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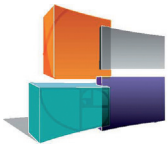

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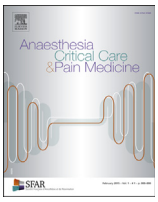

Original Article

A combined approach for the early recognition of acute kidney injury after adult cardiac surgery

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ABSTRACT

Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a frequent complication. The current criteria to detect CSA-AKI rise only when organic dysfunction has occurred. The Doppler Renal Resistive Index (RRI) and the urinary G1 cell cycle arrest proteins (TIMP-2 and IGFBP7) have been advocated to predict CSA-AKI at an early stage after cardiac surgery. The primary objective was to determine the predictive value of these new markers to detect CSA-AKI after elective heart surgery in patients at risk to develop AKI.

Methods: In a prospective observational trial, we studied 50 patients scheduled for elective on-pump heart surgery at high risk for CSA-AKI. The primary outcome was the incidence of AKI according to the KDIGO criteria recording the urine output every hour until ICU discharge and measuring the serum creatinine levels on each postoperative day until the post-procedure peak values were reached or until the 7th postoperative day. The RRI and the urinary proteins [TIMP-2]*[IGFBP7] were measured concomitantly: before surgery, 1 hour (H1), 4-hour (H4), 12-hour (H12), and 24-hour (H24) after surgery.

Results: Thirty-seven patients (74%) developed CSA-AKI. Urinary [TIMP-2]*[IGFBP7] at H12 were significantly higher in patients that developed AKI (0.62, [interquartile] [0.20–1.18] vs. 0.30 [0.07–0.47] $P = 0.044$) with an area under the receiver-operating characteristic curve of 0.69 [0.53–0.84]. The best sensitivity (65%) and specificity (62%) was achieved for a cutoff value of 0.3 $(ng.mL^{-1})^2.1000^{-1}$. The H12 time-point was the only in which the RRI values measured showed a trend toward statistical significance in patients that developed AKI (0.72 (Standard deviation) ± (0.06) vs. 0.68 ± (0.07) $P = 0.065$). The combination of the two markers ([TIMP-2]*[IGFBP7] + RRI) at H12 showed an increased performance of the accuracy with an area under the receiver-operating characteristic curve of 0.78 [0.62–0.93].

Conclusions: In a population at risk of developing CSA-AKI, neither the RRI nor urinary [TIMP-2]*[IGFBP7] detect CSA-AKI occurring in the first post-operative week within the first 24 postoperative hours.

1. Introduction

Deaths attributable to cardiovascular disease are declining, but from 2000 to 2010 the total number of inpatient scheduled for cardiovascular procedures increased by 28% [1]. More importantly, up to 50% of patients scheduled to undergo cardiac surgery with cardiopulmonary bypass (CPB) are prone to develop acute kidney injury [2]. Patients with Cardiac Surgery-Associated Acute Kidney Injury (CSA-AKI) requiring Renal Replacement Therapy (RRT) have a mortality rate that can reach up to 60% [3]. The incidence of CSA-AKI is constantly increasing along with the morbidity and the death related [4]. This complication is becoming a substantial burden for the society because CSA-AKI is responsible for longer patients hospital stay, as well as, long-term consequences such as chronic kidney disease [5], increased mortality [6] and considerable high costs related [7]. Therefore, CSA-AKI is a complication of paramount importance and early diagnosis to guide strategies to preserve renal function is critical. Current guidelines recommend the use of Kidney Disease Improving Global Outcomes (KDIGO)

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criteria for the diagnosis of AKI which are based on persistent low urinary output and serum creatinine (sCr) rise [8]. Urinary output is a poor marker of renal injury because it is influenced by dehydration, hypovolaemia and anti-diuretic hormone release [9]. An sCr increment is not renal specific and rises only 48–72 hours after the injury [10] when at least 50% of the functioning renal reserve is damaged [11]. Therefore, these conventional criteria are neither specific nor precise enough and most importantly appear only after advanced renal lesions. On the other hand, there is a flourishing body of evidence showing that new biomarkers allow early kidney injury recognition [12]. Regrettably, these new biomarkers seem to have flaws to detect CSA-AKI at an early stage [13]. Consequently, newer early acute kidney injury (AKI) markers have been proposed to diagnose CSA-AKI. Such markers are the Doppler-based Renal Resistivity Index (RRI) [14] and a specific urine test measuring the concentration of two urinary G1 cell cycle arrest proteins, the insulin-like growth factor-binding protein 7 (IGFBP7) and the tissue inhibitor of metalloproteinases-2 (TIMP-2) [2].

The aim of this prospective observational single-centre study conducted in adult cardiac surgery patients was to assess the predictive value of the RRI and the urinary G1 cell cycle arrest proteins as early markers of CSA-AKI. The hypothesis of the present trial was that these new markers could predict CSA-AKI earlier than the KDIGO criteria in patients at high risk of AKI undergoing on-pump heart surgery.

2. Methods

2.1. Participants

After obtaining the Bordeaux University Hospital Centre ethics committee's approval (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France, Ethical Committee No. DC2014/90) on August 27th 2014, we studied 50 patients scheduled for elective on-pump heart surgery at high risk for CSA-AKI from September 2014 to November 2014. Agreement from the 'Commission Nationale de l'Informatique et des Libertés' was also obtained before starting the study (registration number 1791831v0). The trial was registered on clinicaltrials.gov (NCT02325726). The Research Ethics Board waived the requirement for written informed consent from the study participants because renal ultrasonography data and urine specimen collection are non-invasive and were collected according to the standard of care of our institution [15,16]. Nevertheless, patients planned to be included in the trial were informed orally and could decline to participate at any time. Patients were enrolled in the study if they presented at least two of the following risk factors previously described to increase the risk of CSA-AKI [14]: patients older than 60 years of age, severe lower limb arteriopathy, carotid stenosis superior than 50%, diabetes, valvular or combined surgery [14]. Exclusion criteria were as follow: patients with dementia, patients who underwent a previous sternotomy, off-pump cardiac surgery, patients presenting with endocarditis, chronic renal disease (defined as a GFR < 90 mL.min.$^{-1}$1.73 m^{-2}), renal artery stenosis, pregnant women, emergent surgery. In addition, to avoid misinterpretation of the RRI values patients with a non-sinus cardiac rhythm and/or patients presenting renal artery stenosis were not included in the present trial.

2.2. Perioperative patients' care

In the operating room, patients were monitored with a two-channel EKG, a pulse oximeter, an arterial line, a bispectral index monitor to reach and maintain values within 40 and 60. A total intravenous anaesthesia was administered using target-controlled infusion with either sufentanil or remifentanil and propofol. Endotracheal tube insertion was facilitated injecting cisatracurium 0.2 mg.kg^{-1}. After intubation, mechanical ventilation was ensured before and after CPB to maintain normocapnia with fractional inspired oxygen of 60%. A central line in the right internal jugular vein, a Foley catheter with a temperature sensor, as well as, a transesophageal echocardiography probe were inserted before the surgical incision. Twenty minutes before skin incision, cefuroxime 1.5 g and a bolus of 20 mg.kg^{-1} followed by a continuous infusion of 2 mg.kg^{-1}.h^{-1} of tranexamic acid until skin closure were administered. Before starting non-pulsatile CPB, 300 IU.kg^{-1} of unfractioned heparin were injected to attain an activated coagulation time ≥ 400 s. Initiation of CPB was facilitated using a circuit primed with 800 to 1200 mL of PlasmaLyte solution depending on the body surface area of the patients. The flow rate was set around 2.4 l.min^{-1}.m^{-2} and mean arterial blood pressure was kept above 60 mmHg using norepinephrine if necessary. After CPB flow rate stabilization, lungs were ventilated at 10 cycles per minute with a tidal volume of 3 mL.kg^{-1} with 5 cm H_2O of PEEP with a fraction of inspired oxygen of 40% throughout the entire heart-lung assistance. During CPB a normothermic strategy was planned, tolerating a body temperature not lower than 35 °C. Before separation from CPB, patients were re-warmed to 36.5 °C and heparin was fully reversed with protamine. Intraoperatively, the haemodynamic assessment was performed using transesophageal echocardiography. Haemodynamic stability was achieved with fluid loading and/or with a continuous infusion of norepinephrine to maintain a mean arterial pressure > 65 mmHg. If a low cardiac output, defined as a cardiac index lower than 2.0 l.min^{-1}.m^{-2}, was found dobutamine was initiated at doses ranging from 2.5 to 10 μg.kg^{-1}.min^{-1}. During patients' ICU stay, hypovolaemia was excluded by systematic cardiac function and volume status assessment determined either transesophageal or transthoracic echocardiography or a Swan-Ganz catheter. The latter was inserted in patients with a left ventricle ejection fraction below 40%. Diuretics were administrated based on the presence of oliguria associated with a status of volume overload. Discontinuation of catecholamine infusion occurred in ICU and was left to the attending intensivist's discretion. In a transfusion standpoint, the strategy consisted in preserving a haematocrit above 22% during CPB and a haematocrit $> 25\%$ during patients' ICU stay. Decisions for ICU and hospital discharge were left to the attending intensivist and the attending surgeon, respectively.

2.3. Data collection

The following data were collected preoperatively: anthropomorphic data, patients' drug therapy affecting the kidney function, risk factors for AKI, logistic EuroSCORE 1 and 2, preoperative left ventricular ejection fraction estimation, preoperative sCr levels (IDMS-traceable Jaffé method, Olympus BCF), preoperative estimation of the glomerular filtration rate (calculated using the Modification of Diet in Renal Disease formula) and medical history. The intraoperative data collected were: type of surgery, duration of CPB, cross-clamp time, mean MAP during CPB, mean SvO_2 during CPB, lowest haematocrit level during CPB, highest CPB serum lactate level, number of patients that received diuretics and number of patients transfused. Postoperative data recorded in ICU were: the proportion of patients transfused, the proportion of patients who received diuretics in ICU, the proportion of patients requiring renal replacement therapy (RRT), the length of ICU stay and the length of hospital stay.

2.3.1. New markers measurements for early detection of acute kidney injury

The RRI measurements and the urine samples necessary to measure TIMP-2 and IGFBP7 concentrations were obtained

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