

Kidney Congress 2018: Efficacy of Nicorandil in the Prevention of Contrast-Induced Nephropathy among Patients with Chronic Kidney Disease Undergoing Coronary Angiography: a meta-analysis of randomized controlled trials - Eliezer James Aguila, Anthony Gerodias, Andrea Marie Reyes, Carina Dalay-Dizon - St. Luke's Medical Center, Quezon City, Philippines

Eliezer James Aguila, Anthony Gerodias, Andrea Marie Reyes, Carina Dalay-Dizon
St. Luke's Medical Center, Quezon City, Philippines

Contrast induced nephropathy (CIN) is a reversible form of acute kidney injury that occurs soon after administration of contrast media. Current accepted methods for prevention of CIN include intravenous (IV) hydration, administration of oral n-acetylcysteine, and use of atorvastatin. Nicorandil, a novel anti-anginal drug has been studied to have a beneficial effect as well in preventing CIN. This paper aims to determine the efficacy of nicorandil in the preventing the incidence of contrast induced nephropathy in patients who will undergo coronary angiography. Search for randomized controlled trials was done, evaluating the efficacy of nicorandil in preventing contrast induced nephropathy in patients undergoing coronary angiography. Articles were critically appraised for inclusion. Pooled analysis revealed a Chi2 value of 4.32, dF=3 (P=0.21), I2 of 31%. Computed relative risk for incidence of CIN following Nicorandil administrations was 38% (CI: 0.19, 0.71). Administration of Nicorandil showed absolute risk reduction in incidence of CIN by 8% as compared to iv hydration seen in the Forest plot with a number needed to treat of 12. It showed a trend favoring nicorandil for the prevention of contrast induced nephropathy. The studies also showed that nicorandil together with IV hydration significantly caused reduction in cystatin C levels and change from baseline eGFR as compared with standard intravenous hydration.

Contrast-induced nephropathy (CIN), a form of acute kidney injury, is a serious complication that occurs after exposure to the iodinated contrast media. With the ever-increasing use of iodinated contrast media with coronary interventional procedures, the incidence of CIN is increasing, especially in patients with poor renal function. Recent studies have recognized that CIN is associated with long-term adverse events and mortality. Several approaches, such as hydration, N-acetylcysteine, sodium bicarbonate, and statins, have been studied to prevent CIN, but their therapeutic effects still need further investigation. Nicorandil (2-nicotinamidoethyl-nitrate ester) is a hybrid compound

derived from an adenosine triphosphate-sensitive potassium channel (K-ATP channel) opener and a nitric oxide donor, and has been widely used in the treatment of angina pectoris and acute heart failure. Nicorandil exhibits a vasodilatory effect on the coronary vasculature and a pharmacologic preconditioning effect to protect the heart from ischemia. Moreover, nicorandil could ameliorate ischemia-reperfusion injury in the rat kidney due to its ischemic preconditioning and antioxidant properties. Several studies have investigated the potential role of nicorandil in CIN prevention, but the results remain inconsistent. To the best of our knowledge, there has been no previous study with a long-term follow-up to evaluate the nephroprotective effect of nicorandil against CIN. This randomized, prospective trial was to assess the short-term and long-term protective effect of nicorandil against CIN and associated adverse events in patients with chronic renal dysfunction undergoing an elective coronary procedure. A total of 278 consecutive patients with renal dysfunction scheduled for coronary angiography or percutaneous coronary intervention (PCI) at our institution from January 2016 to January 2018 were considered for participation in our study. Renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m² calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Exclusion criteria were the following: end-stage renal disease; a history of kidney transplantation; left ventricular ejection fraction (LVEF) $< 35\%$ or New York Heart Association (NYHA) IV class; acute myocardial infarction; previous contrast media exposure within 1 week; allergy to contrast medium or nicorandil, and the administration of other medications, such as N-ace-tylcysteine, metformin, and sodium bicarbonate to prevent CIN. End-stage renal disease was defined as eGFR < 15 mL/min/1.73 m² or the need for long-term dialysis or kidney transplantation. LVEF was measured by echocardiography and calculated from the end-diastolic and end-systolic volumes calculated using the Simpson method from two orthogonal apical views.

The study was a prospective, open-labeled, randomized controlled trial. Eligible patients were randomly allocated into either control or nicorandil groups, using a balanced block randomization method. Patients in the nicorandil group received 10 mg of nicorandil three times per day (t.i.d.), from 2 days before to 2 days after an elective coronary procedure. An elective coronary procedure was performed according to the standard technique by a radial or femoral approach. All enrolled patients received standard hydration with an intravenous infusion of 0.9% saline at a rate of 1 mL/kg/h for 6 h before and 12 h after an elective coronary procedure. The nonionic contrast agent (Iopamidol injection, BRACCO Sine Ltd., China) was used for all patients. Blood samples were collected at 24 h before and 24, 48, and 72 h after the procedure. Serum creatinine (SCr) was measured by an enzymatic method (Creatinine Diagnosis Kit, Roche Diagnostics, Germany), and Cystatin C (CysC) was determined by the immune turbidimetric method (Cystatin C Determination Kit, Mike Biotechnology Co. Ltd, China). CIN was defined as an SCr increase of $\geq 25\%$ and/or ≥ 0.5 mg/day within 72 h after exposure to the contrast medium. The median follow-up period of the study was 12.8 months. The follow-up endpoints were adverse events, including all-cause mortality, stroke, non-fatal myocardial infarction, percutaneous coronary revascularization, coronary artery bypass graft surgery, congestive heart failure, pulmonary edema, and end-stage renal disease. If more than one adverse event occurred in the same patient, the first event was used for the analysis. The follow-up data were obtained from electronic medical records and/or telephone interview with the patients or patients' caregivers. During the follow-up period, all the patients continued their regular medications without interruption.

The incidence of CIN in the control group was approximate at 20%, while the incidence of CIN in the nicorandil group was hypothesized to be 5% according to the previous studies [15, 16]. The sample size was determined based on a two-sample, two-sided inequality test. The required number of participants was 93 per group, with the power of the test set at 90% and the significance level at 0.05. Taking into account the patients lost to follow-up (estimated at 20%), the number of patients enrolled in this study was at least 112 per group. The continuous data are expressed as the mean \pm standard deviation (SD) or median (interquartile range). The Kolmogorov-Smirnov test was used to

analyze the normal distribution of continuous data. The Student t test, Mann-Whitney U test, or Wilcoxon rank-sum test was used for the comparisons of continuous variables. The categorical data were compared using χ^2 tests. Univariate and multivariate logistic regression analyses were used to identify the factors for CIN, while univariate and multivariate Cox proportional hazard analyses were carried out to determine the independent predictors for adverse events during 1 year of follow-up. Covariates with a p value < 0.10 after univariate analysis were entered into multivariate regression models. The cumulative adverse event rates were estimated by the Kaplan-Meier analysis and statistical differences were carried out using the log-rank test. The statistical significance was considered as a 2-tailed p < 0.05 . Statistical analyses were performed using SPSS version 22.0. Of the 278 patients enrolled in this study, 8 (2.88%) were excluded because of incomplete medical data, and another 5 (1.80%) were withdrawn from the study at their own request. A total of 265 patients (95.32%) were randomized to either receive nicorandil and hydration (nicorandil group, n = 133) or hydration only (control group, n = 132). During the 1-year follow-up period, 6 patients from the nicorandil group and 7 patients from the control group missed the follow-up. Consequently, 127 patients in the nicorandil group and 125 patients in the control group completed the study.