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Evaluation of Protective Effects of N-Acetyl Cysteine and Vitamin C on Perioperative Renal Function in High-Risk Patients Undergoing Coronary Artery Surgeries, a Randomized Clinical Trial

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Abstract: Perioperative renal failure is one of the major complications following coronary artery surgeries, leading to increased morbidity and mortality rates in patients; necessitating renal replacement therapy and longer hospital and ICU stay. Considering the antioxidative effects of N-Acetyl Cysteine (NAC) and vitamin C in decreasing inflammatory factors, this study was designed to evaluate and compare the protective effects of these two agents on renal function of high-risk patients undergoing coronary artery surgeries. This study was a randomized clinical trial research. Ninety patients undergoing cardiac bypass surgery, who were considered as high-risk for postoperative renal failure, were randomized into 3 groups. Group A received NAC, group B received NAC plus vitamin C and group C received Dextrose water 5% as placebo. The agents were administered during and 12 and 24 h after the operation. Serum creatinine levels one day before the operation and also on 1st, 2nd and 3rd days after the operation were recorded and compared. The results revealed no significant differences in serum creatinine levels between the three groups in any of the evaluated days. Based on the results of our study, administration of NAC or its combination with vitamin C does not affect the outcome of renal function in high-risk patients undergoing cardiac bypass surgery.

Key words: Antioxidants, coronary artery bypass, acetylcysteine, renal insufficiency, ascorbic acid

INTRODUCTION

Acute Renal Failure (ARF) presents as a post-operation complication in 1-30% of patients undergoing cardiac surgeries, leading to mortality rates of 15-30%. The 1-5% of patients will require dialysis postoperatively (Noortgate *et al*., 2003; Rosner *et al*., 2006; Rosner and Portilla, 2008). Mortality may occur in 50-80% of the patients with severe post-operation ARF. The renal function impairment following cardiac surgery is considered to be independent of all other factors and manifests in a spectrum of subclinical injury to established renal failure, leaving many patients in need of lifelong dialysis therapies (Rosner and Okusa, 2006; Omar and Ratnatunga, 2006). The pathogenesis of ARF includes multiple pathways such as hemodynamic, inflammatory and nephrotoxic etiologies (Rosner and Okusa, 2006). Risk factors leading to postoperative ARF include advanced age, preexisting chronic renal failure, type of cardiac surgery, duration of cardiopulmonary bypass and aortic cross-clamping, valve replacement and/or reconstruction surgery, non-pulsatile flow, combined valve and Coronary Artery Bypass Graft (CABG) surgery. In addition, co-morbidities such as diabetes mellitus and impaired left ventricular function have been mentioned as the most important independent risk factors for ARF (Omar and Ratnatunga, 2006; Sirvinskas *et al*., 2008). High-risk patients should be targeted for renal protective managements (Rosner and Okusa, 2006). Even though no single method has been conclusively capable of ARF prevention, administration of various compounds including Atrial Natriuretic Peptide (ANP), NAC, dopamine and its analogues, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, sodium bicarbonate, antioxidants, erythropoietin and hydration fluids have been shown as promising interventions offering hope for protection of renal function in the perioperative period (Rosner and

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Okusa, 2006; Rosner *et al*., 2008; Zacharias *et al*., 2008; Conlon *et al*., 1999). The protective effects of NAC against ARF is through increasing Nitric Oxide (NO) which acts as an antioxidant and not its role as a vasodilator agent per se (Guru and Fremes, 2004). It has also been suggested that NAC can decrease ARF-originated morbidity and mortality in high-risk patients undergoing CABG (Burns *et al*., 2005). Considering the rise in IL-6 and IL-8 during cardiac bypass surgery, theoretically, an antioxidant such as vitamin C can play a role in renal function protection; although, its role is contraversial (Jouybar *et al*., 2012). The aim of our study was to assess the protective effects of intravenous NAC and vitamin C, administered during and after operation, on perioperative renal function of high-risk patients undergoing coronary artery surgeries.

MATERIALS AND METHODS

Trial design: Our study was a triple-blind randomized clinical control trial, which was performed from Jan 2014 to May 2014. The staff involved in the clinical care, members collecting and analyzing the data and the randomization operator were all blind to group allocations. The study protocol was approved by the Institutional Review Board (IRB) of Shiraz University of Medical Sciences and the approval of the Ethics Committee was achieved before the study was commenced. All the participants gave their informed written consent. The study protocol was registered at Iranian registry of clinical trials (www.IRCT.IR) in August 2014 (registration number: IRCT2014072815102N4).

Participants: Ninety patients with Coronary Artery Disease (CAD), who were scheduled for CABG surgery and were considered high-risk for perioperative renal complications were selected. The inclusion criteria consisted of ages over 70 years, confirmed renal failure, serum Cr level above 1.4 mg dL^{-1}, heart ejection fraction of below 35%, concomitant valve surgery and bypass surgery, history of previous coronary artery surgeries and diabetes under treatment with oral agents or insulin. The exclusion criteria included the emergency CABG surgery, off-pump CABG, positive history of heart transplantation, ARF (>1.1 mg dL^{-1} rise in serum Cr level since admission or operation), serum Cr level higher than 4.5 mg dL^{-1}, positive history of renal transplantation, hypersensitivity to NAC and NAC consumption in the last 5 days prior to the operation. All participants were required to fill out an informed written consent form. The participants were allocated into 3 equal groups with random numbers. A random assignment approach was taken using the Research Randomized Program (available at: http://www.randomizer.org/form.htm) to generate random numbers. The first group received 600 mg NAC for four times; the first dose of NAC was administered immediately after induction of anesthesia, the second one after successful weaning from the pump and the remaining two doses with 12 and 24 h intervals from the 1st dose. In the second group, 3 g Vitamin C was co-administered with NAC and in the 3rd group, only placebo (DW5%) was given, all with the same timings described above. All patients underwent standardized general anesthesia with the similar method; Midazolam 0.1 mg kg^{-1}, Morphine 0.2 mg kg^{-1}, Sufentanil 0.2 μg kg^{-1} and intubation with hypnotic dose of Sodium thiopental and pancuronium 0.1 mg kg^{-1} as a muscle relaxant. The same type of pump, initial pump solution, oxygenator and arterial filter were used for all the participants. The flow was adjusted in a way so that a perfusion pressure of 60-80 mmHg and minimal 2.4 L/mL/m^2 were provided. In case the perfusion pressure was lower, norepinephrine was infused. In order to sustain myocardial function, cold antegradecardioplegic agents were used. After successful weaning from pump, Protamine Sulfate 1 mg per 100 USP units of heparin was used to reverse heparin effect. All patients were transferred to ICU, without extubation. Patients were observed in the post-operation period for necessary interventions such as administration of vasoactive drugs; adjustment of dopamine dose according to the patient's renal function; renal replacement therapy; mechanical ventilation; re-intubation; postoperative complications such as Myocardial Infarction (MI), cerebrovascular accident, mediastinitis, sepsis and adverse drug reactions. In our assessments, renal function disorder was defined as a rise of 0.5 mg dL^{-1} or 25% from basal level in serum Cr within the 1st 3 days following the surgery. Data were collected on patients weight; serum Cr level; accompanying disorders such as congestive heart failure, peripheral vasculopathies, cerebral vascular diseases and transient ischemic attack as well as MI in the succeeding 30 days prior to the operation; chronic obstructive pulmonary disease, diabetes, hypertension, medication history and number of grafts and duration of cross clamp and pump. The technician who collected and recorded data was blind to randomization of patients and differed from the person responsible for injecting NAC, vitamin C or placebo. The χ^2-test or Fisher test were used for comparing the results in the two groups.

RESULTS AND DISCUSSION

Eighty four patients entered the study and 6 patients were excluded. Group A (NAC only) consisted of 26 patients: 18 males (69.2%) and 8 females (30.8%) with the

Table 1: Demographic variables of the three groups

	Group A		Group B		Group C		Total	
Variables	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range
Age (year)	65.88±9.35	42-80	62.42±10.22	39-80	65.63±11.36	45-85	64.64±10.39	39-85
Weight (kg)	68.50±11.50	50-96	65.30±12.98	41-85	67.60±10.32	47-92	67.19±11.39	41-96
Systolic BP (cmHg)	13.87±1.62	11-16	14.46±2.68	10-23	13.68±2.30	10-18	14.01±2.27	10-23
Diastolic BP (cmHg)	7.75±1.11	6-10	8.03±1.34	4-11	7.62±1.04	6-10	7.80±1.17	4-11

Table 2: Number of grafts, duration of cross clamp and duration of pump in the study groups

	Mean±SD			
Variables	Group A	Group B	Group C	Total
No. of graft	2.84±0.88	2.89 ±0.78	3.03±0.66	2.92±0.77
Cross clamp duration (min)	44.76±21.64	39.50±12.58	36.76±11.87	40.09±15.80
Pump duration (min)	72.80±31.15	63.11±16.11	64.13±17.27	66.43±22.2

Table 3: Comparison of serum creatinine levels among study groups

Days	Group A	Group B	Group C	p-values
The day before the operation	1.2077±0.65	1.15±0.31	1.02± 0.30	<0.05
Day 1	1.10±0.56	1.02±0.26	1.08±0.29	<0.05
Day 2	1.30±0.73	1.09±0.30	1.14±0.30	<0.05
Day 3	1.38±0.80	1.10±0.33	1.12±0.37	<0.05

mean age of 65.88±9.35 years, ranging from 42-80 years old. Twenty eight patients, 19 males (67.9%) and 9 females (32.1%) with the mean age of 62.42±10.22 (range of 39-80 years old) were participants of group B (NAC+ vitamin C). Finally, a total of 30 patients with 21 males (70%) and 9 females (30%), 65.63±11.36 (range of 45-85 years old) were considered as the controls group C (Placebo: DW5%). Other demographic variables of patients are provided in Table 1 and ata including number of grafts, duration of cross clamp and duration of pump are shown in Table 2.

Regarding the postoperative condition of the patients, mechanical ventilation was needed for 17 patients in groups A (65.4%) and B (60.7%), respectively for 24 h but none of the patients in the C group. None of the 84 patients needed re-intubation. A second surgery was necessary in 1 (3.8%) and 2 (7.1%) of the patients in groups A and B, respectively but none of the patients in group C. Postoperative complications including MI, CVA, mediastinitis and sepsis were not noticed in any of the patients and similarly RTT was not required for any patients. The duration of ICU stay was 3.40±1.45 in total, which was 2.44±0.86, 2.47±0.78 and 4.71±1.08 days in groups A-C, respectively. Adverse drug reactions were noticed in 6 patients in group B, 4 of them presenting with hypotension and the other 2 with nausea and vomiting. Only one patient in group A presented with hypotension. With regard to necessity of supportive care, 16 patients in group A, 19 patients in group B and all the patients in group C underwent hemofiltration with a total mean volume of 2192.06±0.6 mL and the mean duration of 65.84±23.33 min for all the 75 patients. Hemofiltration volumes of 2287.50±682.03, 2327.77±787.25 and 2055.17±324.68 mL with the pump duration of 77.73±35.73, 57.06±10.72 and 64.50±17.80 min were noticed in groups A, B and C, respectively. Vasoconstrictor drugs were used for 9 patients in group A, 11 patients in group B and 14 patients in group C with the mean time interval after surgery being 24.88±27.26, 20.27±19.15 and 4.92±3.72 h, respectively. Serum creatinine levels of patients one day before and on the 1st-3rd days after the surgery showed no significant differences (Table 3).

The results of this study demonstrate that neither NAC nor co-administration of vitamin C with NAC can have significant advantages on the renal outcome of high-risk patients undergoing cardiac bypass surgeries. NAC, as an antioxidant, is known to reduce production of proinflammatory cytokines and oxygen radicals, besides ameliorating ischemia reperfusion injury; it has been studied previously regarding its possible protective effects on postoperative acute renal failure in cardiac surgeries (Conlon *et al*., 1999; Zacharias *et al*., 2008). Renal injury is partly caused by formation of free oxygen radicals by activated neutrophils after ischemia (Wijnen *et al*., 2002). There are indications that free radical damage in indirect reperfusion injury can be diminished by administering extra antioxidants before and during reperfusion (Wijnen *et al*., 2002). In this field, there are still controversies as some studies support the idea and some do not. A meta-analysis study by Wang et al declared that NAC has no benefits or risks on outcome of patients (Wang *et al*., 2011). Another study by Ashworth investigating the effects of prophylactic administration of NAC suggested that there is no advantage in reduction of incidence of Acute Kidney Injury (AKI) as well as mortality and length of ICU stay following cardiac surgery

(Ashworth and Webb, 2010). Also, evaluation of occurrence of AKI after cardiac surgery in patients with chronic kidney disease revealed no benefits in protection against ARF and improvement in important clinical outcomes (Naughton *et al*., 2008; Adabag *et al*., 2008). Evaluating the effects of prophylactic IV NAC by Ristikankare *et al*. (2006) in chronic renal failure patients undergoing cardiac surgery was suggestive of no significant renoprotective effect of this agent. Use of NAC in prevention of contrast-media induced nephropathy after coronary angiography has also been controversial. In one study on patients with DM and Chronic Kidney Disease (CKD) as high-risk patients for developing contrast nephropathy, no detectable benefit for the prophylactic administration of oral NAC over an aggressive hydration protocol was found (Amini *et al*., 2009). Another study evaluating efficacy and safety of NAC, did not support reduction of risk of contrast nephropathy (Oldemeyer *et al*., 2003). Oral NAC as an adjunct to saline hydration did not seem to prevent contrast nephropathy in patients with chronic renal dysfunction (Goldenberg *et al*., 2004). Studies on ascorbic acid are scarce and limited, particularly in regard to cardiac surgeries. One study, evaluating the efficacy of the antioxidant ascorbic acid as an adjunct to hydration declared no prophylactic effect of this antioxidant on renal dysfunction in patient exposed to contrast dye for coronary procedures in limiting the incidence of contrast induced nephrotoxicity after coronary procedures (Boscheri *et al*., 2007). Another similar study by Dvorsak *et al*. (2013) assessing the effectiveness of ascorbic acid in prevention of Contrast-Induced Nephropathy (CIN) after coronary angiography in patients with chronic renal impairment found no statistically significant impact of ascorbic acid. However, conflicting evidence suggests that administration of the antioxidant acetyl cysteine may prevent this type of renal impairment (Spargias *et al*., 2004). The overall results of this study do not reveal any clinically significant difference regarding the use of NAC and/or vitamin C for renoprotection in high risk patients as compared to the previous studies.

CONCLUSION

Based on the results of our study, administration of NAC, vitamin C or both does not alter the outcome of renal function in high-risk patients after cardiac bypass surgery.

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