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ORIGINAL RESEARCH

NGAL in trans-catheter aortic valve implantation on and off RenalGuard

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Abstract

Introduction: Acute kidney injury (AKI) is a well-known complication post invasive cardiac procedures. RenalGuard system has been shown to reduce the risk of AKI in high-risk patients by evacuating iodine-based contrast material rapidly. Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein stored in granules of mature neutrophils and is released to the blood stream due to acute tubular damage. This report examined the biomarker as a sub study of the randomized sham control study REDUCE-AKI in the setting of Trans-Aortic Valve Implantation (TAVI).

Methods: Venous blood was drawn from 27 patients. Blood was drawn at designated time intervals: before the procedure, after 12 hours and after 24 hours. Patients were randomly allocated to active versus sham RenalGuard activity.

Results: There was no difference between baseline and 24 hours levels in NGAL values (ng/mL) in the sham group (median 70.3 IQ 21.5, 176.6) versus the active group (median 46.9, IQR 1.3, 127.7) (P = 0.259). There was also no association between NGAL and clinical complications.

Conclusion: Forced diuresis with matched hydration does not prevent AKI in patients undergoing TAVI and measuring NGAL correlates with these findings.

Keywords

TAVI; TAVR; AKI; NGAL; RenalGuard

1. Introduction

Acute kidney injury (AKI) is a well-known complication post invasive cardiac procedure [1]. In the past, contrast material was considered the main culprit. In recent years, AKI has been attributed to a multifactorial cause including inflammation, embolization, contrast material, bleeding, nephrotoxic drugs, hypo-perfusion and cardio-renal syndrome [2]. The implications include prolonged hospitalization, the need for renal replacement therapy and even death. Thus, preventing AKI post procedure is of great value. Furosemide-induced diuresis with matched isotonic intravenous hydration using the RenalGuard system (RenalGuard Medical Systems, Milford, MA, USA) has been shown to reduce the risk of AKI in high-risk patients by evacuating iodine-based contrast material rapidly [3]. AKI has been observed in up to a third of trans-catheter aortic valve implantation (TAVI) patients [4]. The mechanism behind AKI in these patients is not clear as these are elderly patients with multiple comorbidities [5]. There is no one particular mechanism that has a preventable and reversible cause. Studies in the past have shown RenalGuard to protect patients from AKI [6]. Defining AKI is usually based on increase in serum Creatinine (sCr). This usually is examined as a delta over a period of time. However, damage to the kidneys can occur before the rise in sCr. Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein stored in granules of mature neutrophils and is released to the blood stream due to acute tubular damage and this happens faster than the rise of sCr [7]. The aim of the present study was to report the effect of the RenalGuard system on NGAL in patients undergoing TAVI.

2. Methods

We analyzed data from the REDUCE-AKI trial [3]. Patients with reduced renal function planned to undergo TAVI were recruited to active RenalGurad vs. sham treatment. REDUCE-AKI was a single-center, prospective, randomized, double-blind, sham-controlled interventional clinical trial. The selection of patients in the REDUCE-AKI trial was performed in such a way that would simulate real life patients. The primary endpoint of the study was reduction of acute kidney injury. Other endpoints included mortality and diastolic dysfunction. After signing an informed consent, patients were randomized in a 1 : 1 fashion using closed envelopes by block randomization. The RenalGuard system was covered with a black bag to ensure blinding. Urine bags were changed by non-treating personnel. The present sub analysis examined the additive value of NGAL levels in both groups while the original trial examined sCr. Patients with history of acute coronary syndrome

in the past 30 days, history of left ventricular ejection fraction $< 30\%$, chronic dialysis treatment, furosemide hypersensitivity and contraindications to the placement of Foley catheter were excluded from the REDUCE-AKI trial to begin with. We also excluded in our sub-study patients with cardiogenic shock and those needing inotropes, vasopressors, or intra-aortic balloon counter-pulsation. The study protocol was approved by the Tel Aviv Sourasky Medical Center Institutional Review Board/Ethics (Helsinki) Committee (0111-13-TLV). Oral and written informed consent was obtained from all patients prior to inclusion. It was performed in the Cardiology wing of Tel-Aviv Medical Center, Tel-Aviv, Israel. REDUCE-AKI was registered as a clinical trial in 2013 and published in 2019. The RenalGuard system (RenalGuard Medical Systems, Milford, MA, USA) is a CE approved system [8]. It includes a computer system (console) that weighs the urine of the patient, calculates the urine rate, and infuses matched intra-venous normal saline thus maintaining the fluid balance. It induces the required high urine output. The system is designed to replace the urine output with equal volume of sterile saline thus minimizing over and under hydration. The device is comprised of the mentioned console and a single use set for infusion and urine collection (IV and Foley catheters). The user can also set the system to achieve over or under hydration. Medical treatment after the procedure and throughout the hospitalization was left to the discretion of the attending physician on the hospital ward without interfering [3]. The study team did not influence therapies or decisions on any patient. Venous blood was drawn at several time intervals: before the procedure (time "0"), after 12 hours and after 24 hours. Blood was drawn using a butterfly needle. The amount drawn was 20 cc at least. Samples were taken to our facility's laboratory and centrifuged within 10 min using a cooled centrifuge. Plasma and serum were stored at -80 °C. NGAL levels were analyzed using NGAL rapid ELISA kits (Bioporto Diagnostics, Copenhagen, Denmark) [9–11]. The reagent kit includes immune-particle suspension and reaction buffers. The calibrator kit includes 5 vials of 1 mL of prediluted calibrators. The control kit includes 6 vials of 1 mL. All the antibodies are monoclonal affinity purified 1 mg/mL. AKI was defined using the VARC-2 criteria [12] which includes an increase in serum creatinine by 0.3-0.5 mg/dL or more or increase in serum creatinine $>$ 1.5 times baseline or an urine output of less than 0.5 mL/kg/hr. AKI is classified into 3 stages. Stage 1 includes a rise of more than 1.5 times the baseline in sCr with reduced urine output for less than 12 hours. Stage 2 includes a rise in sCr of more than twice the baseline and more than 12 hours of reduced urine output. Stage 3 is a 3-fold rise in sCr and more than 24 hours with decreased urine output. The estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [13]. Chronic kidney disease was defined by an eGFR $\leq$ 60 mL/min/1.73 m^2 based on past medical records. sCr was measured twice daily in the patients of this study.

2.1 Statistical analysis

Categorical variables were expressed as frequencies and percentages. The distribution of continuous variables was assessed using the Shapiro-Wilk test, histograms and Q-Q plots for normality. The χ^2 test was used to evaluate associations between categorical variables. Continuous variables were compared using the Mann-Whitney U test as appropriate or the Kruskal-Wallis test and reported as median and IQR. We also reported mean and SD for convenience purposes even though data was not normally distributed. $P < 0.05$ was considered statistically significant. All analyses were performed using the IBM SPSS 25.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 27 patients were examined. Fourteen patients (52%) were in the Active RenalGuard group ("Active") and thirteen patients (48%) were in the sham group ("Sham"). Baseline characteristics (Table 1) showed no difference between the two groups. We examined the NGAL levels in several manners. First, the delta of NGAL (ng/mL) between time 0 and 12 hours, with a median of 25.3 (3.4, 51.8) in the sham group and 34.1 (-2.5, 86.0) in the active RenalGuard group ($P = 0.905$). There was no difference between baseline and 24 hours in both groups with a median of 70.3 (21.5, 176.6) in the sham group and 46.9 (1.3, 127.7) in the active group ($P = 0.259$). Fig. 1 presents the difference in mean between the groups. There was no difference in the incidence of elevated NGAL between the groups above 100 ng/mL or above 200 ng/mL ($P = 0.385$ and $P = 0.519$). There was no association between AKI and NGAL levels (Table 2). There were in total 19 (70.4%) patients without AKI, 7 (25.9%) with AKI stage 1 and one (3.7%) with AKI stage 3. There was also no association between NGAL and clinical complications (Table 3).

4. Discussion

Our sub analysis shows that the RenalGuard system did not impact NGAL values. The major finding of the REDUCE-AKI trial was that this treatment strategy did not reduce the incidence of AKI. It was theorized even before the study that the use of such a device in TAVI patients does not prevent complications because these patients have many risk factors for AKI [4, 14]. The usage of sCr in a clinical trial may alter results due to the fact that sCr takes time to rise and that there might be tubular injury undetected by sCr [15]. Adding NGAL to studies might help find patients with subtle injury. The occurrence of procedural AKI is multifactorial, and may be affected by many factors which may affect renal perfusion [16]. Earlier identification of AKI by a biomarker such as NGAL should improve the quality of studies [17–19]. NGAL, a 25-kDa protein covalently bound to gelatinase proteins in human neutrophils, was reported as an early marker of kidney tubular injury in various patient populations [20]. Elevated NGAL levels immediately before TAVI are most likely indicative of preexisting renal injury unrelated to the procedure itself. Elevation in NGAL levels following TAVI are probably procedural related. We did not see any difference in NGAL between the two groups. Optimal NGAL cutoffs previously reported in the literature to predict AKI were 142 ng/mL (EDTA plasma) and 148 ng/mL (heparin plasma) [7, 10, 11]. A previous study in PCI patients reported identification

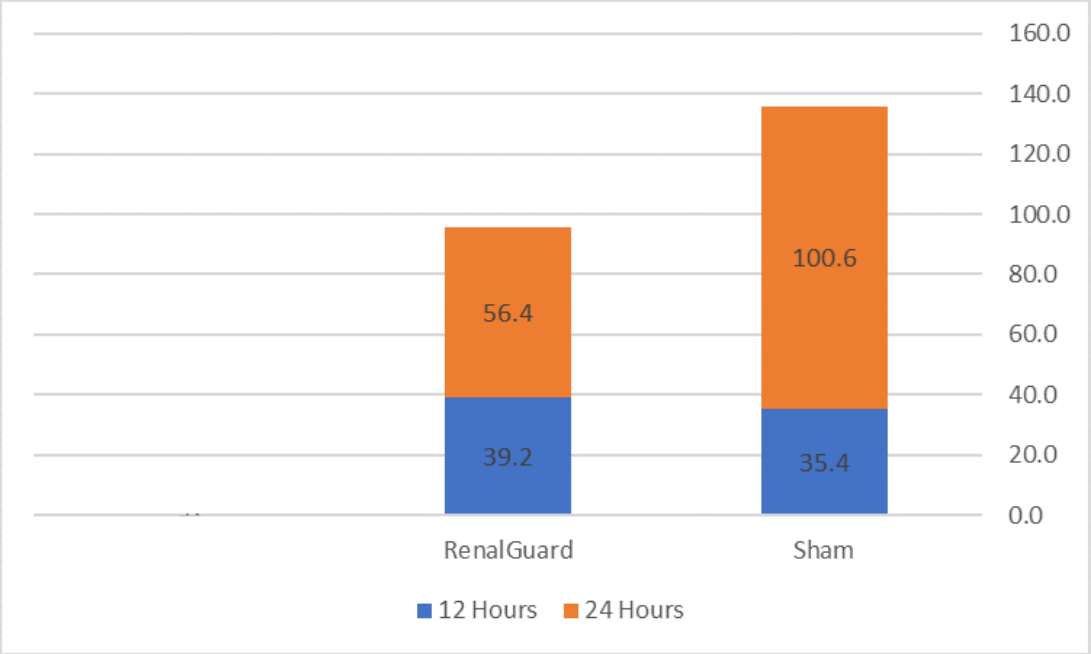

FIGURE 1. Mean Delta NGAL at 12 and 24 hours-RG vs. Sham.

TABLE 1. Baseline Characteristics.

Variable	OFF (n = 13)	ON (n = 14)	*P*-value
Gender (Male, %)	8 (61.5%)	7 (50.0%)	~1.000
Height (cm)	164.2 ± 7.1	163.4 ± 9.6	0.867
Median (Q1, Q3)	165 (158.0, 169.0)	162 (158.8, 168.0)	
Weight (kg)	70.5 ± 12.1	71.4 ± 11.6	0.650
Median (Q1, Q3)	68 (61.5, 83.0)	70 (63.8, 80.0)	
Hemoglobin (g/dL)	11.4 ± 1.6	11.5 ± 0.8	0.860
Median (Q1, Q3)	11.8 (10.7, 12.3)	11.5 (11.1, 11.2)	
Creatinine (mg/dL)	1.3 ± 0.2	1.3 ± 0.2	0.905
Median (Q1, Q3)	1.3 (1.2, 1.5)	1.3 (1.2, 1.4)	
History of Diabetes mellitus (%)	4 (30.8%)	8 (57.1%)	0.168
History of Dyslipidemia (%)	11 (84.6%)	13 (92.9%)	0.596
History of Hypertension (%)	11 (84.6%)	14 (100.0%)	0.222
History of Coronary Artery Disease (%)	10 (76.9%)	11 (78.6%)	~1.000
History of MI (%)	5 (38.5%)	2 (14.3%)	0.209
History of Past Smoker (%)	2 (15.4%)	4 (28.6%)	0.648
History of Atrial fibrillation flutter before (%)	2 (15.4%)	2 (14.3%)	~1.000
Bleeding (%)	1 (7.7%)	3 (21.4%)	0.596
Beta Blockers (%)	9 (69.2%)	7 (50.0%)	0.440
Alpha Blockers (%)	2 (15.4%)	2 (14.3%)	~1.000
Calcium Blockers (%)	6 (46.2%)	5 (35.7%)	0.700
Aspirin (%)	9 (69.2%)	12 (85.7%)	0.385
Furosemide (%)	5 (38.5%)	5 (35.7%)	~1.000
Statins (%)	10 (76.9%)	9 (64.3%)	0.678

of AKI at NGAL ≥ 120 ng/mL according to the ROC curve [9]. NGAL levels > 100 ng/mL were found to be indicative of renal tubular damage in cardiac surgery patients [21]. When referring to studies quoted in this article, we must address several issues. The first issue, is that the RenalGuard system is controversial. The mechanism behind it is logical but different

TABLE 2. AKI and NGAL.

Timing	NGAL ng/mL	AKI	*P*-value
Time Zero	Below 100	7 (36.8%)	0.216
	100 and above	1 (12.5%)	
	Below 200	8 (30.8%)	0.704
	200 and above	0 (0.0%)	
At 12 hours	Below 100	1 (11.1%)	0.149
	100 and above	7 (38.9%)	
	Below 200	6 (27.3%)	0.472
	200 and above	2 (40.0%)	
At 24 hours	Below 100	1 (16.7%)	0.406
	100 and above	7 (33.3%)	
	Below 200	5 (27.8%)	0.550
	200 and above	3 (33.3%)	

TABLE 3. NGAL > 100 ng/mL and Clinical complications (*P*-Values).

Clinical Complication	NGAL at Zero	NGAL-12 hours	NGAL-24 hours
Bleeding	0.336	0.531	0.718
Heart Failure Post-Procedure	0.971	0.483	0.483
Infection-Any	0.971	0.162	0.139
New Atrial Fibrillation	0.593	0.963	0.963
New Left Bundle Branch Block	0.696	0.549	0.147

studies show different results regarding this system. Our institution decided to use this system, but it cannot be ignored that many hospitals do not use it and do not believe in its effectiveness. The second issue is the reliability and validity of NGAL. Studies aimed on showing it as an effective method of assessing renal injury sometimes ignore the false positive results one can get using NGAL. Also, some studies use an NGAL cut-off while other relate to it as a continuous variable.

Our report has several limitations. The population consisted of elderly patients. Not all patients were examined for NGAL levels (patients meeting the inclusion criteria were randomly selected). The number of patients in total is small-this is a major problem. This limitation is due to limited funds. Only 27 of 136 patients were included to this limitation. The patients were selected randomly out of each group. The power of the study is small. There was no comparison of other biomarkers. The addition of urinary NGAL measurements to the analysis would have strengthened our conclusions. It is also a single center study. It should be mentioned that NGAL exists in different molecular forms, monomeric and heterodimeric NGAL are predominantly produced by tubular epithelial cells and the dimeric form primarily originates from neutrophils, and its concentration rises in inflammatory states. This might cause a false positive result. Urinary NGAL might be a better test than serum NGAL and maybe we should have used it instead. Further investigations are needed before firm conclusions about clinical and financial implications of NGAL measurements can be drawn. Another limitation is the lack of data on total urine output, total fluid and total dose of loop diuretics in the two groups. We also do not have long-term outcomes on the specific patients in this study, however, the REDUCE-AKI trial did examine long-term mortality in both groups.

In conclusion, forced diuresis with matched hydration does not prevent AKI in patients undergoing TAVI and measuring NGAL correlates with these findings. The REDUCE-AKI trial has previously shown that RenalGuard does not prevent AKI in TAVI patients. Our usage of another biomarker to examine kidney injury strengthens previous findings.

AUTHOR CONTRIBUTIONS

Yaron Arbel, Shmuel Banai, Ariel Banai and Ariel Finkelstein designed the study. Sapir Sadon, Keren-Lee Rozenfeld, Aviram Hochstadt and Phillipe Taieb collected the data. Ilan Merdler analyzed the results and drafted the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Tel Aviv Sourasky Medical Center Institutional Review Board/Ethics (Helsinki) Committee (0111-13-TLV). Oral and written informed consent was obtained from all patients prior to inclusion.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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