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Editorial

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Nicorandil: What is Beyond the Anti-Anginal Action?

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Incidence of Contrast Induced Nephropathy (CIN) among ischemic heart disease patients subjected to coronary catheterization is highly dependent on the kidney function before contrast media administration and relevant risk factors, of which diabetes mellitus is the most important one.[1] Incidence of CIN ranges from <2% in the general population up to 50% in patients with Advanced Kidney Disease (AKD)[2] and it is the third most common cause of hospital acquired renal failure.[3] Development of contrast media started by the first ionic, high-osmolar contrast agent (sodium acetrizoate) brought by Vernon Wallingford in 1953 and continued till development of the second generation non-ionic media in 1980's.[1] The exact mechanisms underlying CIN are still unclear. However, it was postulated that in addition to their direct toxic effects on renal tubular epithelial cells, contrast media trigger acute renal ischemia by inducing an imbalance between vasodilatory and vasoconstrictive factors.[4] Scientific research for identification of renoprotective agents that can prevent CIN is continuously going on. No pharmacological approach has yet been shown to provide consistent protection. Furosemide, dopamine, atrial natriuretic peptide, sodium bicarbonate, sodium chloride, mannitol, endothelin receptor antagonists, ascorbic acid, fenoldopam, theophylline, N-acetylcysteine, trimetazidine and statins were all previously evaluated in prospective, randomized trials, showing positive or controversial results.[5-7]

Nicorandil is an anti-anginal medication that has the dual properties of a K+ATP channel agonist and a Nitric Oxide (NO) donor.[8] It was reported that activation of the K+ATP channel reduced renal injury (due to ischemia and reperfusion) by preventing accumulation of reactive oxygen radicals. These data suggest that nicorandil may protect the kidney against ischemic injury associated with the use of contrast media by decreasing calcium inflow to the tubular cells, inhibiting the accumulation of reactive oxygen species, suppressing synthesis of endothelin-1, and inducing NO production.[9]

Two prominent studies reported contradicting results concerning feasibility of using Intravenous (IV) nicorandil as a CIN-preventing agent.[10,11] The first one is the PRINCIPLE study (a randomized controlled multicenter study), that was conducted on a total of 166 patients (nicorandil n=81; control n=85) with an estimated glomerular filtration rate <60 mL/min. Nicorandil (12 mg dissolved in 100 mL of 0.9% saline) was administered intravenously for 30 minutes just prior to coronary angiography in the nicorandil group. The same volume of only saline was given to the control group. An iso-osmolar, non-ionic contrast medium, was used. The primary endpoint was the incidence of CIN, defined as >0.5 mg/dL increase or >25% rise in serum creatinine level within 48 hours of contrast exposure compared to baseline. The incidence of CIN did not differ between both groups (6.8% *vs.* 6.6%, p=0.794). It was concluded that prophylactic IV infusion of nicorandil did not decrease the incidence of CIN in patients with renal dysfunction undergoing coronary angiography. Authors assumed that IV nicorandil might be effective when administered at a different dosing regimen. Additionally, the majority (>75%) of the patients included in their study belonged to relatively lower CIN risk groups. percutaneous coronary intervention (PCI) was performed in 38.9% of the patients, and only 24.8% of the included patients required contrast media volume ≥150 mL. These data most probably led to an incidence of CIN that was much lower than what was assumed for the

calculation of the study sample size i.e. underpowered study.[10]

The other study was recently conducted by Nawa, et al.[11] It was a prospective randomized single center trial applying the same definition of CIN. They included 213 patients undergoing elective PCI and with a high serum cystatin C level (greater than 0.95 mg/dL in males and 0.87 mg/dL in females). Patients were randomized in to a saline group (n=107) or a nicorandil group (n=106, 96 mg of nicorandil was dissolved in 100 mL of 0.9% saline then infused in addition to saline for 4h before and 24 h after PCI). A low-osmolar, non-ionic, contrast medium, was used. All patients showed an estimated glomerular filtration rate <60 mL/min. The average percent increases in serum creatinine and cystatin C following PCI were significantly lower in the nicorandil group. The average percent decline in the estimated glomerular filtration rate was lower in the nicorandil group. Accordingly, the incidence of CIN was significantly lower in the nicorandil group (2.0% *vs.* 10.7%, $p<0.02$). Univariate regression analysis revealed nicorandil IV infusion to be the only significant predictor of CIN development. The study still face the limitation of utilizing the uncommonly used indicator of renal dysfunction; cystatin C, in addition to being a single center study.[11]

The main discrepancy between both studies, concerning methodology, can be summarized in two points. The first one is that all patients in the second study underwent PCI, which means a higher mean contrast volume (140 ml *vs.* 125 ml). The second one is related to nicorandil infusion regimen. It is assumed that the detrimental effect of the relatively high contrast volume was negated by more intensive exposure to IV nicorandil in the second study.

The recently published study by Nawa, et al.[11] opens the door for more research work targeting the same subject. Many future perspectives can be addressed, for example; could a more intensive dosing regimen bring more reduction in CIN incidence? Does it worth tackling patients with more severe renal dysfunction? What about using an intensive oral dosing regimen instead of IV infusion? Answers are expected in the near future.

CONFLICTS OF INTEREST

The author has no financial interest in or financial conflict with the subject matter discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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