RESEARCH ARTICLE

The Effect of Post-Cardiopulmonary Resuscitation N-acetylcysteine on Renal Function: A Randomized Clinical Trial

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Background: The purpose of our study was to determine the effect of N-acetylcysteine (NAC) administered after successful cardiopulmonary resuscitation (CPR) on renal function of the survived patients.

Methods: In this double-blinded randomized clinical trial, 44 patients who experienced cardiopulmonary arrest and underwent successful cardiopulmonary resuscitation (CPR) were entered into the study. They were randomly divided into two groups. One group received NAC (150 mg/kg) and the control group received normal saline (NS).

Results: Serum levels of blood urea nitrogen (BUN), creatinine, and neutrophil gelatinase-associated lipocalin (NGAL) were significantly lower in the NAC group when compared to the NS group at 6, 12,24, 48, and 72 hours after resuscitation. However, alanine aminotransferase (ALT), cardiac troponin, creatine kinase MB fraction (CK-MB) and arterial blood gases did not differ between the two groups.

Conclusion: We observed significantly lower serum levels of BUN, creatinine, and NGAL in patients who received NAC after successful CPR following cardiopulmonary arrest. This can be used in clinical practice to decrease the chance of developing renal failure in such patient population.

Keywords: N-acetylcysteine; kidney; creatinine; blood urea nitrogen; cardiopulmonary arrest; cardiopulmonary resuscitation

A concern for clinicians managing patients who have experienced cardiopulmonary arrest and having undergone successful cardiopulmonary resuscitation (CPR) is development of acute kidney injury (AKI). The main reason for this state has been attributed to ischemia insulting the kidneys as a result of developing hypotension [1]. Patients who suffer cardiac arrest experience a generalized state of ischemia and if survived end-organs can be affected by the ischemic/reperfusion state [2-3]. Moreover, rhabdomyolysis and epinephrine used during CPR which causes renal vasoconstriction, have been cited as contributing factors. The prevalence of this condition in post-cardiac arrest is variable and has been reported to be 12% [4], 28% [1], and 50% [5]. These figures apparently surpass the reported incidence of AKI in hospitalized patients which is about 7% [6].

AKI not only affects prognosis of hospitalized patients [6], but also prognosis of patients who survive from cardiac arrest and CPR has poorer prognosis when AKI exists. In this regard, serum creatinine concentration has also been referred to as a useful marker to predict outcome of such patients [5]. In fact, elevated serum creatinine has been used as the most frequent tool to define renal failure after resuscitation [4]. In addition to serum creatinine which has been used for a long time in studies to define the renal function, a marker which has gained attention in determining the renal function is plasma neutrophil gelatinase-associated lipocalin (NGAL). In former clinical studies, this marker has been found to be a sensitive laboratory tool to define AKI which enabled the AKI diagnosis faster than serum creatinine elevation [7-9].This marker has mostly been studied in patients, both adults and children after cardiac surgery.

N-acetylcysteine (NAC), as a free radical scavenger, is a precursor to the antioxidant glutathione which is considered an important factor in the balance of reactive oxygen species (ROS) and homeostasis [10]. The most well-known use of NAC in clinical practice is its administration in management of paracetamol intoxication [11]. It can be observed from the literature that clinical application of NAC has been broadened in the recent decade and patients with conditions such as human immune suppression virus (HIV) infection

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[12], chronic obstructive pulmonary diseases [13], and Alzheimer's disease [14] benefit from NAC. Undoubtedly, one of the popular indications of using NAC is prevention of contrast-induced nephropathy (CIN) [15]. NAC has been shown to prevent worsening of renal function in those who receive contrast media [15]. Renoprotective effect of NAC is attributed to the ability of NAC to deal with raised nitric oxide (NO) production in those who receive contrast media, for example after coronary angiography [16].

Considering the above mentioned facts about renoprotective effect of NAC, we decided to test the hypothesis as to whether administration of NAC to patients who have survived from cardiopulmonary arrest benefit from NAC or not. In case of finding significant effect of NAC on renal function of such patients, NAC may be proposed to be used for this population.

Methods

In this double-blinded randomized clinical trial, patients who experienced cardiopulmonary arrest and underwent successful CPR and Advanced Cardiovascular Life Support (ACLS) were considered eligible to enter into the study. The study protocol was approved by the Ethics Committee of our university. Informed consent was obtained from the relatives of patients who accompanied them at the hospital. The study protocol was in conformity with the ethical guidelines of the 1975 Declaration of Helsinki [17]. The patients were recruited in 2 major university hospitals. The inclusion criteria were patients who experienced cardiopulmonary arrest, who aged 20-60 years, baseline serum creatinine level of less than 1.2 mg/dL, and spontaneous establishment of circulation within one hour after CPR/ACLS. Establishment of spontaneous circulation was defined as recording of systolic blood pressure of more than 90 mmHg. Exclusion criteria were isolated respiratory arrest, hemorrhagic shock, renal failure, opioid addiction, lack of spontaneous establishment of circulation within one hour after starting CPR. To calculate the sample size, serum creatinine level upon discharge of patients who had undergone successful CPR in a pilot study was determined. Mean of creatinine value was determined to be 2±3.1. Since we expected to observe a 50% decrease in this value by administering NAC and considering the power of the study as 80%, the sample size in each group was calculated as 22 patients. The patients were randomly divided into two groups using computer-based randomization software. One group (NAC group) received a bolus of NAC (150 mg/kg) on day 1 within one hour after establishment of circulation. The same doses were administered on days 2 and 3. For control group the same-volume of normal saline (NS) was injected in the same time course.

The following laboratory markers were measured immediately after resuscitation and at 6, 12, 24, 48, and 72 hours after resuscitation: blood urea nitrogen (BUN), creatinine, NGAL, arterial blood gases (ABG), alanine aminotransferase (ALAT), aspartate transaminase (AST), creatine kinase MB fraction (CK-MB), and cardiac troponin I (cTnI). Vital signs of the patients (pulse and blood pressure) were also documented in each encounter. These values were compared between the two groups studied. All data were entered into the SPSS software for Windows (ver. 18.0). Mean and standard deviation (±SD) were used to express continuous data and frequency for categorical data. To compare the laboratory markers at different time points, repeated measures test was applied. Since the analyses were done at 6 time points, P values at 0.05 were considered significant.

Results

There were 12 males (54.5%) and 10 females (45.4%) in NAC group and 10 males (45.4%) and 12 females (54.5%) in NS group (P= 0.41). Mean ages of patients in NAS and NS groups were 49.8±4.7 and 52.3±1.8 years, respectively (P= 0.37). (Table 1) presents the comparison between laboratory markers indicative of renal function between NAC and NS groups. As observed mean values for all renal function markers assayed were significantly lower in NAC group when compared to NS group. This difference was seen in all time points when measurements were done. (Table 2) depicts cardiac biomarkers assayed at different time points between the two studied groups. No statistically significant difference was detected regarding these markers between NAC and NS groups. (Table 3) presents the comparison of liver function tests (ALT and AST) between NAC and NS groups. Serum AST level was significantly lower in NAC group than in NS group. However, such a difference was not seen with respect to serum ALT level. No significant differences were observed regarding ABG findings between the two studied groups (Table 4).

Table 1- Comparison of mean (±SD) values of serum creatinine, blood urea nitrogen (BUN), and neutrophil gelatinase-associated lipocalin (NGAL) between NAC group and NS groups.

Time	Creatinine, mg/dL			BUN, mg/dL			NGAL, ng/mL		
	NAC group	NS group	Sig.	NAC group	NS group	Sig.	NAC group	NS group	Sig.
0	0.95 (0.17)	1.02 (0.11)	< 0.001	23.3 (1.4)	25.3 (3.3)	< 0.001	157.4 (43.1)	253.9 (32)	< 0.001
6 h	1.03 (0.21)	1.22 (0.36)		23.7 (2.6)	25.8 (7.3)		211 (48.2)	463.2 (120)	
12 h	1.08 (0.24)	1.44 (0.32)		24.7 (3.7)	26.7 (3.5)		272 (44)	535.1 (137.5)	
24 h	1.07 (0.25)	1.51 (0.4)		25.1 (4.06)	30.04 (4.7)		338.2 (80.1)	769.4 (236.1)	
48 h	1.03 (0.28)	1.51 (0.4)		24.5 (6.7)	32.9 (5.2)		321.2 (127.4)	694.6 (120.3)	
72 h	1.05 (0.26)	1.66 (0.32)		24.1 (4.7)	33.7 (5.3)		287.7 (137.1)	681.2 (140.3)	

Table 2- Comparison of mean (±SD) values of serum cardiac troponin I and creatine kinase MB fraction (CK-MB) between N-acetylcysteine (NAC) and normal saline (NS) groups at different time points after resuscitation

Time	Troponin I, ng/mL			CK-MB, ng/mL		
	NAC group	NS group	Sig.	NAC group	NS group	Sig.
0	0.3 (0.17)	0.35 (0.25)	0.65	31.09 (6.2)	28.5 (7.7)	0.35
6 h	0.5 (0.17)	0.54 (0.21)		47.04 (10.7)	47.2 (11.2)	

Table 2- Comparison of mean (±SD) values of serum cardiac troponin I and creatine kinase MB fraction (CK-MB) between N-acetylcysteine (NAC) and normal saline (NS) groups at different time points after resuscitation (continued)

Time	Troponin I, ng/mL			CK-MB, ng/mL		
	NAC group	NS group	Sig.	NAC group	NS group	Sig.
12 h	0.81 (0.25)	0.76 (0.18)		61.9 (14.1)	66.5 (13.7)	
24 h	0.95 (0.23)	0.91 (0.19)	0.65	61.4 (17.8)	64.7 (11.9)	0.35
48 h	1.01 (0.16)	1.06 (0.17)		59.7 (18.02)	54.5 (11.3)	
72 h	0.84 (0.24)	0.88 (0.25)		57.3 (16.3)	46.8 (14.9)	

Table 3- Comparison of mean (±SD) values of liver function tests including alanine aminotransferase (ALAT) and aspartate transaminase (AST) between N-acetylcysteine (NAC) and normal saline (NS) groups at different time points after resuscitation.

Time	ALT, mg/dL			AST, mg/dL		
	NAC group	NS group	Sig.	NAC group	NS group	Sig.
0	41.6 (13.7)	40.3 (17.4)	0.21	71.04 (14.9)	76.3 (7.16)	< 0.001
6 h	57.2 (16.5)	63.7 (16.03)		82.5 (11.6)	84.1 (11.1)	
12 h	72.1 (16.8)	65.6 (15.9)		122.4 (16.1)	133.5 (38.7)	
24 h	71.9 (13.6)	81.4 (11.4)		161.1 (30.3)	184.8 (37.2)	
48 h	73.5 (21.5)	78.2 (14.9)		190.9 (56)	257.6 (24.04)	
72 h	73.9 (19.8)	82.3 (13.6)		234.9 (47.7)	260.6 (51.8)	

Table 4- Comparison of mean (±SD) values of arterial blood gases (ABG) between N-acetylcysteine (NAC) and normal saline (NS) groups at different time points after resuscitation.

Time	PH			Bicarbonate, mg/dL			PaCO2, mmHg		
	NAC group	NS group	Sig.	NAC group	NS group	Sig.	NAC group	NS group	Sig.
0	7.35 (0.03)	7.35 (0.02)	0.21	14.3 (1.78)	14.4 (1.79)	0.51	34.9 (2.1)	34.7 (2.07)	0.47
6 h	7.27 (0.07)	7.26 (0.07)		13.7 (2.06)	14.04 (1.8)		34.9 (2.1)	35.2 (2.1)	
12 h	7.25 (0.09)	7.24 (0.08)		12.5 (3.1)	12.5 (3.3)		34.5 (2.2)	34.1 (2.4)	
24 h	7.24 (0.09)	7.23 (0.09)		12.04 (3.07)	12.8 (2.9)		33.7 (2.2)	33.6 (2.3)	
48 h	7.28 (0.1)	7.25 (0.12)		13.3 (3.1)	13.5 (1.9)		33.5 (2.4)	32.6 (2.02)	
72 h	7.28 (0.09)	7.23 (0.07)		12.3 (2.6)	12.7 (2.7)		33.5 (2.1)	33.7 (2.2)	

Discussion

According to the observed findings, NAC group patients demonstrated significantly lower serum levels of all three renal markers investigated here including BUN, creatinine, and NGAL. However, other markers assayed regarding liver function, cardiac markers and ABG findings except for AST did not differ between the two groups.

To the best of our knowledge, this is the first study to determine the application of NAC in post-cardiac arrest patients. Several studies have been conducted in animal models to assess the role of NAC regarding hypoxic brain injury. In a study on newborn piglets [18], it was reported that NAC (30 mg/kg bolus then 20 mg/kg/h infusion) significantly attenuated the increase in cerebral cortical H2O2 level, but not nitric oxide production. The authors also found that treatment with NAC improved cerebral blood flow. Liu et al. [19] likewise reported that post-resuscitation administration of NAC in swine model deceased oxidative stress in the brain and improved oxygen delivery to the brain, and attenuated apoptosis in newborn piglets with hypoxia-reoxygenation insults. In addition to studies performed on NAC influences on brain tissue, it has been shown that it attenuated acute lung injury and AKI following hemorrhagic shock in rats [20].

There is controversy about the effect of NAC in this setting. For example, in anther animal study [21], 28 pigs were exposed to gunshot injury. After life-saving surgery and first aid measurements, NAC was administered to one group. The authors reported that NAC did not influence post-traumatic endotoxin tolerance. Adding NAC to the immediate resuscitation fluid also did not affect significantly the early post-traumatic organ injury or initiation of inflammatory responses. In another report on a canine model, it was found that NAC administration did not have any neuroprotective effect after cardiac arrest and resuscitation [22].

ALT is a better marker representative of acute hepatic injury. We did not observe any difference between the two studied groups regarding ALT. Only AST level was lower in NAC group. In a previous randomized clinical trial, Rank et al. [23] showed that NAC administration (150 mg/kg/IV) over 15 minutes and a subsequent continuous infusion of 12.5 mg/kg/hr over 90 minutes) to septic shock patients improved hepatic blood flow. They measured microsomal hepatic function using the plasma appearance of monoethylglycinexylidide (MEGX) which showed significant increase in NAC group.

We observed significantly lower serum levels of BUN, creatinine, and NGAL in patients who received NAC after successful CPR following cardiopulmonary arrest. This can be used in clinical practice to decrease the chance of developing renal failure in such patient population.

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