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Original Article

Nephroprotection Prevents Incidence of AKI in Patients Undergoing Elective Percutaneous Coronary Interventions

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Abstract

Introduction. It has been described that acute kidney injury due to contrast administration is a common complication after coronary angiography, particularly for high risk patients. The aim of this study was to confirm if current radiocontrast preventive strategy is protective in patients who undergo elective coronary angiography.
Methods. The study included 43 consecutive patients who underwent elective coronary angiography. Patients were divided into subgroups regarding diabetes, age and presence of chronic renal failure. All patients received standard nephroprotective prevention: pre and post-interventional hydration (0.9% saline), N acetyl cystein (600 mg bid, PO), statins (10-20 mg bid, PO), vitamin C (500 mg IV) and iso-osmolar contrast media (Iodixanol- Visipaque), at a dose of 70-100 ml per procedure. Renal function was determined by Cockroft-Gault equation for estimation of Creatinine clearance (CCl) and early marker of acute kidney injury; neutrophil gelatinase-associated lipocalin (NGAL) was measured in urine by using automated platform ARCHITECT (Abbott Diagnostics).
Results. After coronary angiography, CCl and urinary NGAL levels did not change significantly as compared with baseline values in all groups of patients. Also, renal function remained stable after coronary angiography in the subgroup of patients with diabetes, pre-existent chronic renal failure and in the subgroup of elderly patients ($\geq$65 years).
Conclusions. Nephroprotective measures including isotonic contrasts prevent acute kidney injury even in high-risk groups of patients. We need more investigations comprising a larger number of patients to confirm if current preventive measures are sufficient.

Key words: acute kidney injury, contrast media, neutrophil gelatinase-associated lipocalin

Introduction

Acute kidney injury (AKI) is defined by the Acute Kidney Injury Network (AKIN) as functional and structural disorder or signs of renal damage including any defect from blood and urine test, or tissue imaging that is less than 3 months. AKI biomarkers can be components of serum or urine. Traditional biomarkers are far away from satisfying the requirements of the perfect predictors of AKI [1]. Serum creatinine remains the cornerstone of AKI diagnosis, but it has several serious limitations. Its value varies with age, gender, diet, muscle mass, drugs, and exercise. Creatinine is secreted by the urinary tubules and this stands for 10-40% of its clearance. Its values become abnormal when more than 50% of GFR is lost, and it takes up to 24 hours before creatinine increases in blood. Novel markers that rise earlier than creatinine in AKI could allow early detection and intervention to prevent further progression and better outcome of the disease. Among these biomarkers, neutrophil gelatinase-associated lipocalin (NGAL) is a promising predictor for AKI, which shows up in urine or serum 48 h earlier than serum creatinine [1].
NGAL is a small molecule of 178 amino acids that belongs to the lipocalin superfamily of 20 structurally related secreted proteins. Human NGAL was originally identified as a 25-kD protein covalently bound to gelatinase from human neutrophils. NGAL is expressed at very low levels in human tissues, including kidney, trachea, lungs, stomach and colon, and its expression increases in the presence of inflammation and injured epithelia [2]. NGAL is freely filtered by the glomerulus, and it is largely reabsorbed in the proximal tubules.
NGAL as a renal biomarker was discovered in 2003. Both plasma and urine NGALs are increased after a renal insult. Decrease in GFR resulting from AKI would decrease the renal clearance of NGAL, with its accumulation in plasma [3]. Elevated urine NGAL is caused

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by both proximal and distal nephron injury after a nephrotoxic insult [4].

Until now, NGAL was proved to be a reliable and early marker of AKI in different clinical settings, among which radiocontrast nephropathy is one of the leading causes. Recently, there has been major growth in contrast enhanced imaging. It has been described that AKI due to contrast administration is a common complication after coronary angiography, particularly in high risk patients [5]. The causes of radiocontrast induced AKI are multifactorial, such as combination of ischemia due to vasoconstriction and direct cytotoxicity to the renal tubules mediated by reactive oxygen species [6].

Pre-existing risk factors for radiocontrast induced nephropathy (RCIN) include diabetes, advanced age, chronic kidney failure, higher dose of contrast agent, route of contrast administration, congestive heart failure, hypertension, anemia, use of nephrotoxins, and non-steroidal anti-inflammatory medications, volume depletion and some other factors that have been associated with increased risk of radiocontast acute kidney injury [7,8].

The aim of this study was to confirm if current radiocontrast preventive strategy is protective in patients who undergo elective coronary angiography.

Materials and Methods

The study included 43 consecutive patients who underwent elective coronary angiography. Urine and plasma samples were taken at admission, 4h and 24h after the angiography. Patients were divided into subgroups regarding diabetes, age and presence of chronic renal failure. All patients received standard nephroprotective prevention before and after the procedure. The prevention included pre and post-interventional hydration (0.9% saline), use of N acetyl cystein (NAC, 600 mg bid, PO), statins (mostly Atorvastatin or Simvastatin at a dose of 10-20 mg bid, PO), vitamin C (500 mg IV) and iso-osmolar contrast media (Iodixanol- Visipaque), at a dose of 70-100 ml per procedure.

Serum creatinine level was measured in blood samples and clearance was calculated by the Cockroft-Gault equation. For the measurement of NGAL in urine samples we used the automated platform ARCHITECT (Abbott Diagnostics). Values of these two biomarkers were correlated and their trend was followed during the time and within the three subgroups.

Since NGAL is stable in urine if stored at 4^{o}C for up to 7 days and plasma or urine samples are stable if stored at -80^{o}C for a long time, urine was centrifugated to remove neutrophils that may produce NGAL *in vitro* conditions.

Table 1. Characteristics of patient groups

	Diabetic status		Renal function		Age	
	DM	Non DM	CRF	Non CRF	< 65 yrs	≥65 yrs
Male	8(80%)	23(70%)	10(71%)	21(71%)	19(66%)	12(86%)
Female	2(20%)	10(30%)	4(29%)	8(29%)	10(30%)	2(14%)
Age, years	64.3±7.3	58.1±10.0	67.4±9.3	56.3±7.9	54.9±6.4	71.6±5.2
HTA	8(80%)	26(79%)	8(80%)	22(79%)	23(79%)	12(86%)
DM	8(80%)	-	2(20%)	8(80%)	5(50%)	5(50%)
CCl, ml/min	87.6	80.7	52.25	97.2	93.1	60.1

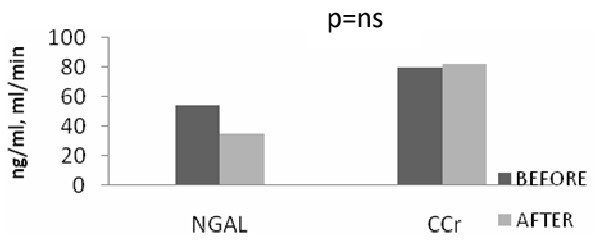

Fig. 1. Creatinine clearance and urine NGAL levels before and after coronary angiogram in all patients

Results

Table 1 shows baseline characteristics of examined patients. There was no statistical difference in gender, CCl, and prevalence of hypertension between patients' groups. From the total number of patients, 10 had diabetes mellitus and this group of patients was older than those without diabetes. At the same time, there was no diffe-

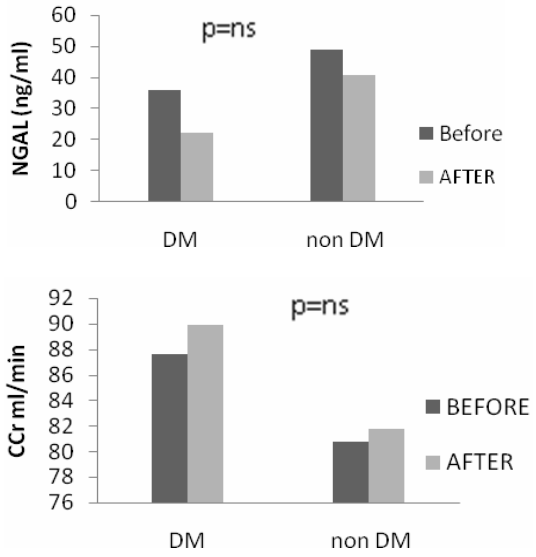

Fig. 2. Creatinine clearance and urine NGAL levels before and after coronary angiogram in patients with and without diabetes mellitus

rence between groups in regard to baseline CCl and prevalence of hypertension. Levels of CCl and urinary NGAL did not change significantly after the procedure as compared with baseline values neither in patients with diabetes nor in patients without diabetes (Figure 2).

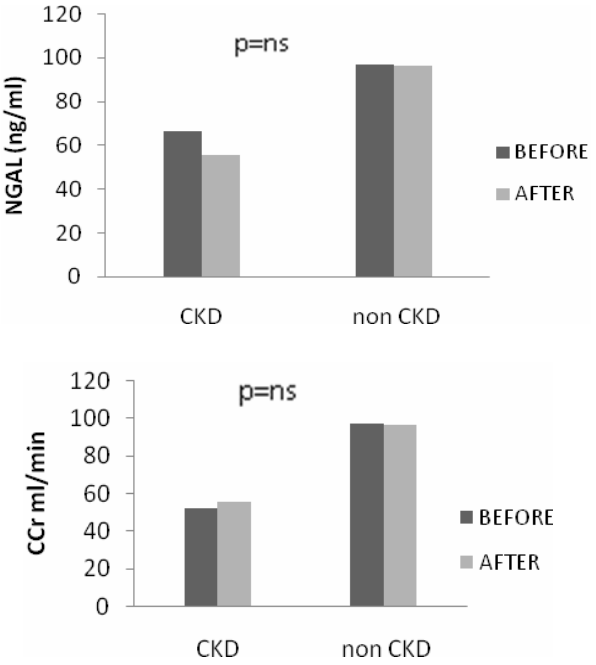

Fig. 3. Creatinine clearance and urine NGAL levels in patients with chronic kidney disease and in patients with normal kidney function before and after coronary angiography

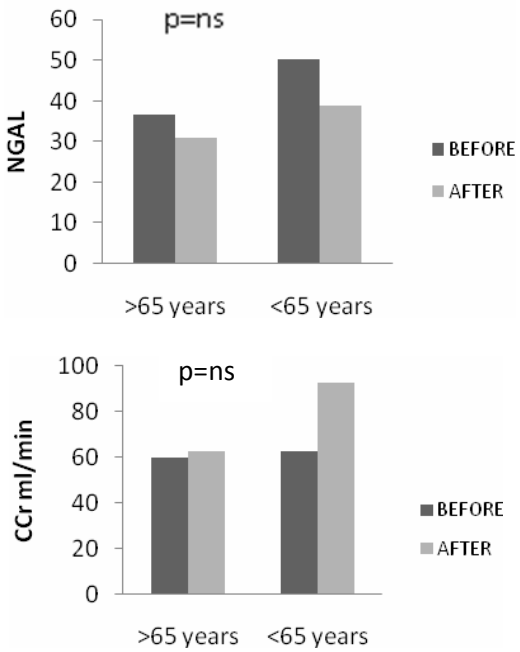

Fig. 4. Creatinine clearance and urine NGAL levels before and after coronary angiogram in patients older than 65 years and younger than 65 years

Similar results were observed in the subgroup of patients with previous chronic renal failure (No=14) and in patients with normal renal function (N=29).Patients with previous CRF were significantly older, but the two subgroups of patients were similar in the prevalence of diabetes and hypertension. In both subgroups, renal function remained stable after the procedure with no significant change in the values of CCl and urinary NGAL (Figure 3).

Finally, renal function remained stable in both elderly (No= 14) and younger (N=29) subgroup of patients with no change in CCl and urinary NGAL after the procedure (Figure 4).

Discussion

Radiocontrast induced nephropathy has been defined as the acute deterioration of renal function after parenteral administration of radiocontrast media in the absence of other causes [9]. There is no effective therapy once injury has occurred; therefore, prevention is the cornerstone in all patients at risk for AKI. There is some evidence showing that prevention of AKI is associated with a reduction in adverse outcomes. The optimal strategy for preventing RCIN has not yet been established [10]. In the present study, preventive strategy included adequate hydration, N acetyl cystein, statins, vitamin C and iso-osmolar contrast media at a dose of 70-100 ml per procedure. This strategy was officious in preventing deterioration of kidney function and AKI even in high-risk patients (diabetic and elderly).

Several studies have been investigating the correlation between the amount of administrated contrast media and risk for developing AKI. Some authors, such as Mc Cullough, *et al*. and Kane, *et al.* [11] have shown that minimizing of contrast amount is one of the most important factors for prevention of AKI especially in the high-risk population.

Also, the type of the contrast media is a key element for nephroprotection in contrast mediated imaging. Contrast media is classified by its osmolality, and it can be high, low or isoosmolar [12]. There have been a lot of randomized trials and several meta-analyses that compared different types of contrast media regarding the development of radiocontrast induced nephropathy [13-17]. Although there was no definite conclusion, we could certainly claim that there is a significant benefit of usage of low and isoosmolar contrast as compared with high osmolarity contrast media. More recent studies have focused on the comparative nephrotoxicity of iso-osmolar and low osmolar contrast media [18-19]. Some of them have showed that use of iso-osmolar contrast is associated with lower risk for AKI, especially in patients with risk factors such as diabetes mellitus, preexisting chronic kidney disease and in geriatric population [20-22]. However, there are also studies that showed no difference or even showed benefit of using low osmolar contrast media [23]. Therefore, no consensus has been reached.

In this study we used lower concentrations of iso-osmolar contrast media and it has been shown that there

was no deterioration in kidney function in patients with diabetes, chronic kidney failure and elderly.

The pharmacological prophylaxis for radiocontrast induced nephropathy includes antioxidant strategy and inhibition of renal vasoconstriction. There have been a lot of investigations regarding the benefit of NAC, vitamin C and statins in prevention of radiocontrast AKI.

NAC is a potent antioxidant that removes oxygen-derived free radicals, and it may be capable of preventing radiocontrast nephropathy by improving renal hemodynamic and by diminishing direct oxidative tissue damage. The first study that proved a decrease of the incidence of radiocontrast AKI by NAC administration at a dose of 600 mg twice a day was performed in 1993 by Tepel, *et al*. [24]. After the initial trial there have been many studies that confirmed this finding. Briguori et al have shown that double dose of NAC can be even more protective [25]. In contrast, the protective effect of NAC was not proved by some other studies [26,27]. Therefore, clinical data regarding the efficacy of NAC in preventing of radiocontrast AKI remains controversial. Considering the very low toxicity and cost of this drug the use of oral NAC at a dose of 1.2 g twice daily on the day before and on the day of the procedure is recommended in patients at risk for contrast nephropathy.

The use of vitamin C in radiocontrast nephropathy prevention is based on the antioxidative effect of the ascorbic acid. Studies that included vitamin C as a prophylaxis for the AKI after the contrast imaging concluded that its role is unclear and its use often is not justified [28-30].

The rationale for the use of statins in prevention of contrast induced AKI is based on its antioxidative and anti-inflammatory properties. The first study by Attallah, *et al*. showed that patient who used statins 24-72h before the coronary catheterization had a significantly lower risk for developing AKI [28]. Even though, many other studies [31,32] confirmed these findings, the first prospective, randomized, double blind, controlled study did not show benefits of taking these medications in AKI prophylaxis [33]. In the meta-analysis that included six cohort studies, four of them showed preventive effects against radiocontrast induced nephropathy [34].

In our study all patients were already using statins before angiography and we can not differentiate the extent of the protective role of statins as compared to other preventive measures that have been used.

The most common and frequent way of preventing radiocontrast nephropathy is periprocedural hydration. There are three types of this method: oral fluids, intravenous 0.45% saline and intravenous 0,9% saline. On the basis of the Mueller's study it has been generally accepted that isotonic saline is superior to hypotonic saline for the prevention of radiocontrast induced nephropathy [35].

The explanation for the prophylactic application of sodium bicarbonate is that the alkalinization of tubular fluid diminishes the production of free radicals and protects renal tissue from the oxidative stress [36,37]. Since the study of Merten, *et al*. [38], which showed significantly lower risk for developing AKI in the group of patients receiving sodium bicarbonate, there have been many trials with controversial conclusions [39-41]. As a result, the use of sodium bicarbonate in a single bolus in addition to pre-interventional hydration could be helpful.

The present study has its limitations. Since we used multiple preventive measures, we cannot determine the contribution of each particular measure. During the study, we used NGAL as a very early marker of AKI. However, apart from NGAL, there are other biomarkers recommended by different authors and combination of these biomarkers could be more conclusive. Finally, we need more patients in every subgroup for better understanding the role of the current strategy during elective coronary angiography.

Conclusions

Administration of the radiocontrast did not cause acute kidney injury in patients who underwent elective coronary angiography including subpopulations of patients with diabetes mellitus, elderly patients and those with preexisting chronic kidney failure. These results were obtained by using nephroprotective strategy including isotonic contrasts. However, further research including a larger number of patients is necessary in order to confirm whether current preventive measures are sufficient in different clinical settings.

Conflict of interest statement. None declared.

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