected and radiologically diagnosed deep venous thrombosis or pulmonary embolism. Patients were divided based on admission creatinine and dialysis history into five groups: normal kidney function, RIFLE classes R, I and F (combined = acute kidney injury [AKI]) and endstage renal disease (ESRD). We compared VTE prophylaxis practices and VTE incidence in these groups and evaluated renal failure as a VTE risk factor using multivariate Cox regression analysis.
Results: Of the 798 patients, 27.2% had AKI and 10.1% had ESRD. Unfractionated heparin use was similar in the five groups but enoxaparin use was less frequent in AKI (13.4%) and ESRD (3.8%) patients compared with patients with normal kidney function (39.0%). VTE occurred in 7.6% of patients with normal renal function, 7.8% AKI patients and 2.5% ESRD patients ($p = 0.22$). The adjusted hazard ratios for VTE compared to patients with normal kidney function were 0.35 (95% confidence interval [CI], 0.08-1.47) for RIFLE class R, 1.19 (95% CI, 0.83-1.70) for RIFLE class I, 0.82 (95% CI, 0.59-1.14) for RIFLE class F and 0.71 (95% CI, 0.49-1.02, $p = 0.06$) for ESRD.
Conclusions: Neither AKI nor ESRD was an independent risk factors for critically ill patients.

Introduction

Critically ill patients are at increased risk for venous thromboembolism (VTE) [1,2] during their stay in the intensive care unit (ICU). Additionally, many of them either have chronic kidney disease (CKD) or develop acute kidney injury (AKI) [3]. Studies that evaluated the relationship between the kidney function and VTE are scarce. A community-based population study of non-dialysis-dependent patients found that after adjustment for age, gender, race and center, the relative risk for VTE was 1.28 (95% confidence interval [CI], 1.02-1.59) for those with mildly decreased kidney function and 2.09 (95% CI, 1.47-2.96) for those with stage 3/4 CKD, compared with people with normal kidney function [4]. A large 1996 US cohort study found that end-stage kidney disease (ESRD) was associated with 2.1 increased risk of pulmonary embolism (PE) compared to the general population [5]. Whether kidney function is a risk factor for VTE in critically ill patient is not well studied. A prospective cohort study evaluated the incidence of proximal lower extremity deep venous thrombosis (DVT) in 261 critically ill patients using periodic ultrasonographic screening and found that ESRD, but not AKI, was associated with increased DVT risk (hazard ratio [HR], 3.7; 95% CI,1.2-11.1) [2]. PE was not evaluated in this study [2].

Because of the paucity of evidence, we evaluated the relationship between VTE and both AKI and ESRD using data from a prospective cohort of medical and surgical ICU patients followed for the development of VTE. Additionally, we reported the incidence of VTE and described VTE prophylaxis practices according to kidney function on ICU admission.

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Materials and Methods

Patients and Setting

This was a post-hoc analysis of data from a prospective observational cohort study performed to determine the incidence, predictors and outcomes of VTE in critically ill patients [6]. The cohort was comprised of 798 consecutive adult patients (age ≥ 18 years) admitted to the ICU of King Abdulaziz Medical City between July 2006 and January 2008 and expected to stay in the ICU for more than 48 hours. The ICU was a closed medical and surgical ICU staffed by board-certified critical care physicians 24 hours per day, 7 days per week. The hospital was a 900-bed tertiary-care academic center in Riyadh, Saudi Arabia, had been accredited by Joint Commission International and had its own thromboprophylaxis guidelines. These patients were followed for the development of VTE (both DVT and PE) during ICU stay and up to 5 days after ICU discharge to the wards. DVT was diagnosed by Doppler compression ultrasound of extremities and PE by spiral computerized tomography of the chest or lung ventilation-perfusion scans. These tests were ordered at the discretion of the treating intensivist when VTE was clinically suspected. Patients were excluded if they had any of the following: Do-Not-Resuscitate order or brain death within 24 hours of admission, chronic anticoagulation with warfarin or heparin, admission to the ICU with acute PE or DVT diagnosed on admission or within first 24 hours of ICU admission. The original study was approved by the Institutional Review Board of King Abdulaziz Medical City-Riyadh.

Data Collection

The following baseline information were noted: patients' demographics including age, gender, body mass index, Acute Physiology and Chronic Health Evaluation (APACHE) II [7], admitting diagnostic category (respiratory, cardiovascular, neurological, other medical illness, trauma and postoperative), admission Glasgow Coma Scale (GCS) score, admission creatinine, bilirubin, lactate, platelet count and International Normalized Ratio (INR) and pre-defined VTE risk factors. In addition, the following data were collected on a daily basis for a period of 30 days or until ICU discharge to the wards or mortality, whichever earlier: use of pharmacologic thromboprophylaxis (unfractionated heparin or low molecular weight heparin [enoxaparin]), the use of mechanical thromboprophylaxis (graduated compression stockings and intermittent pneumatic compression device), number and location of central lines, and requirement for mechanical ventilation and renal replacement therapy. The primary outcome of this study was the incidence of VTE among critically ill patients according to kidney function. The secondary outcomes were VTE prophylaxis practices, ICU and hospital mortality, ICU and hospital length of stay (LOS), and duration of mechanical ventilation.

Categorization of Patients According to Renal Function

For the purpose of this study, patients who had chronic renal failure requiring dialysis before ICU admission were classified as ESRD. The other patients were divided into four groups according to the RIFLE classification of kidney function. For this classification, baseline creatinine was estimated using back-calculation with the Modification of Diet in Renal Disease (MDRD) formula as per the following equation [8]: estimated baseline creatinine = $(GFR/[186 \times age^{-0.203} \times Sex \times Race])^{-0.867}$ (mg/dL), where the glomerular filtration rate (GFR) is the baseline GFR assumed to be 75 ml/min [9]; Sex = 1 if male and 0.742 if female; Race = 1.21 if black, otherwise Race = 1; and Age is in years. Patients were classified as having normal kidney function if admission creatinine was ≤1.5x estimated baseline creatinine. The other patients had AKI and were divided into RIFLE class R (Risk) if admission creatinine was >1.5x estimated creatinine but <2x, class I (Injury) if admission creatinine was ≥2x estimated baseline creatinine but <3x and class F (Failure) if admission creatinine ≥3x estimated baseline creatinine [9,10].

Statistical Analysis

Statistical analysis was performed using the Statistical Analysis Software (SAS, Release 8, SAS Institute Inc., Cary, NC, 1999, USA). Baseline characteristics and clinically relevant interventions of patients, as well as outcomes, in the five groups were summarized by providing the numbers and percentages for categorical variables and mean and standard deviation for continuous variables. The Chi-square test was used to assess differences among groups for categorical variables and ANOVA test for continuous variables. To evaluate if kidney function was a risk factor for VTE, proportional Cox regression analysis was performed with patients with normal renal function on ICU admission being the reference group. Baseline demographic and clinical characteristics that were significantly different among the patients with the different kidney function groups, VTE risk factors and thromboprophylaxis practices were entered in the model. These variables were age, gender, body mass index, admission APACHE II score, admission diagnostic categories, platelets count, INR, mechanical ventilation, bedridden status before admission, admission related to femur/hip fracture or surgery, presence and location of central venous catheter, use of oral contraceptives, history of venous insufficiency, presence of sepsis on admission, spinal cord injury, history of malignancy, history of congestive heart failure, history of recent surgery, history of previous PE or DVT, previous stroke, use of mechanical prophylaxis, use of unfractionated heparin and low molecular weight heparin for thromboprophylaxis. The results are presented as adjusted HRs with 95% CI. P-values < 0.05 were considered significant for all analyses.

Results

Baseline Characteristics and VTE Risk Factors

Of the 798 patients in the cohort, 37.3% had abnormal renal function on ICU admission, with 217 (27.2%) patients having AKI (8.0% RIFLE class R, 9.2% RIFLE class I and 10.0% RIFLE class F) and 10.1% having ESRD. Table 1 describes the characteristics of patients according to RIFLE classification. Patients with renal failure were older and had higher APACHE II score. Patients with renal failure were more likely to be admitted because of cardiovascular disease and sepsis and were less likely to be admitted postoperatively. Most patients required mechanical ventilation with no significant difference among the different groups. Renal replacement therapy was required during ICU stay for 4.0% of patients who had normal kidney function on admission, compared with 41.5% of with AKI patients (RIFLE classes R, I and F). Additionally, there were significant imbalances in other VTE risk factors among the three patient groups as described in Table 1.

Practices of VTE Prophylaxis

Table 2 describes thromboprophylaxis practices according to kidney function on ICU admission. The use of unfractionated heparin was similar in the five groups. Patients with renal failure received enoxaparin less frequently (13.4% of AKI patients and 3.8% of ESRD patients) compared with patients with normal kidney function (39.0%). Recent surgery, intracranial hemorrhage and other bleeding risks were the most common reasons cited for not administering pharmacologic prophylaxis. Graduated compression stockings were applied for similar proportions of patients in the different kidney function groups. However, there were more differences in the rate of application of intermittent pneumatic compression devices. Moreover, the percentage of patients